EXCESS MORBIDITY ATTRIBUTABLE TO SEASONAL INFLUENZA IN THAILAND DURING 1994-2008

THANTHIP SUNGSING

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE (PUBLIC HEALTH)
PROGRAM IN INFECTIOUS DISEASES AND EPIDEMIOLOGY
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2015

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entitled

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Thanthip Sungsing
Miss Thanthip Sungsing
Candidate

Aronrag C. Meeyai
Asst. Prof. Aronrag Cooper Meeyai,
Ph.D.(Modern Epidemiology)
Major advisor

Mathuros T.
Asst. Prof. Mathuros Tipayamongkholgul,
Ph.D.(Epidemiology)
Co-advisor

Prabda
Mr. Prabda Praphasiri,
Dr.P.H.(Epidemiology), Ph.D.
Co-advisor

Prof. Patcharee Lertrit,
M.D., Ph.D.(Biochemistry)
Dean
Faculty of Graduate Studies
Mahidol University

Supawadee Boonchuen
Lect. Supawadee Boonchuen,
Ph.D.(Tropical Medicine)
Program Director
Master of Science (Public Health)
Program in Infectious Disease and
Epidemiology
Faculty of Public Health
Mahidol University

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was submitted to the Faculty of Graduate Studies, Mahidol University
for the degree of Master of Science (Public Health)
Program in Infectious Diseases and Epidemiology
on
September 17, 2015

.....Thanthip Sungsing.....
Miss Thanthip Sungsing
Candidate

.....
Mr. Jame William Rudge,
Ph.D.(Infectious disease Epidemiology)
Chair

.....
Asst. Prof. Aronrag Cooper Meeyai,
Ph.D.(Modern Epidemiology)
Member

.....
Mr. Prabda Praphasiri,
Dr.P.H.(Epidemiology), Ph.D.
Member

.....
Asst. Prof. Mathuros Tipayamongkholgul,
Ph.D.(Epidemiology)
Member

.....
Prof. Patcharee Lertrit,
M.D., Ph.D.(Biochemistry)
Dean
Faculty of Graduate Studies
Mahidol University

.....
Assoc. Prof. Prayoon Fongsatitkul,
Ph.D.(Environment Engineering)
Dean
Faculty of Public Health
Mahidol University

ACKNOWLEDGEMENTS

I would like to express my sincerest gratitude and deepest appreciation to Asst. Prof. Dr. Aronrag Cooper Meeyai, my major advisor, for her guidance, invaluable support, and advice throughout the thesis to lead me to the right direction with her patience and great kindness. I wish to say a heartfelt thank you that she can bring me to be better and better at doing the thesis. More importantly, she has been a wonderful inspiration and ideal as a very diligent person. I am deeply honored to have her as my teacher and my thesis committee.

I would also like to extend my appreciation to my co-advisor, Asst. Prof. Dr. Mathuros Tipayamongkholgul and Dr. Prabda Prapasiri, for their kindness, all the encouragement and helpfulness. They were involving and providing elaborate and detailed comments and suggestions for the improvement. And I would like to thank to Dr. James William Rudge, my external examiner for his suggestion and helpful guidance.

I also thank all lecturers and staff at the Department of Epidemiology, Faculty of Public Health, Mahidol University for their assistance throughout the study. I would also like to express my deep appreciation to the staffs of National Institute of Health, Ministry of Public Health for their kindness help, especially Mrs. Malinee Chittaganpitch for his never ending support. Also, we deeply appreciated the kind supports of data of Meteorology Department.

Finally, my special thanks to all my family, who had a dominant influence on my student life and they gave me opportunity to pursue my dreams, greatest love and all my friends for their moral support and encouragement.

Thanthip Sungsing

EXCESS MORBIDITIES ATTRIBUTABLE TO SEASONAL INFLUENZA IN THAILAND DURING 1994-2008

THANTHIP SUNGSING 5337841 PHPH/M

M.Sc.(PUBLIC HEALTH) PROGRAM IN INFECTIOUS DISEASES AND EPIDEMIOLOGY

THESIS ADVISORY COMMITTEE: ARONRAG COOPER MEEYAI, Ph.D.(MODERN EPIDEMIOLOGY), MATHUROS TIPAYAMONGKHOLGUL, Ph.D.(EPIDEMIOLOGY), PRABDA PRAPHASIRI, DrP.H.(EPIDEMIOLOGY), Ph.D.

ABSTRACT

The impact of seasonal influenza epidemics can be quantified by excess morbidity or mortality of seasonal influenza. Assessing the excess morbidity of seasonal influenza will help quantify the burden of disease of seasonal influenza.

The monthly numbers of seasonal influenza patients (ICD 10 code: J09 to J11) from annual epidemiological surveillance reports from four regions in Thailand (Central, North, North-East, and South) during 1994-2008 were used. Estimates of excess monthly seasonal influenza morbidities were calculated as per the difference between observed and predicted baseline morbidities during the epidemic period. The baseline morbidities excluding seasonal influenza were calculated using 2 methods: 1) moving average method and 2) Poisson seasonal regression method.

Overall, the results using the moving average method and Poisson seasonal regression method found that the peak of excess morbidity of seasonal influenza in each of the four regions occurred during the months of June and July (rainy season). The levels of excess morbidities of seasonal influenza estimated by Poisson seasonal regression method were lower than the moving average method. The Southern region had the highest level of the excess morbidities (24.66 and 21.14 per 100,000 populations using the moving average method and Poisson seasonal regression method, respectively), followed by the North, Central and North-East.

