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Economic Burden of Influenza in Thailand: A Systematic Review

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Abstract

Thailand has a high incidence and high mortality rates of influenza. This study summarizes the evidence on economic burden or costs of influenza subsequent to the occurrence of influenza illness in the Thai population by specific characteristics such as population demographics, health conditions, healthcare facilities, and/or cost types from published literature. A systematic search was conducted in six electronic databases. All costs were extracted and adjusted to 2018 US dollar value. Out of 581 records, 11 articles (1 with macroeconomic analysis and 10 with microeconomic analyses) were included. Direct medical costs per episode for outpatients and inpatients ranged from US$4.21 to US$212.17 and from US$163.62 to US$4577.83, respectively, across distinct influenza illnesses. The overall burden of influenza was between US$31.1 and US$83.6 million per year and 50-53% of these estimates referred to lost productivity. Costs of screening for an outbreak of influenza at an 8-bed-intensive-care-unit hospital was US$38242.75 per year. Labor-sensitive sectors such as services were the most affected part of the Thai economy. High economic burden tended to occur among children and older adults with co-morbidities and to be related to complications, non-vaccinated status, and severe influenza illness. Strategies involving prevention, limit of transmission, and treatment focusing on aforementioned patients' factors, containment of hospitalization expenses and quarantine process, and assistance on labor-sensitive economy sectors are likely to reduce the economic burden of influenza. However, a research gap exists regarding knowledge about the economic burden of influenza in Thailand.

Keywords

economic burden, costs of illness, influenza, Thailand, systematic review

Highlights

What do we already know about this topic?

- Influenza occurs all year round in Thailand and the epidemiological burden such as mortality is relatively high compared to other countries.

What is the impact?

- The economic burden of influenza in Thailand was substantial, especially for children under two years and older adults with co-morbidities, and the main burden was due to lost productivity and direct medical costs during hospitalization.

What are your research's implications toward theory, practice, or policy?

- The following management strategies may substantially reduce the economic burden of influenza: strategies including prevention, limit of transmission, and treatment with focus on specific groups of the population such as children under 2 years, older adults with co-existing conditions, non-vaccinated individuals, and individuals with severe influenza illness or complications, containment on hospitalization expenses and quarantine process, and assistance on labor-sensitive economy sectors.

Introduction

Influenza in humans is an acute respiratory infection mostly caused by influenza viruses types A and B.[1] Influenza A viruses can be classified into subtypes such as A (H5N1), A (H3N2), and A (H1N1) while influenza B are subdivided into lineages and strains such as B/Yamagata. Influenza symptoms include fever, cough, headache, muscle and joint pain, feeling of discomfort, sore throat, and a runny nose.[1] The illness ranges from mild to severe and death; its duration

lasts about 2 weeks or more. Influenza can cause health complications such as pneumonia, and can worsen pre-existing chronic conditions such as chronic obstructing pulmonary disease (COPD) and heart diseases.[2] Vulnerable groups at high risk of severe influenza or complications when infected include pregnant women, children under 5 years, adults aged 60 and above, and people with chronic conditions or immunosuppressive conditions.[3] Globally, the burden of influenza inter-pandemics can result in 1 billion cases and 3 to 5 million cases will sustain severe illness each year.[4] Moreover, between 291 243 and 645 832 individuals worldwide die annually from seasonal influenza-related respiratory illnesses.[5]

In Thailand, a middle-income country with a tropical climate in Southeast Asia, influenza cases occur throughout the year with 2 high peaks during the rainy season (June-August) and the winter (October-February).[6,7] The overall incidence of influenza cases over 8.5 months between January 1st and September 18th, 2017 was 177.75 per 100 000 population (approximate range: 76.88 to 594.59 per 100 000 population).[8] The estimated mortality rate of influenza-related respiratory illnesses in Thai population was 6.1 (95% confidence interval: 0.5-12.4) per 100 000 population or about 3600 deaths (range: 300-7000 deaths) per year.[9] The mortality rates in Thailand were relatively high compared with those from other 32 countries worldwide (e.g. 118.9 deaths/100 000 population in Thailand vs 17.9-223.5 deaths/100 000 population in the 32 countries for adults aged 75 years and greater).[5]

Economic burden of influenza is another measure evaluating impact of influenza illness in terms of individual utility and/or social welfare which can be evaluated at the microeconomic level (eg, individual's income loss), or assessed as a whole at the macroeconomic level (eg, an overall change in gross domestic product).[10] There is an increasing need to understand microeconomic consequences of a disease at the household level in middle- and low-income countries because protecting populations from financial risk has been a main focus of global health policy development.[10,11] Economic burden at the microeconomic level is often found in cost-of-illness studies which evaluate costs incurred due to illness in 3 categories of direct medical items (eg, medications and services), direct non-medical items (eg, transportation), and indirect costs (eg, lost income). Economic burden and cost-of-illness studies are useful for considering funding priorities and evaluating areas where savings may be made by decision policy makers,[12] and they are used by organizations such as WHO, World Bank, and the US National Institute of Health.[13]

A number of previous studies evaluated and reviewed costs of influenza in Thailand.[6,14,15] However, the information was not comprehensively compiled and not reported by characteristics such as specific influenza illnesses, populations, vaccination status, or healthcare facilities which can later become focus of interventions dealing with influenza. This study had an objective to summarize the evidence on the estimated economic burden or costs of influenza subsequent to occurrence of influenza illness among Thai population by specific characteristics including population's demographics, patients' health conditions, healthcare facilities, and/or cost types from published literature in Thailand.