The burden of seasonal influenza in Thailand and the four regions as calculated by excess morbidity indicated the morbidity over the baseline. The choice for both methods gave a similar peak time but not level of excess morbidity of seasonal influenza in Thailand.

KEY WORDS: SEASONAL INFLUENZA, EXCESS MORBIDITY, THAILAND, MOVING AVERAGE, POISSON SEASONAL REGRESSION

71 pages

การป่วยส่วนเกินของไข้หวัดใหญ่ตามฤดูกาลในประเทศไทยในปี พ.ศ.2537 - 2551
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ธารทิพย์ สังข์สิงห์ 5337841 PHPH/M

วท.ม.(สาธารณสุขศาสตร์) สาขาวิชาเอกโรคติดเชื้อและวิทยาการระบาด

คณะกรรมการที่ปรึกษาวิทยานิพนธ์: อรุณรักษ์ คูเปอร์ มีใย, Ph.D.(MODERN EPIDEMIOLOGY), มธุรส ทิพยมงคลกุล, Ph.D.(EPIDEMIOLOGY), ปราบดา ประภาศิริ, Dr.P.H.(EPIDEMIOLOGY), Ph.D.

บทคัดย่อ

การประเมินผลกระทบของไข้หวัดใหญ่ตามฤดูกาลสามารถบอกได้จากการป่วย หรือการเสียชีวิตที่เกิดขึ้นมากกว่าปกติ การประเมินภาระของไข้หวัดใหญ่ตามฤดูกาลจะช่วยบอกผลกระทบจากการเกิดไข้หวัดใหญ่ตามฤดูกาลของประเทศไทย

ข้อมูลที่ใช้ในงายวิจัย คือ จำนวนผู้ป่วยรายเดือนของไข้หวัดใหญ่ (แยกตาม ICD 10 คือ J09 ถึง J11) จากการรายงานการเฝ้าระวังประจำปี กระทรวงสาธารณสุข ของประเทศไทย และ 4 ภูมิภาค (ภาคกลาง ภาคเหนือ ภาคตะวันออกเฉียงเหนือ และภาคใต้) ระหว่างปี พ.ศ.2537 - 2551โดยใช้ baseline 2 แบบ คือ แบบค่าเฉลี่ยเคลื่อนที่ และแบบปัวซอง คำนวณการป่วยส่วนเกินได้จากผลต่างของค่าที่ได้จากการสังเกต กับค่าคาดหวัง baseline

การป่วยส่วนเกินของไข้หวัดใหญ่ตามฤดูกาลแบบค่าเฉลี่ยเคลื่อนที่ และแบบปัวซอง พบว่าประเทศไทยและ4 ภูมิภาค เกิดการป่วยส่วนเกินของไข้หวัดใหญ่ตามฤดูกาลสูงสุดในเดือนมิถุนายนถึงกรกฎาคม (ฤดูฝน) อัตราส่วนเกินของไข้หวัดใหญ่ตามฤดูกาลแบบปัวซองมีค่าน้อยกว่าแบบค่าเฉลี่ยเคลื่อนที่ ในขณะที่ภาคใต้เกิดการป่วยส่วนเกินของไข้หวัดใหญ่ตามฤดูกาลสูงสุด เมื่อใช้ baseline แบบค่าเฉลี่ยเคลื่อนที่ และแบบปัวซอง คิดเป็น 24.66 และ 21.14 ต่อ 100,000 ประชากร ตามลำดับ รองลงมาได้แก่ ภาคเหนือ กลาง และตะวันออกเฉียงเหนือ

ภาระการเจ็บป่วยเนื่องจากไข้หวัดใหญ่ตามฤดูกาลของประเทศไทยและแยกตามภูมิภาค จากการคำนวณการป่วยที่เกิดขึ้นพบว่า มีค่ามากกว่าค่า baseline การคำนวณการป่วยส่วนเกินของไข้หวัดใหญ่ตามฤดูกาลในประเทศไทยจากทั้งสองวิธีพบว่า ค่าสูงที่สุดที่คำนวณได้เป็นช่วงเวลาเดียวกัน แต่ค่าที่ได้ต่างกัน

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CHAPTER I
INTRODUCTION

1.1 Background Information

Human influenza virus causes substantial mortality and morbidity worldwide [1]. Influenza is one of the respiratory pathogens that can cause serious health problems in both mortality and morbidity worldwide [2]. While the significant mortality and morbidity caused by influenza have been well documented and established in many developed countries, its burden and public health significance in the developing world, particularly in tropical and subtropical regions [3]. The clinical severity of influenza increase with age and in individuals with underlying health disorder. During seasonal epidemics more than 90 percent of all influenza-related deaths involve persons aged 65 years and more [4]. Although the majority of infections are mild, some influenza virus infections can lead to complications such as viral pneumonia or secondary bacterial pneumonia [1]. However, unspecific presenting symptoms of influenza, absence of laboratory tests in clinical practice make it difficult to estimate the disease burden of influenza directly from the clinical diagnosed cases [2]. It is therefore necessary to assess influenza associated excess mortality or hospitalization by statistical modelling and use the estimate as a measurement for severity of influenza epidemics [5].

There were substantial influenza associated morbidity and mortality during pandemic periods, however, the deaths from seasonal influenza virus infection are also up to 500,000 people per year worldwide [6]. In countries with cold climates (temperate regions), seasonal influenza usually occurs during winter i.e. the Northern hemisphere seasonal influenza usually occurs from November to April, while in the Southern hemisphere usually it occurs from May to September and present remarkable impact [7]. For example, about 36,000 deaths and 226,000 hospitalizations are estimated to occur in the USA each year due to seasonal influenza [8].Some studies reported that the disease burden of influenza was nearly equivalent across some

temperate countries [9], but others noticed that effects of influenza occasionally exhibited disparities between geographical areas even in the same influenza season [10]. However, geographical variations in influenza associated disease burden in the tropics and subtropics have not been explored. Some environmental factors those are critical for survival and transmission of viruses [11].

1.2 Influenza Viruses

Influenza is a disease which has been spreading repeatedly since many centuries. Although the symptoms of influenza infection may be relatively mild and self-limiting, its complications can lead to hospitalization or death [12]. Generally, influenza viruses are spread by coughing/sneezing directly or by inhalation of aerosol spray of sputum, mucus and saliva [13]. Influenza viruses can be classified into 3 mains groups: Influenza A, B and C. Influenza A viruses are further divided into subtypes based on the antigenic differences found in its surface or envelope glycoprotein hemagglutinin (H) and neuraminidase (N). So far, 16 H and 9 N subtypes have been identified. Influenza B infection is mainly restricted to humans, meanwhile, Influenza C only causes trivial infections and is not regarded as clinically important [14]. Influenza viruses are constantly changing due to antigenic variation. The antigenic variation of influenza virus can be of two types: antigenic shift and antigenic drift. Antigenic shift is an abrupt, major change, resulting in new hemagglutinin and/or new hemagglutinin and neuraminidase proteins in influenza viruses that infect humans. The antigenic shift can cause pandemic as most people have little or no protection against the new virus. The antigenic shift happens only occasionally and is found mostly in type A influenza virus [15]. In 1918-1919, human pandemic occurred from the H1N1 virus which was spread from North America to Europe and named as the “Spanish Influenza”. It caused 20-30 million deaths worldwide, mostly among young people [16]. In 1957, the “Asian influenza” spread of A (H2N2) virus caused 1-4 million deaths, mostly children. In 1968, the “Hong Kong Influenza” spread of A (H3N2) affected all ages and caused 1 million deaths[16]. The second type of antigenic variation is antigenic drift which is a minor change in the genes of influenza viruses that happen continually over time as the virus replicates. This causes the

changes to the seasonal influenza. The antigenic drift is found in all species of influenza viruses [15]. Influenza viruses are changing by antigenic drift all the time.For example in 1977-1978, Influenza virus type A/Victoria/3/75/H3N2 and A/Texas/1/77/H3N2 spread as epidemics [17]. This work focuses light on antigenic drift, which cause seasonal influenza in Thailand.

1.3 Excess Morbidity and Mortality of Influenza

The US Centers for Disease Control and Prevention (CDC) used a 7-component national surveillance system for influenza that includes: virologic, influenza-like illness, hospitalization, and mortality data [18]. Current surveillance data from these programs, together with national hospitalization and mortality data have been used in statistical models to estimate the annual burden of disease associated with influenza in the United States for many years [18]. As those incidence proxies can be used to define a linear relation between influenza incidence and excess mortality [19].

Estimating the burden of influenza-related disease is useful for determining the risk of morbidity and mortality in different segments of the population, guiding vaccination programs, evaluating the use of diagnostic tests, antiviral drugs and planning for seasonal epidemics and future pandemics[18].During seasonal influenza epidemics, the impact of influenza on annual death and hospitalization rates is more difficult to estimate. During interpandemic periods, the health effects of infection are usually less severe, the symptoms of infection are similar to those caused by other respiratory tract infections, illnesses consistent with influenza are often not confirmed by virologic testing, and influenza is rarely specifically recorded on death certificates[20].

Assessing the burden of influenza epidemics on morbidity is difficult. Influenza diagnoses are generally not laboratory confirmed, and illness related to influenza are often attributed to pneumonia and other secondary complications that occur well after the influenza virus infection. The excess morbidity or mortality approach is justified by numerous observations of increased morbidity or mortality during influenza epidemics [5]. This excess highlights the increased morbidity or

mortality due to influenza (extra disease burden) between influenza seasons. According to the influenza epidemic in America during 19th century, morbidity and mortality rate due to influenza was calculated. It was initiated by, using excess mortality and excess morbidity started as an indicator to assess burden from seasonal influenza in the temperate countries[21]. The excess morbidity of influenza has been used in tropical countries and semi-tropical countries to quantify the impact of epidemic seasonal influenza.As used a measurement for severity of influenza epidemics[2]. For instance, it has been calculated to assess the characteristics of influenza-associated morbidity in Taiwan during 1999-2006[22], and to estimate the impact of influenza in HongKong, to calculate the burden of influenza during 1999-2000[23].