Methods

The current study attempted to collate the information about economic burden of influenza after infection of influenza occurred which can be costs at the individual level, costs of screening, or change in the economy of Thailand. A systematic review using 6 key databases comprising PubMed, CINAHL, EMBASE, Scopus, Web of Science, and EconLit was performed. A systematic search used the following key words and its controlled vocabulary or subject heading list of "(influenza OR flu) AND (economic burden OR cost OR cost of illness OR cost of disease OR economic burden of disease OR health care cost OR health expenditure) AND (Thailand OR low-income country OR middle-income country)". Detailed medicine controlled vocabulary or subject heading list (MeSH Terms) from PubMed is presented on the Supplement. The search collected all articles including the search terms that appear in any place of the text. The search timeline was from the inception of the databases to 15th December 2018. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used as a guideline in this review.[16]

Eligible studies were those peer-reviewed studies written in English or Thai language. They needed to clearly evaluate or present economic burden of influenza, costs of influenza diagnosis, or costs of influenza treatment in a Thai setting. Types of studies were not limited. If a review study was retrieved from the search, original research from the review

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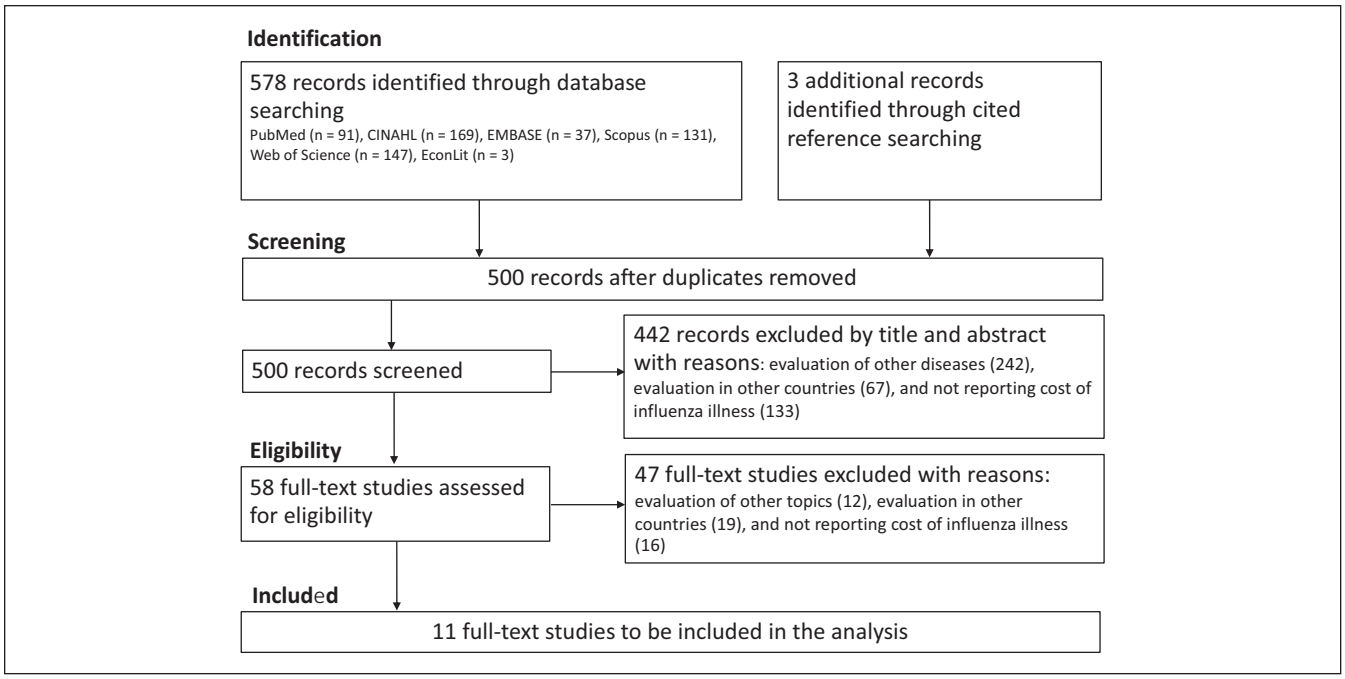

Figure 1. Flow diagram of systematic review results.

study was used instead. Exclusion criteria were studies evaluating other diseases, using settings in other countries and not including Thailand, not reporting costs of influenza illness or diagnosis, and evaluating costs of prevention strategies (eg, vaccine) alone. Studies from the search were screened first by titles and abstracts, and then by full text. After a final set of relevant articles was selected, manual searching was performed by looking at the titles, abstracts, and full text of references of the selected studies to collect further eligible studies. The screening, selection, manual searching, quality assessment, and data extraction processes were completed by a reviewer (PK). Another independent reviewer checked the processes. The conflicts were solved by discussion between the reviewer and the independent reviewer.

To evaluate the quality of the included studies in this present review and their credibility, a guideline of economic burden report from the WHO manual for estimating the economic burden of seasonal influenza was utilized.[17] This guideline was chosen because it is specific to the topic of this current study. It had a checklist of items that an economic-burden study should report and possess. For example, a good economic-burden study should clearly state illness definitions, sources of epidemiology data and costs, and funding sources, should explain items of costs, unit of costs, and methods of cost estimation, should perform cost discounting and sensitivity analysis, and should have results consistent with the methods.

The extracted data from the included studies mainly covered study characteristics such as settings and funding, study population, definition of influenza illness, cost methodology, and economic burden or costs of influenza illness. Costing methods can be categorized to 2 types: micro-costing and macro-costing. By micro-costing or an ingredient approach, the calculation is the multiplication of utilization of resource quantity and unit cost price. By macro-costing, costs are calculated from a diagnosis-related group or cost-to-charge ratio. Costs of influenza illness would be reported stratified by the population's age, cost types, facilities (outpatient and inpatient departments), vaccination status, and influenza illness. The cost types were composed of direct medical costs, direct non-medical costs, indirect costs, and total costs, which were generally used by health economic studies.

The extracted costs were adjusted to US dollar value in 2018. If the original costs were reported in Thai baht or international dollars earlier than 2018, they were first converted to Thai baht in 2018 using the Thai consumer price index from Bank of Thailand.[18] Then, the costs in 2018 Thai baht were converted to US dollars in 2018 using an average exchange rate of all months in 2018 (32.49 baht per US$1). If the original costs were reported in US dollars earlier than 2018, they were converted to US dollars in 2018 using the annual average consumer price index from the U.S. Department of Labor Bureau of Labor Statistic.[19] The cost conversion was done by Microsoft Excel 2019.

Results

There were 581 records found in the search from 6 databases and other sources (Figure 1). After removing duplicates, 500 records were screened and 442 articles were excluded by their titles and abstracts. Of 58 full-text articles, 11 articles were included in this review.

The quality of the included studies was generally good (see details on Supplemental Table 1). All studies clearly explained the definitions of influenza and the sources of data, and they all reported costs consistent with the methods used. However, some studies did not explain some costing methods in detail. Three studies out of 11 (27%) did not specify the costing year;[20-22] therefore, it was assumed that the costs were from the years of the study period. Total costs were not disaggregated in 4 studies (36%).[21,23-25] Discounting of the costs was not performed in 7 studies (64%) but this was acceptable because discounting is not necessary when a study period is short. Nine studies (82%) had no sensitivity analysis of cost estimation; however, this was defensible as their study designs did not have assumptions on cost estimation or different cost scenarios. Four studies (36%) did not have information about funding and it was assumed that there was no financial support for those studies.