1.3.1 Excess mortality of influenza

The excess mortality typically estimated as the increasing of sum of deaths during the influenza season that exceeds a baseline of expected deaths in the absence of influenza; and the excess in deaths was used as a measure of the total impact of influenza on mortality[7]. In Hong Kong 1996-1999, Poisson regression models have been used to predict seasonally adjusted baseline trend in mortality [12]. In 3 Asians cities (Guangzhou, Hong Kong, and Singapore) during 2004-2006 estimated the excess disease burden of influenza associated and the determinants for severity of seasonal influenza [24]. In Thailand estimated excess mortality was also used to quantify mortality due to seasonal influenza during 2005-2009 [25].

1.3.2 Excess morbidity of influenza

In general, calculating the excess morbidity from influenza will use the same formula with the formula for calculating mortality which is a difference between observed value and expected value due to morbidity or excess mortality. Many method for calculate the baseline, for example, cut out the epidemic period and then calculate the average[26], univariate linear regression analysis[3], moving average an advantage over regression models in that they capture the dynamic relation between dependent and independent variables in the model[27].

1.4 Seasonal Influenza in Thailand

1.4.1 Economic Burden of Influenza in Thailand

The National Health Security Office (NHSO), Thailand, estimated the total economic burden of annual seasonal influenza using projected statistical life values to amount 87.1 dollar billion (95% CI, 47.2, 149.5) [28].Direct medical costs averaged 10.4 dollar billion (95% CI, 4.1, 22.2) annually. Projected lost earnings due to illness and loss of life amounted to 16.3 dollar billion (C.I., 8.7, 31.0) annually.

1.4.2 Seasonal Influenza Vaccination in Thailand

Since 2004, the Thailand Ministry of Public Health (MOPH) has offered free influenza vaccination to approximately 400,000 health care workers each year. In 2007 this coverage was extended to persons 65 years of age and older with underlying risk factors and development began on a domestic influenza vaccine production facility [25, 29]. In 2008, the MOPH recommended influenza vaccination of persons aged ≥65 years with one or more medical conditions. In 2009, the MOPH expanded the recommendation to include all persons aged ≥ 65 years and all persons with one or more medical conditions, but not for pregnant woman. An evaluation of NHSO influenza vaccination program 2009-2012 studied influenza vaccinesince2008 and thetargetpopulationaged65 and overat riskinsixchronic diseases including heart disease, kidney disease, stroke, asthma, chronic obstructive pulmonary disease, cancer and undergoing chemotherapy to evaluate the cost effectiveness of the implementation of this project . By providing vaccines in the elderly with listed chronic diseases, the average total cost got reduced to 969 baht from an average of 993baht or 24.40 baht net savings and helped extend the life quality 0.009 QALY [29]. Since 2010-2012, the seasonal influenza vaccine has expanded to all ages who suffer from six chronic diseases. In 2000, 72,102 influenza vaccine doses were distributed; 750,000 doses were distributed in 2006; 1.3 million doses were distributed in 2008, and approximately 2.4 million doses were distributed in the public and private sectors in 2009.

1.4.3 Influenza Viruses in Thailand

Seasonal influenza infections are associated with substantial mortality in Thailand and during 2005-2009 in both total mortality due to influenza A and relative importance of A (H1N1) and A (H3N2) [25]. Influenzaviruses occurred throughout the year but major peaks of influenza viruses in most regions were found in the rainy season (June-August) average 3 months range,18-33 percent positive with influenza A viruses dominating and a minor peak in the winter season (October-February) average 5 months range, 11-17 percent positive. The most frequently identified circulation of influenza viruses in 2005 was influenza A(H3N2), in 2006 show influenza A(H1N1), in 2007 there were influenza A(H3N2) and influenza B, in 2008 occurred the 3 types and happened the pdmH1N1 in June 2009. Among the 3,896 influenza viruses from patient with influenza 2,612 (67 percent) were influenza A viruses and to be subtype (21 percent influenza A (H1N1), 25 percent influenza A (H3N2), 21 percent pandemicH1N1] and 1,284 (33 percent) were influenza B viruses[30].

1.4.4 Seasonal Influenza Morbidity and Mortality in Thailand

Thailand is a middle-income country located in Tropical area and with a well-developed public health system [31]. The climate is subtropical with monsoon rains during the months of May to October. Influenza virus circulation was found to peak during June-October with a second peak sometimes occurring in January-April [29]. In Thailand, the report of number of influenza morbidityis from the annual epidemiological surveillance report (R506). Including ICD10codesas followed:

J09 (J09.00-J09.99): avian Influenza, new influenza A (H1N1)

J10 (J10.00-J10.99): Influenza

J11 (J11.00-J11.99): Influenza, virus not identified.

J09: Influenza due to certain identified influenza virus, the definition of J09 is influenza caused by influenza virus strains of special epidemiological importance with an animal-human or inter-human transmission limited to the inclusions.

J10: Influenza due to other identified influenza virus, J10 divided J10.0 and J10.1 is influenza with acute upper respiratory infection, laryngitis, pharyngitis, pleural effusion and other influenza virus identified.

J11: Influenza, virus not identified as specific virus not stated to have been identified such as encephalopathy due to influenza, had symptom such as gastroenteritis, acute myocardial unspecified or specific virus not identified [32].

The overall rate of seasonal influenza morbidity gradually declined in 1992, representing a rate of7.23casesper 100,000 populations. In the year1990, the rate was 10.77casesper 100,000 populations and the incidence rate was stable until the year1999 (7.18 per 100,000 populations). Seasonal influenza morbidity gradually declined further in 2000 (incidence rate was 5.34 per 100,000 populations) [33]. In term of geographical variations of influenza morbidity in Thailand during year 1998-2000, it was found that the highest rate of influenza morbidity in the South occurred in July 1997 (37.41 per 100,000 populations), in the North occurred in July 1994 (14.22 per 100,000 populations), in Central occurred in May 1999 (10.90 per 100,000 populations), and in the North-East occurred in July 2001 at 8.02 per 100,000 populations. (Figure 1.1)

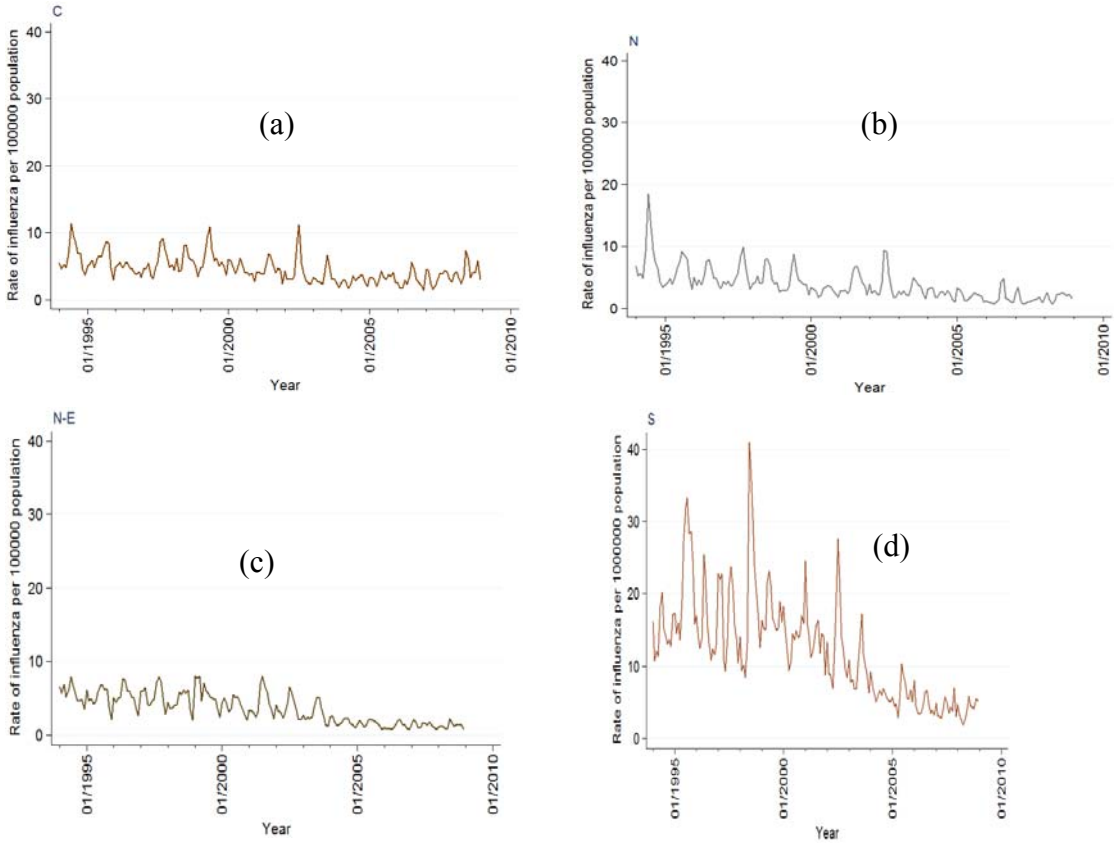


Figure 1.1 Rate of influenza (J10-11) per 100,000 populations in Central (a), North (b), North-East (c) and South (d) during 1994-2008 [33].

However, the death by seasonal influenza from the surveillance data, Epidemiology, Ministry of Public Health in 1997, 1998, 1999 and 2001 were only 4, 9, 2 and 2 person, respectively [33]. The study of Cooper BS, et.al estimated seasonal influenza-related mortality by using routine surveillance data [1, 19, 21, 24, 34-38] in Thailand between 2005-2008. Their work aimed at separate mortality time series into varies components (i.e. annual periodicity and long-term trends) using the regression technique. They found that there was variation between the 4 years (2005-2008) in both mortality due to influenza A and the relative importance of A (H1N1) and A (H3N2), in Thailand. The estimated number of influenza-related mortality per 100,000 populations were -0.1 (95%CI,-5.7, 5.6), 7.7 (95% CI, 1.6, 17.8), 1.8 (95% CI, -5.3, 8.7) and 7.8 (95% CI, 1.1, 15.5) by total influenza A in 2005, 2006, 2007, 2008, respectively and were 3.3 (95%CI,-2.1, 10.6), 1.2 (95%CI,-2.9,6.7), 1.5 (95%CI,-7.2, 8.6) and 1.4 (95% CI,-9.0, 8.8) by Influenza B in 2005, 2006, 2007, 2008, respectively [25].