Details of study characteristics, populations, influenza illnesses, cost methodology, and economic burden are provided on Table 1. Briefly, most studies had funding by non-profit organizations and employed a survey and/or hospital database for their cost estimation. Those 11 articles evaluated economic burden of influenza in the 3 main population groups: a) children,[23-25] b) older adults,[20,21,26] and c) individuals across various age groups/country.[6,14,22,27,28] Types of influenza illness varied across the studies: (i) influenza-like illness (ILI) which is considered a mild spectrum of influenza, (ii) seasonal influenza, (iii) influenza-associated acute respiratory illness or febrile respiratory illness, (iv) influenza-associated pneumonia, (v) avian influenza (H5N1), and (vi) the 2009 (H1N1) influenza pandemic.

Extracted economic burden or costs of influenza illnesses arranged by the population's age, cost types, facilities (eg, outpatient and inpatient departments), vaccination status, and influenza illness are shown in the last column of Table 1. The costs for outpatients were expenses for patients who did not have hospitalization and the costs for inpatients were expenses for patients who had hospitalizations. Concisely, 5 studies estimated only direct medical costs with a healthcare provider perspective and a patient perspective, and the remaining 5 studies included direct medical costs together with direct non-medical costs and/or indirect costs with a societal perspective and a patient perspective. There was 1 macroeconomic study with assessment of change in economy after the influenza A (H1N1) 2009 pandemic. Economic burden of influenza is summarized into 3 areas below: costs of illness at the individual and national levels, screening costs at a hospital, and macroeconomic impact on the Thai economy.

Costs of Illness for Outpatients

Figure 2 shows a comparison of direct medical costs per episode of various influenza illnesses for outpatients across different studies. On the graph, only the costs per episode were presented but there were costs with other units such as costs per visit reported on Table 1. The costs per episode for outpatients ranged from US$4.21 in a sample of patients with the average age of 37 years who had ILI and lived in a rural area[14] to US$212.17 in a sample of the elderly with the average age of 68.2 years who had ILI and lived in an urban community.[21] High direct medical costs among the outpatients were likely to occur in the elderly and children. However, the direct medical costs across studies may not contain exactly the same cost items. To compare the costs across age groups in the same study, children under 2 years old and children between 12 and 17 years old had the highest costs.[28] Vaccination status did not seem to affect the direct medical costs for outpatients as reported that the non-vaccinated elderly people and the vaccinated elderly ones did not have statistically significant difference in the costs of ILI (US$211.71 and US$212.17, respectively).[21] Furthermore, direct medical costs for outpatients varied in the facilities they visited; direct medical costs of influenza per visit ranged from US$4.95 for a health center to US$18.92 for a private hospital (Table 1).[6]

In the study evaluating all related costs with disaggregation report,[14] direct medical costs and transportation costs (US$4.21 and US$4.04, respectively) in outpatients were much lower compared with the lost income (US$20.24). The patients from this study were ill for a median of 5 days with at least 3 symptoms; 50% of the sample (8 persons) reported missing school or work.[14]

Costs of Illness for inpatients

Direct medical costs per episode of different influenza illnesses for hospitalized patients across studies are shown on Figure 2. The costs ranged between US$163.62 from a study sample of children aged 18 years and younger who had a median of hospitalization period of 3 days (range: 1 to 73 days)[23] and US$4577.83 from a study sample with the mean age of 67.6 years who had COPD and stayed in the hospital between 10 to 48 days.[20] From this figure, direct medical costs tended to be high in the cases with co-existing conditions (ie, COPD and ACS), complication (ie, pneumonia), adults and older adults, and non-vaccinated status. Inpatient costs across studies should be compared with caution as different studies had slightly different cost items. To compare the costs across age groups in the same study, adults (18-59 years) had the highest costs followed by older adults (60 years and older) and children under two years old.[28] Moreover, from Table 1, direct medical costs for inpatients per day varied across different facilities ranging from US$163.11 at a district hospital to US$230.00 at a private hospital.[6] Generally, the direct medical cost estimates for hospitalized patients were reported as a lump sum of several cost components (Table 1) and the cost of each component was not reported. However, 1 study with COPD patients reported that greater than 90% of the total costs of treatment were attributed to mechanical ventilatory support.[20]

Table 1. Study Characteristics and Economic Burden of Influenza Illness in Thailand.