As major impact of epidemic seasonal influenza (which may be preventable) can be quantified by excess morbidity or mortality. However, the mortality due to seasonal influenza from the surveillance data, Epidemiology, Ministry of Public Health in 1997, 1998, 1999 and 2001 were only 4, 9, 2 and 2 person, respectively [33]. As those incidence proxies can be used to define a linear relation between influenza incidence and excess mortality [19]. Asunspecific presenting symptoms of influenza, therefore a lot of under reported cases due to influenza in particular during non-pandemic influenza usually presented. To estimate the disease burden of seasonal influenza that can capture those under reported is therefore necessary to assess influenza associated excess morbidity (as excess morbidity can be used as proxy for excess mortality, through a linear) [19] by statistical modelling. This work focuses on excess morbidity rate due to seasonal influenza in Thailand as a whole. The excess morbidity rate for 4 different regions also considered in order to investigate spatial variation of the pattern of excess morbidities of seasonal influenza in Thailand. The environmental factor (e.g. temperature, relative humidity and rainfalls) and virus circulation also used to quantify their effect to theexcess morbidities of seasonal influenza in Thailand.

1.5 Research Questions

1. What is an excess morbidity of influenza in Thailand?
2. Is there any spatial variation (at regional region) of the pattern of excess morbidities of seasonal influenza in Thailand?

1.6 Research Objectives

1. To quantify the burden of seasonal influenza, and estimating the impact of influenza-associated morbidity in Thailand during 1994-2008.
2. To quantify the spatial variation in each region of Thailand during 1994-2008.

1.7 Research Hypotheses

1. There is a significant burden of seasonal influenza in Thailand.
2. Excess morbidity of seasonal influenza in each region part of Thailand is not different.

1.8 Scope of the Research

1. This research investigated the rate of seasonal influenza in Thailand (overall and each region) and studied the factors related to the excess morbidity caused by seasonal influenza in Thailand.
2. Using monthly time-series data of numbers of morbidities with influenza (J10-11), from the annual report of surveillance during 1994-2008, Bureau of Epidemiology, Ministry of Public Health Thailand[39].
3. Data collecting for this research was approved by the ethics Committee on Human Research from Mahidol University (see Appendix A).

1.9 Operational Definitions

Seasonal influenza: Influenza that occurs during interpandemic period [40].

Morbidity: Illness or disability, in relation to influenza, J09 to J11, the term is frequently used fairly loosely to describe significant illness, complications and hospitalizations [40].

Influenza viruses: Refer to viruses that caused influenza included in the Orthomyxovirus group divided into 3 species which are A, B and C, which able to be contracted by humans and animals as poultry, pigs and horses [41].

Excess morbidity of influenza: Excess morbidity is calculated as the difference between observed and predicted baseline morbidities during epidemic periods [22]. This excess morbidity can represent the impact of influenza.

CHAPTER II
LITERATURE REVIEW

2.1 Influenza

Influenza A and B cause primarily an acute respiratory illness, with fever, cough, coryza and headache. The incubation period for influenza infection average 2 days (range 1-4 days). The classic illness has an abrupt onset with headache, high-grade fever, chills, dry cough, myalgia and malaise. Rhinorrhoea, nasal congestion and pharyngitis may also be present. Fever typically peaks within the first 24 hours of illness. It begins to decline on the second or third day and is usually resolved by day 6; however, fever may be continuous or intermittent. Systemic symptoms usually resolve within a similar timescale. Weakness and fatigue, which on occasion can be accompanied by cough, can persist for an additional 1-2 weeks. However, other respiratory virus infections, such as rhinovirus or respiratory syncytial virus are also associated systemic symptoms to influenza.Influenza attack rates are higher in children compared to adults, with fever, cervical lymphadenopathy, nausea and vomiting being frequent manifestations; bronchiolitis and croup (laryngotracheitis) may also occur. Subclinical or asymptomatic infection can also occur, particularly in individuals with pre-existing infection immunity to the circulating strains of virus [42]. Influenza in human are quite non-specific, making it difficult to distinguish individual cases of influenza from other respiratory virus infections, unless supported by laboratory testing or surveillance data indicating the presence of influenza in the community.

2.2 Influenza Viruses

Influenza viruses are classified under the family Orthomyxoviridae. Influenza viruses are classified into 3 types, Influenza A, B and C. Influenza A viruses are further divided into subtypes based on the antigenic differences found in its surface

or envelope glycoprotein hemagglutinin (H) and neuraminidase (N). 16 H and 9 N subtypes have been identified. Influenza A can infect humans as well as birds, pigs and other animals. Influenza A and B are associated with seasonal influenza and most outbreaks and epidemics of influenza. Influenza B infection is mainly restricted to humans, though the virus has been isolated from seals. Influenza C only causes trivial infections and is not regarded as clinically important [14]. Influenza B and C are human pathogens [43].

2.2.1 Types of Influenza Viruses

Influenza A viruses are divided into subtypes based on differences in their surface glycoprotein antigens. All of these subtypes have been isolated in birds but only 3 different HA and two different NA subtypes have been isolated in humans (Table 2.1).

Table 2.1 Influenza Subtypes

Host	HA Subtypes	NA subtypes
Humans	H1, H2, H3	N1, N2
Birds	H1 - H14	N1-N9

The influenza viruses are unique amongst the respiratory viruses in that they undergo significant antigenic variation. Antigenic drift involves minor antigen changes from one season to the next and may result in epidemic spread of the new strain. Antigenic shift involves major antigenic changes of the HA and NA molecules and occurs only with Influenza A viruses. These changes can result in the appearance of pandemic viruses. Influenza A causes a more severe illness than influenza B, often resulting in hospitalization and death in the elderly and those at risk. World epidemics and pandemics have been due to influenza A [43].

2.2.2 Laboratory Testing of Influenza

During outbreaks, some of the samples should include culture so that influenza subtypes can be determined and for surveillance for new strains that my

need to be included in the next year's influenza vaccine. Viral culture can also help identify other causes of illness if influenza is not the agent. Viral culture detects both Influenza A and B. Viral culture provides results in 3 to 10 days.Serological testinginvolves testing serum samples for influenza antibody to diagnose recent infection. Two samples of blood are collected, one sample within the first week of illness and the second sample 2 to 4 weeks later. If antibody levels are higher in the second sample than in the first, it is likely that influenza virus was present [43].

Rapid influenza tests provide results within 24 hours, however they only offer about 70 percent sensitivity and 90 percent specificity (i.e. up to 30 percent of influenza cases would show a negative test result). Acceptable specimens for rapid testing include nasopharyngeal swabs, throat swabs, nasal wash, and nasal aspirate. Results are often available within 30 minutes. Some rapid tests detect both Influenza A and B, others only detects Influenza A.

2.3 Pandemic and Seasonal Influenza

2.3.1 Pandemic Influenza

Influenza pandemics are rare but able to spread easily from person to person as most or all of the population has little or no immunity for new virus. The result of pandemic is an outbreak of influenza encompassing the whole world, lasting 12-18 months, with distinct waves of infection. In order for a pandemic to occur, four key criteria must be met: 1) a new influenza virus substantially different (antigenically) from the circulating pre-pandemic strains must emerge or evolve and circulate in human, 2) little or no pre-existing immunity to the new subtype in major segments of the global population, 3) the new virus must cause significant clinical illness, and 4) the virus must be able to spread efficiently from person to person and as a result spread globally [44]. Because of circulation of similar or related viruses decades before a pandemic, and which have long since have been replaced, there is usually an age above which the population has been exposed to these ancestral viruses and subsequently has some persistence of immunity. Therefore, attack rates in such older individuals can be lower than in younger individuals; the specific age involved

and degree of protection varies from pandemic to pandemic. While attack rates are always high in pandemics, at least in younger individuals, mortality varies, often dramatically [42].

2.3.2 Seasonal influenza

Seasonal epidemics can seriously affect all populations, but the highest risk of complications mainly occur among children younger than age 2 years, adults aged 65 years or older, pregnant women, and people of any age with certain medical conditions, such as chronic heart, lung, kidney, liver, blood or metabolic diseases (such as diabetes), or weakened immune systems.

In temperate climates, seasonal influenza occurs mainly during winter while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly.Influenza epidemics can result in high levels of worker/school absenteeism and productivity losses. Clinics and hospitals can be overwhelmed during peak illness periods [45]. Influenza occurred globally with an annual attack rate estimated at 5-10 percent in adults and 20-30 percent in children. Illnesses can result in hospitalization and death mainly among high risk groups in industrialized countries most deaths associated with influenza occur among people age 65 or older.

2.4 Transmission of Influenza

An aspect of influenza transmission is the precise mechanism by which the virus spreads from an infected individual to another. Direct contact, small droplet, and aerosol spread all have been thought to be involved.Influenza viruses invade human's body by droplet transmission; inhalation of the virus which is spread surroundingin the air, the effective distance is 1 meter far from the body [46]. The other transmission pathway is receiving or contamination of the infectious nasal secretion and saliva into respiratory tract. Normally, respiratory tract is covered by mucus membrane which is able to catch the virus and prevent viral invasion into the body. However, the invasion of virus into the cell will be succeeded by the action of neuraminidase enzyme, an antigen which potentially reduces the thickness of mucosa membrane. Without mucosa, virus is able to attach the receiver on the uncovered cells and this enzyme also

facilitates virus to reach the lower respiratory tract. Influenza virus will be found at the nasopharyngeal area within 1-2 days before or after the symptoms are settled. Incubation period of influenza is approximately 2-3 days. After 3 days of present symptoms, the number of virus is increased to the maximum [47]. When the body is infected by influenza virus for many days until the body is not able to resist that virus, the complication will be occurred. Pneumonia is the most common complication due to the influenza virus or bacteria infected repeatedly [41]. Moreover, there are more complications found for instance; cardiac arrest, muscle inflammation, Encephalomyelitis, Guillain-Barre syndrome, Reye's syndrome and Perimyocarditis. Seasonal influenza would be detected by nasal swab, sputum gram stain and blood test for antibodies/antigens. By using Polymerase chain reaction (PCR) step and Imunofluorescent in order to help physicians decide to prescribe antivirus medication correctly[9]. In case of those had found influenza virus infected, the antiviral and anti-symptomatic medicines are prescribed by the physician.

2.5 Treatment of Influenza

Treatment of influenza usually involves making the person more comfortable increasing fluid intake and getting plenty of rest. Antibiotics do not kill viruses and have no role in treating influenza in otherwise healthy people, although they may be used to treat complications, such as pneumonia. Antiviral drugs for influenza are an important adjunct to influenza vaccine for the treatment and prevention of influenza. However, they are not a substitute for vaccination. When taken before infection or during early stage of the disease (within two days of illness onset), antivirals may help prevent infection, and if infection has already taken hold, their early administration may reduce the duration of symptoms by one to two days.