CHILDREN

Author	Study	Population	Influenza illness	Cost methodology	Costs per unit (in 2018 US dollar value) by cost types, vaccination status, and influenza illness
Punpanich et al.[23]	**Objective:** To evaluate clinical and economic outcomes of hospitalized children with influenza **Study type:** Retrospective **Setting:** Public hospital **Study funding:** None	**Target population:** Children (1 month to 18 years) **Sample:** 289 children (60.9% were children less than 5 years and 39.1% were children aged 5 years and older)	**Type of influenza illness:** Seasonal influenza (Influenza A and B) **Confirmation of influenza:** RT-PCR and rapid testing	**Costing methods:** Micro-costing **Sources of cost data:** Hospital database **Cost perspective:** Healthcare provider **Original cost year:** 2010	**Direct medical costs:** *Outpatients*: NA *Inpatients*: (The sum of diagnostics, therapeutics, accommodations, supplies, health care services, and out-of-pocket payments) About 99% were non vaccinated Median costs per episode • Seasonal influenza in children (1 month to 18 years): 175.94 • Seasonal influenza (influenza A) in children: 186.62 • Seasonal influenza (influenza B) in children: 163.62 **Direct non-medical costs:** NA **Indirect costs:** NA **Total (direct + indirect) costs:** NA
Kittikraisak et al[24]	**Objective:** To evaluate cost-effectiveness of seasonal influenza vaccination **Study type:** Prospective **Setting:** Public hospital **Study funding:** Centers for Disease Control	**Target population:** Children (≤5 years) **Sample:** 1149 enrolled children (659 healthy and 490 high-risk)	**Type of influenza illness:** Influenza-associated ARI **Confirmation of influenza:** RT-PCR	**Costing methods:** Micro-costing **Sources of cost data:** Interview survey and hospital database **Cost perspective:** Society **Original cost year:** 2012, 2013, and 2014	**Direct medical costs:** *Outpatients*: Not reported separately *Inpatients*: Not reported separately **Direct non-medical costs:** Not reported separately **Indirect costs:** Not reported separately **Total (direct + indirect) costs:** (The sum of medical and diagnostic costs paid by out-of-pocket and by health insurance, transportation costs, and self-reported actual income loss or monetary value of productive work time loss.) Non-vaccinated Median costs per episode • Influenza in healthy children aged <60 months treated in outpatient department: 29.39 • Influenza in high-risk children aged <60 months treated in outpatient department: 21.38 • Influenza in healthy children aged <60 months treated in inpatient department: 454.79 • Influenza in high-risk children aged <60 months treated in inpatient department: 1666.66 Vaccinated Median costs per episode • Influenza in healthy children aged <60 months treated in outpatient department: 27.73 • Influenza in high-risk children aged <60 months treated in outpatient department: 43.22 • Influenza in healthy children aged <60 months treated in inpatient department: 312.46 • Influenza in high-risk children aged <60 months treated in inpatient department: 521.36
Kittikraisak et al[25]	**Objective:** To evaluate influenza incidence and cost between healthy and high-risk children **Study type:** Prospective **Setting:** Public hospital **Study funding:** Centers for Disease Control	**Target population:** Children (≤5 years) **Sample:** 1150 enrolled children (659 healthy and 490 high-risk)	**Type of influenza illness:** Influenza-associated ARI **Confirmation of influenza:** RT-PCR	**Costing methods:** Micro-costing **Sources of cost data:** Interview survey and hospital database **Cost perspective:** Society **Original cost year:** 2015	**Direct medical costs:** *Outpatients*: Not reported separately *Inpatients*: Not reported separately **Direct non-medical costs:** Not reported separately **Indirect costs:** Not reported separately **Total (direct + indirect) costs:** (The sum of medical and diagnostic costs paid by out-of-pocket and by health insurance, transportation costs, and self-reported actual income loss or monetary value of productive work time loss.) Mixed vaccine status: >70% non-vaccinated Median costs per episode • Influenza-associated ARI in healthy children aged <60 months: 24.37 • Influenza-associated ARI in high-risk children aged <60 months: 24.37 • Mild influenza-associated ARI in healthy children aged <60 months: 23.31 • Mild influenza-associated ARI in high-risk children aged <60 months: 26.49 • Severe influenza-associated ARI in healthy children aged <60 months: 245.79 • Severe influenza-associated ARI in high-risk children aged <60 months: 336.90

(continued)

Table 1. (continued)

Author	Study	Population	Influenza illness	Cost methodology	Costs per unit (in 2018 US dollar value) by cost types, vaccination status, and influenza illness
OLDER ADULTS					
Wongsurakiat et al[20]	**Objective:** To evaluate cost-effectiveness and cost-benefit of influenza vaccination **Study type:** Prospective **Setting:** University hospital **Study funding:** National Research Council of Thailand and influenza vaccines were supported by Aventis Pasteur (Thailand) Ltd.	**Target population:** Adults with COPD **Sample:** 125 COPD cases (average age: 67.6 years in vaccine group and 69.1 years in placebo group)	**Type of influenza illness:** Influenza-associated ARI **Confirmation of influenza:** Indirect immunofluorescence or HI test	**Costing methods:** Micro-costing **Sources of cost data:** Hospital database **Cost perspective:** Healthcare provider **Original cost year:** 1997 and 1998	**Direct medical costs:** *Outpatients*: (Medication costs from the hospital dispensary) Non-vaccinated Average costs per episode • Influenza-associated ARI in patients with mild-airflow-obstruction COPD: 46.75 • Influenza-associated ARI in patients with moderate-airflow-obstruction COPD: 10.50 • Influenza-associated ARI in patients with severe-airflow-obstruction COPD: 19.14 • Average non-vaccinated patients with COPD: 25.46 Vaccinated Average costs per episode • Influenza-associated ARI in patients with mild-airflow-obstruction COPD: NA • Influenza-associated ARI in patients with moderate-airflow-obstruction COPD: 36.32 • Influenza-associated ARI in patients with severe-airflow-obstruction COPD: NA • Average vaccinated patients with COPD: 36.32 *Inpatients*: (Costs of treatment, hotel, food, medical monitoring, ventilation support) Non-vaccinated Average costs per episode • Influenza-associated ARI in patients with mild-airflow-obstruction COPD: 782.52 • Influenza-associated ARI in patients with moderate-airflow-obstruction COPD: 4577.83 • Influenza-associated ARI in patients with severe-airflow-obstruction COPD: 4363.71 • Average non-vaccinated patients with COPD: 3241.35 Vaccinated Average costs per episode • Influenza-associated ARI in patients with mild-airflow-obstruction COPD: 192.95 • Influenza-associated ARI in patients with moderate-airflow-obstruction COPD: NA • Influenza-associated ARI in patients with severe-airflow-obstruction COPD: 772.25 • Average vaccinated patients with COPD: 482.60 **Direct non-medical costs:** NA **Indirect costs:** NA **Total (direct + indirect) costs:** NA
Praditsuwan et al[21]	**Objective:** To evaluate cost-effectiveness of influenza vaccination **Study type:** Prospective **Setting:** Urban communities **Study funding:** National Research Council of Thailand and influenza vaccines were supported by Aventis Pasteur (Thailand) Ltd.	**Target population:** Elderly (≥60 years) **Sample:** 635 elderly (average age: 68.2 years in vaccine group and 68.1 years in placebo group)	**Type of influenza illness:** ILI **Confirmation of influenza:** Symptoms-based methods	**Costing methods:** Micro-costing **Sources of cost data:** Survey **Cost perspective:** Patient **Original cost year:** 1998 and 1999	**Direct medical costs:** *Outpatients*: (Costs of treatments from the clinics and hospitals) Non-vaccinated Average costs per episode • ILI in elderly aged 60 years or older: 211.71 Vaccinated Average costs per episode • ILI in elderly aged 60 years or older: 212.17 *Inpatients*: NA **Direct non-medical costs:** NA **Indirect costs:** NA **Total (direct + indirect) costs:** NA

(continued)

Table 1. (continued)

Author	Study	Population	Influenza illness	Cost methodology	Costs per unit (in 2018 US dollar value) by cost types, vaccination status, and influenza illness
Sribhutorn et al[26]	**Objective:** To evaluate the effect of annual influenza vaccination on cardiovascular events and pneumonia prevention **Study type:** Retrospective **Setting:** Country (Thailand) **Study funding:** None	**Target population:** Adults with ACS **Sample:** Simulation of individuals with ACS starting to have pneumonia or ILI at 65 years	**Type of influenza illness:** Influenza-associated pneumonia andI LI **Confirmation of influenza:** ICD-10 codes (J9-J180) for Influenza and pneumonia	**Costing methods:** Micro-costing and Macro-costing **Sources of cost data:** Hospital database and standard unit cost **Cost perspective:** Society **Original cost year:** 2016	**Direct medical costs:** *Outpatients*: NA *Inpatients*: (Hospitalization costs, fare cost, and additional food cost) No information regarding vaccination Average costs per episode • Influenza-associated pneumonia and ILI in hospitalized patients with ACS at the age over 65: 1033.84 **Direct non-medical costs:** Additional food cost was included in the direct medical costs **Indirect costs:** (Lost income for both patients and caregivers) No information regarding vaccination Average cost per episode • Influenza-associated pneumonia and ILI in hospitalized patients with ACS at the age over 65: 20.67 **Total (direct + indirect) costs:** No information regarding vaccination Average cost per episode • Influenza-associated pneumonia and ILI in hospitalized patients with ACS at the age over 65: 1054.51
VARIOUS AGE GROUPS					
Apisarnthanarak et al[22]	**Objective:** To estimate costs of avian influenza (H5N1) screening and prevalence of influenza (H5N1) and influenza A pneumonia in an H5N1 endemic area **Study type:** Prospective **Setting:** University hospital **Study funding:** National Center and Genetic Engineering and Biotechnology, National Science and Technology Development Agency, and Thai Research Fund.	**Target population:** Adults with community-acquired pneumonia at the intensive care unit **Sample:** 115 adults with the age range of 17 to 82 and the average age of 64 years were screened (7% had influenza A (H3N2); none had influenza A (H5N1))	**Type of influenza illness:** Avian influenza (H5N1) **Confirmation of influenza:** Viral culture, Real-time RT-PCR, and microneutralization test for H5-specific antibody	**Costing methods:** Micro-costing **Sources of cost data:** Hospital database **Cost perspective:** Healthcare provider **Original cost year:** 2005 and 2006	**Direct medical costs:** *Outpatients*: NA *Inpatients*: No information regarding vaccination Costs per screening in a year (during the study period) • Diagnostic testing costs of screening for influenza H5N1 in inpatients (ICU) (Diagnostics included viral culture, RT-PCR, and H5 antibody test): 9186.08 • Isolation costs involved with staff time, gowns, gloves, and surgical masks for probable H5N1 cases in inpatients (ICU): 29056.67 • Total costs of diagnostic testing and isolation management for influenza H5N1 screening: 38242.75 **Direct non-medical costs:** NA **Indirect costs:** NA **Total (direct + indirect) costs:** NA
Clague et al[14]	**Objective:** To evaluate the burden of influenza-like illness **Study type:** Retrospective **Setting:** Rural province in Thailand (Sa Kaeo) **Study funding:** None	**Target population:** Individuals across various age groups **Sample:** Out of 718 individuals interviewed, 16 reported ILI (average age: 37 years; range: (1, 79))	**Type of influenza illness:** ILI **Confirmation of influenza:** Symptoms-based methods	**Costing methods:** Micro-costing **Sources of cost data:** Household Interview survey **Cost perspective:** Patient **Original cost year:** 2003	**Direct medical costs:** *Outpatients*: (Average out-of-pocket medical care at doctor visits, traditional healer visits, and pharmacy visits) No information regarding vaccination Average costs per episode • ILI calculated from all ages: 4.21 *Inpatients*: NA

(continued)

Table 1. (continued)

Author	Study	Population	Influenza illness	Cost methodology	Costs per unit (in 2018 US dollar value) by cost types, vaccination status, and influenza illness
					Direct non-medical costs: (Transportation) No information regarding vaccination Average costs per episode • ILI calculated from all ages: 4.04 **Indirect costs:** (Lost wages) No information regarding vaccination Average costs per episode • ILI calculated from all ages: 20.24 **Total (direct + indirect) costs:** No information regarding vaccination Average costs per episode • ILI calculated from all ages: 28.49
Simmerman et al[6]	**Objective:** To estimate the incidence and direct and indirect costs of influenza-associated illness for inpatients and outpatients **Study type:** Prospective **Setting:** Country (Thailand) **Study funding:** None	**Target population:** Individuals across various age groups **Sample:** 761 hospital inpatients (0-88 years) and 1092 outpatients (0-73 years) were enrolled (positive influenza: 11% and 24%, respectively)	**Type of influenza illness:** Influenza-associated pneumonia for inpatients and influenza-associated febrile respiratory illness for outpatients **Confirmation of influenza:** RT-PCR and HI for inpatients A rapid test, cell culture, and RT-PCR for outpatients	**Costing methods:** Micro-costing **Sources of cost data:** Mixed types including interview, medical records, survey, and databases **Cost perspective:** Society **Original cost year:** 2004	**Direct medical costs:** No information regarding vaccination Average costs per year (National level) • Laboratory-confirmed influenza in outpatients and influenza-associated pneumonia in inpatients: 13.56 to 36.02 million *Outpatients*: (Household expenditure to manage the illness) No information regarding vaccination Average costs per visit • Laboratory-confirmed influenza at a health center: 4.95 • Laboratory-confirmed influenza at a district hospital: 11.18 • Laboratory-confirmed influenza at a provincial hospital: 16.87 • Laboratory-confirmed influenza at other public hospitals: 19.63 • Laboratory-confirmed influenza at a private clinic: 8.59 • Laboratory-confirmed influenza at a private hospital: 18.92 • Laboratory-confirmed influenza (average from all facilities): 13.36 Average costs per year (National level) • Laboratory-confirmed influenza: 8.51 million *Inpatients*: (Inpatient costs included routine service costs at the hospital and ancillary costs including pharmaceutical products, laboratory investigations, and therapeutic interventions) No information regarding vaccination Average costs per inpatient day • Influenza-associated pneumonia at a district hospital: 163.11 • Influenza-associated pneumonia at a provincial hospital: 167.12 • Influenza-associated pneumonia at other public hospitals: 175.40 • Influenza-associated pneumonia at a private hospital: 230.00 • Influenza-associated pneumonia (average from all facilities): 183.91 Average costs per year (National level) • Influenza-associated pneumonia: 5.05 to 27.52 million

(continued)

Table 1. (continued)

Author	Study	Population	Influenza illness	Cost methodology	Costs per unit (in 2018 US dollar value) by cost types, vaccination status, and influenza illness
					Direct non-medical costs: (Transportation) No information regarding vaccination Average cost per visit • Laboratory-confirmed influenza in outpatients (average from all facilities): 2.11 Average cost per admission • Influenza-associated pneumonia in inpatients: 12.39 Average costs per year (National level) • Laboratory-confirmed influenza in outpatients: 1.99 million • Influenza-associated pneumonia in inpatients: 0.13 to 0.93 million • Laboratory-confirmed influenza in outpatients and influenza-associated pneumonia in inpatients: 2.13 to 2.92 million **Indirect costs:** (Lost wages) No information regarding vaccination Average costs per year (National level) • Laboratory-confirmed influenza in outpatients: 14.76 to 33.10 million • Influenza-associated pneumonia in inpatients: 0.66 to 11.57 million • Laboratory-confirmed influenza in outpatients and influenza-associated pneumonia in inpatients: 15.42 to 44.66 million **Total (direct + indirect) costs:** No information regarding vaccination Average costs per year (National level) • Laboratory-confirmed influenza in outpatients and influenza-associated pneumonia in inpatients: 31.11 to 83.61 million
Smith and Keogh-Brown[27]	**Objective:** To estimate the macroeconomic impact of pandemic influenza **Study type:** Retrospective + Modeling **Setting:** Country (Thailand) **Study funding:** World Health Organization	**Target population:** Entire population **Sample:** Entire population	**Type of influenza illness:** Influenza A (H1N1) 2009 pandemic **Confirmation of influenza:** Estimates were from published sources	**Costing methods:** Macroeconomic study using computable general equilibrium model **Sources of cost data:** Published databases were used as the input and the output estimates were from the model **Cost perspective:** Society **Original cost year:** 2004	**Direct medical costs:** *Outpatients*: NA *Inpatients*: NA **Direct non-medical costs:** NA **Indirect costs:** NA **Total (direct + indirect) costs:** NA **A brief result is percentage change in gross domestic products, sectorial impact, household consumption, and imports and exports at the national level for influenza A (H1N1) 2009 pandemic:** <1% change in gross domestic products; lost productivity due to influenza generally made declines in household consumption and exports for almost all sectors while it resulted in increase in imports of public administration and health goods.

(continued)

Table 1. (continued)

Author	Study	Population	Influenza illness	Cost methodology	Costs per unit (in 2018 US dollar value) by cost types, vaccination status, and influenza illness
Meeyai et al[28]	**Objective:** To evaluate the cost-effectiveness of influenza vaccination policies **Study type:** Retrospective **Setting:** Country (Thailand) **Study funding:** World Health Organization	**Target population:** Individuals across various age groups **Sample:** Simulation of individuals into 6 age groups: <2, 2-5, 6-11, 12-17, 18-59, and 60 years and older	**Type of influenza illness:** Seasonal influenza (Influenza A and B) **Confirmation of influenza:** Confirmation of inpatient cases by ICD codes A rapid test, cell culture, and RT-PCR for outpatients	**Costing methods:** Micro-costing **Sources of cost data:** National hospital database and literature **Cost perspective:** Healthcare provider **Original cost year:** 2012	**Direct medical costs:** *Outpatients*: (Cost items not specified in detail) No information regarding vaccination Average costs per episode • Seasonal influenza cases with symptoms who did not receive medical care from a clinic/hospital (from all ages): 0.11to 0.86 • Seasonal influenza aged <2 years: 96.01 • Seasonal influenza aged 2 to 5 years: 95.43 • Seasonal influenza aged 6 to 11 years: 94.86 • Seasonal influenza aged 12 to 17 years: 96.01 • Seasonal influenza aged 18 to 59 years: 71.86 • Seasonal influenza aged 60 years or older: 71.29 *Inpatients*: (Cost items not specified in detail) No information regarding vaccination Average costs per episode • Seasonal influenza aged <2 years: 432.32 • Seasonal influenza aged 2 to 5 years: 419.67 • Seasonal influenza aged 6 to 11 years: 398.98 • Seasonal influenza aged 12 to 17 years: 324.82 • Seasonal influenza aged 18 to 59 years: 599.61 • Seasonal influenza aged 60 years or older: 479.46 **Direct non-medical costs:** NA **Indirect costs:** NA **Total (direct + indirect) costs:** NA

RT-PCR, Reverse transcription-polymerase chain reaction; NA, Not available; ARI in Kittikraisak et al[24] and Kittikraisak et al[25] was defined as presence of at least 2 of the following symptoms: fever, nasal discharge/congestion, cough, or sore throat with onset during the preceding 7 days; COPD, Chronic obstructive pulmonary disease; ARI, Acute respiratory illness in Wongsurakiat et al[20] was defined as influenza-like illness, acute exacerbation of COPD and pneumonia; Mild airflow obstruction COPD in Wongsurakiat et al,[20] Chronic obstructive pulmonary disease with forced expiratory volume in 1 s (FEV1) ≥70% of predicted value; Moderate airflow obstruction COPD, COPD with FEV1 between 50% and 69% of predicted value; Severe airflow obstruction COPD, COPD with FEV1 <50% of predicted value; HI, Hemagglutination inhibition; ILI, Influenza like illness; ACS, Acute coronary syndrome; ICD-10, The 10th revision, international classification of diseases; ICU, Intensive care unit. Febrile respiratory illness in Simmerman et al[6] was defined as fever greater than 38-degree Celsius and either cough or sore throat; Outpatient and inpatient costs in the same studies[6,20,28] were estimated from different cases or episodes.

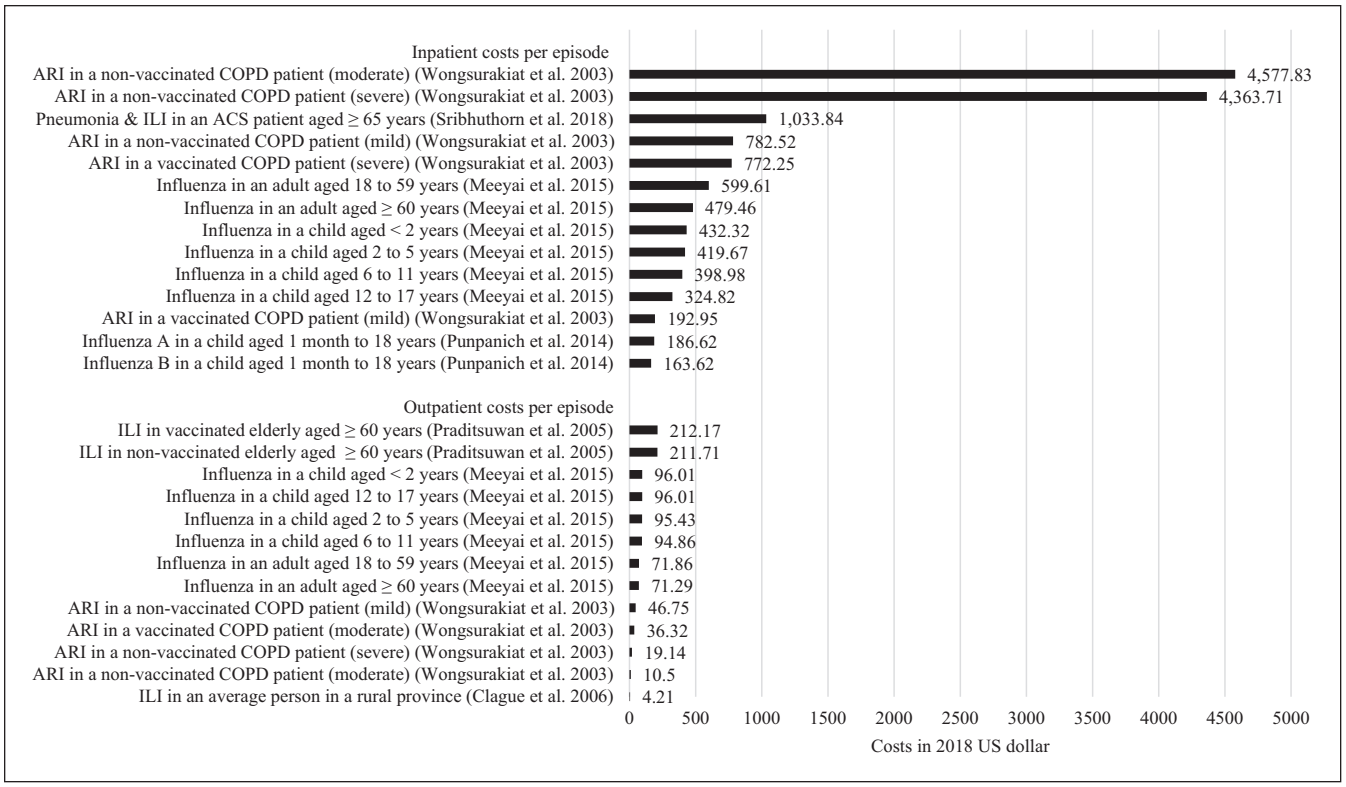

Figure 2. Direct medical costs in 2018 US dollar value for outpatients and inpatients across influenza illnesses from different studies.

Indirect costs for inpatients were evaluated in 2 studies (Table 1) and they were found to be smaller compared with the direct medical costs for inpatients.[6,26] The total costs for inpatients tended to depend on concurrent conditions and the severity of influenza as seen that children with high-risk incurred higher total costs than healthy children[24] and severe cases had higher costs than mild cases.[25]

Costs of Illness at the National Level

At the national level, the estimate of overall influenza economic burden incorporating cases of outpatients and inpatients ranged between US$31.11 and US$83.61 million per year (direct medical costs ranged between US$13.56 and US$36.02 million, direct non-medical costs ranged between US$2.13 and US$2.92 million, and income loss ranged between US$15.42 and US$44.66 million). Indirect cost or cost of productivity loss was the major component (50%-53% of the total cost) followed by the direct medical costs (43%-44%) and transportation (3%-7%).[6]

Screening costs at a hospital setting

Costs of screening for avian influenza (H5N1) in an 8-bed intensive care unit at a teaching hospital was estimated to be US$38 242.75 per year.[22] This total cost was applied to 115 adults screened and the isolation costs were the major contribution of the total costs which was much higher than the diagnostic testing costs. The isolation costs included staff time and materials involving gowns, gloves, and surgical masks.

Macroeconomic Impact

The macroeconomic impact of the influenza H1N1 (2009) pandemic in Thailand has been demonstrated.[27] Different scenario assumptions about clinical attack rates, case fatality rates, antivirals, vaccines, working days, and school closure were adopted in their model. Case fatality rates had more influence on change in economy compared with clinical attack rates. Gross domestic product (GDP) losses across all scenarios were less than 1%. Aggregated economic sectors which are capital-intensive such as mining and extraction had smaller losses due to the pandemic compared with labor-intensive sectors such as services or processed food. Regarding household consumption, the largest losses occurred in public administration and health (0.1-0.9%). This goes along with the biggest losses in exports in the public administration and the health sector (0.25-3%). The Thai imports in the public administration and health sector increased by approximately between 0.17% and 1.3% but most other sectors such as trade transport and communication decreased by between 0.02% and 0.5%.

Discussion

This systematic review summarized the costs of influenza illness classified by certain characteristics including population's demographics (ie, age), patients' health conditions (eg, comorbidities or vaccination status), health care facilities (eg, outpatient and inpatient departments), and types of costs (ie, direct, indirect, and total costs) and its macroeconomic burden in Thailand. Influenza incurred a substantial burden on patients, the healthcare system as well as the society. At the individual level, inpatient costs were much higher than outpatient costs. When aggregating costs to the national level from patients infected with influenza who had no need for hospitalization and who needed hospitalization, their indirect costs due to lost productivity were the major part followed by the direct medical costs. In the view of a hospital setting, the largest cost component of avian influenza (H5N1) screening during its outbreak was costs related to isolating suspected cases. The high costs of influenza illness were likely to be associated with children especially under 2 years at outpatient settings, adults (18-59 years) and older adults (60 years and above) at inpatient settings, being in private or larger healthcare facilities, having concurrent conditions such as COPD and ACS, having complications such as pneumonia after being infected with influenza virus, non-vaccination status, and severe influenza. The macroeconomic analysis predicted that influenza H1N1 pandemic had most impact on labor-intensive sectors.

The national indirect cost estimates were found to be the largest cost component (ie, between US$15.42 and US$44.66 million contributing to 50-53% of the total cost) is similar to findings from the US where 71% of the overall cost burden were the indirect costs[29] and other countries such as Norway, France, Germany, and Columbia.[15,30] Some insights from this present review are the following. A small survey by Clague et al[14] showed that the indirect cost per person during influenza illness was US$20 on average over a median period of 5 days.[14] This was relatively high because it was around $4 daily compared with an average daily wage of US$10 in Thailand.[31] Additionally, the same survey reported that 44% of Thai patients in a rural area took a personal loan for their medical expenses and 50% of them sought healthcare from more than one place.[14]

Hospitalization costs (ie, costs for inpatients) were the outstanding burden of influenza. The findings from this present study showed that inpatient costs could be at least three times higher[28] or more than 100 times[20] than outpatient costs. This is consistent with other studies worldwide including the US, Germany, the UK, Finland, Italy, Spain, Argentina, Columbia, and China.[30,32] Direct medical costs appeared to be the biggest part of hospitalization costs (68.8%-86.5%)[6] in this review, similar to the study in China revealing that direct medical costs were 69% of the costs for inpatients. Different from the previous studies where the costs from older adults were the highest,[15,32] the hospitalization costs in this review were the highest in adults followed by older adults. Such result from this review may need further investigation because it was drawn from only 1 study.[28]

Three key areas to reduce economic burden of influenza can be prevention by vaccines, mechanisms to reduce spread of disease, and treatments. One of the most effective interventions to prevent influenza is vaccination because it reduces the overall incidence of influenza.[33,34] Although the vaccination rate in Thailand has improved over the years, it is still low (around 30%) in young children.[35] Therefore, there is room for improving vaccine coverage in Thailand.

Moreover, access to paid sick days or permission to employees to take time off from work during their sickness without losing their salaries was associated with the greater probability of staying home when they or their child/children are sick especially on minorities, women, and families.[36] This is likely to help reduce economic burden by limiting the spread of the disease and stopping lost income. Under the Thai law, employees can have paid sick leave up to 30 days.[37] This can be a great opportunity for patients to quarantine themselves and get recovery, or parents to provide care for their children.

Effective treatment for influenza also plays an important role in alleviating the economic burden of influenza. Treatment of influenza should follow evidence-based medicine in a timely manner and limit the spread of the disease. Influenza treatment for uncomplicated individuals is usually based on specifically presented influenza symptoms (eg, antipyretics for fever).[34] However, it is recommended that individuals with high-risk of severe influenza/complications and patients with severe clinical illness are treated with antivirals, and in some cases with corticosteroids for asthma and antibiotics for secondary bacterial infection.[1,34] Early treatment of antivirals within 48 h of symptoms onset in persons with complicated influenza could lower the probability of mortality by 52% compared with the late treatment.[34] Antiviral treatments reduced hospital length of stay and healthcare costs due to the lower risk of complications and severity.[38] However, antiviral treatments pose some disadvantages such as side effects of nausea and vomiting.[34] In addition, as influenza viruses are changing constantly, further knowledge of drug resistance may be required when considering antiviral treatments.

There are some limitations of this review. First, underreporting of influenza cases or lost cases to follow-up[6,14,21] is 1 of the challenges in estimating economic burden. Future research should have a study period long enough to cover the season of influenza and to address fluctuations of seasonal influenza varied by the year-by-year incidence and severity. A minimum of 3 years of surveillance data is recommended to average out data from multiple influenza seasons. Additionally, next research may attempt to address patient behavior of non-seeking medical care and loss to follow-up issues possibly by performing primary data collection such as conducting a survey or an interview although this approach is time-consuming and costly.

Second, it was impossible to combine the costs of influenza across studies in a meta-analysis because of the heterogeneity of the included studies that possessed various objectives, populations, costing methods and cost categories. Due to the heterogeneity, comparing the costs across studies should be done with caution. Third, the costs of influenza presented may not provide the whole picture of the economic burden because most studies did not evaluate direct non-medical costs, indirect costs, and other influenza-associated non-respiratory diseases. Other than direct costs which was often evaluated, productivity loss and national economy effects due to seasonal influenza may be next areas to explore. Furthermore, costs were not itemized. For example, the direct medical costs were reported as the lump sum of all items including diagnostics, medications, supplies, services, accommodation, and out-of-pocket payments. This prevents us from identifying which item is a major expense.

There are some knowledge gaps warranting further research. Rigorous costing methodology to evaluate economic burden or costs of influenza is needed. Recent guidelines of how to evaluate economic burden[10,17] will be useful to achieve consistency in the methodology. There are other specific high-risk groups such as pregnant women or individuals with immunosuppressive conditions that were not assessed in the previous research. Furthermore, research such as evaluating determinants affecting economic burden of influenza or ranking of interventions reducing the burden may help policy makers to better manage influenza. Not have done much, evaluation of broader economic burden can be informative to policy makers. Some of other economic-burden-of-influenza topics are impact on specific economic sectors such as poultry industry during the avian flu outbreak or tourism during the influenza pandemic, medical insurance policy and patient behavior as a response to an influenza outbreak, malnutrition or poverty as an impact of influenza outbreak, or foreign investment change due to influenza pandemic.[15]

Conclusion

This study provides a comprehensive review of the economic burden of influenza in Thailand revealing the influenza burden was substantial. The costs of influenza illness appeared to be very high among children under 2 years old and older adults with chronic conditions. Medical costs during hospitalization and costs of lost productivity were the major economic burden of influenza in Thailand. Costs of a quarantine process were the most expensive for screening during an outbreak of influenza. The sectors of the economy involving with use of labors would be affected most by influenza. Strategies involving prevention, limit of transmission, and treatment with the focus on young and old populations with co-morbidities, containment on hospitalization expenses and quarantine process, and assistance on labor-sensitive economy sectors will tend to reduce the economic burden of influenza.

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Author Contributions

All authors had significant contribution on research proposal, research methods, and data analysis. Dr. Kiertburanakul and Ms. Kulchaitanaroaj played an important role on writing the manuscript.

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Supplemental Material

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