For several years, Amantadine and Rimantadine were the only antiviral drugs. However, whilst relatively inexpensive, these drugs are effective only against type A influenza, and may be associated with severe adverse effects (including delirium and seizures that occur mostly in elderly persons on higher doses). When used for prophylaxis of pandemic influenza at lower doses, such adverse events are far less likely. In addition, the virus tends to develop resistance to these drugs.A new class

of antivirals, the neuraminidase inhibitors, has been developed. Such drugs, Zanamivir and Oseltamivir, have fewer adverse sides affects and the virus less often develop resistance. However, these drugs are expensive and may not be available for use in many countries.In severe influenza, admission to hospital, intensive care, antibiotic therapy to prevent secondary infection and breathing support may be required.

2.6 Global Surveillance of Influenza

Countries throughout the world use a variety of different surveillance systems to monitor influenza activity, characterize strains, and document burden. Surveillance of influenza has historically focused on person seeking care for and presenting with mild influenza disease (fever, cough, and malaise), often term ILI (influenza-like illness). This type of surveillance, when performed systematically, can establish a sensitive marker for influenza activity. Moreover, systematic sampling of patients is often added in order to confirm influenza diagnosis, detect viruses that can be antigenically characterized for vaccine collection, or perform antiviral resistance testing. Influenza is also monitored outside of systemized surveillance in countries that routinely tests for influenza. However, additional systems are required to understand the full burden of severe and fatal seasonal influenza infection and associated risk factors. In addition to ILI, many countries now also conduct systematic hospital-based surveillance for influenza disease, screening persons admitted for respiratory illness using a broad case definition of fever and cough or severe acute respiratory illness (SARI). Along with ILI, SARI is now one of the syndromes recommended by the World Health Organization (WHO) for influenza surveillance globally [42].

Historically, the seasonality of influenza was recognized in the northern temperate region because of the clear increase of ILI in the colder months. When virologic assays became available, influenza transmission in northern temperate region was found to occur rarely before November and to wind down in April-May, though substantial year-to-year variation was apparent [48]. In some (but not all) years, influenza A viruses predominated at the beginning of the season, and influenza B viruses took over in later months. This seasonality allowed for recognition of influenza as an important cause of morbidity and mortality, and assessment of the impact of

influenza related hospitalization and death using models without the necessity for laboratory confirmation of individual cases. In the southern temperate regions, the seasons are reversed and influenza seasonal activity is generally underway by June. Seasonality of influenza becomes more complicated, however, at intermediate, subtropical, and tropical latitudes, with variation related to different climate factors and possibly altitude [49]. Generally, in these areas periods of influenza circulation during the year become longer and the timing less predictable, yet some periods of increased spread are maintained. A consistent pattern of two major periods of transmission has been observed in Hong Kong for a number of years, with one peak starting in February and another starting in the Northern Hemisphere summer, but with year-to-year variation in intensity [50]. A similar pattern has been observed in Singapore.

2.7 Burden of Disease Seasonal Influenza

Currently, the WHO estimates a total of 250,000-500,000 deaths and 3-5 million cases of severe illness annually due to seasonal influenza [42]. One of the biggest problems related to fully estimating the burden of seasonal influenza relates to case ascertainment. Influenza related hospitalization frequently occurs due to disease complications; there is again little perceived clinical value in making a diagnosis of influenza at this late stage in the illness and indeed less chance of a positive test several days after the onset of symptoms because virus shedding is likely to have declined. Thus, in all probability, true disease burden remain significantly underestimated [44].

2.7.1 Hospitalizations

The impact of seasonal influenza infection on hospitalizations has been measured largely in temperate regions using robust hospital discharge data, taking advantage of a clear seasonality in influenza transmission. In the United States, the mean estimate of hospitalizations per year form models of hospital discharge data is about 55,000-431,000 with considerable variation by year and by predominant virus [23]. As for hospitalization rates rise rapidly with age, especially among the elderly,

rising from average of 190 per 100,000 person-years in 65 to 69 years old to 1,200 per 100,000 person-years in over 85 years old [23]. However, infants and young children, who rarely die of influenza infection in settings with high access to healthcare, also have high rates of influenza-associated hospitalization. Based on hospital discharge data, the highest rates are among children less than 6 months of age; in addition to being at high risk of disease, this group is also not eligible for vaccination. The influenza-attributable hospitalization rates in this group have been reported as high as 1,000 per100,000 child-years, comparable to rates in the very elderly [51].

In Hong Kong, the mean excess numbers of hospitalizations attributable to influenza were estimates to be 3,327 for pneumonia and influenza during 1999-2000 [3]. The influenza-associated excess hospitalization rates per 100,000 population were lowest in the 15-39 age group and highest in the over 75 age group [12]. In Philippines, 1994 influenza was recorded as the fourth leading causes of morbidity with annual rates of 472 per 100,000 populations [52].

2.7.2 Deaths

In France during 1980-1990, found that the average mortality rate was 216 per 100,000 population for the elderly (75 years old and above). In Australia, the average recorded mortality in over the 20 years during 1975-1994 was 0.925 (range 0.321-2.516) per 100,000 population per year from influenza. The total annual mortality in Japan due to influenza was 95.3 cases per 100,000 populations with a peak in January and February. Data from sentinel practices in New Zealand showed the average annually mortality rates over 20 years were 1.77 (range, 0.6-6.3) per 100,000 for influenza [52]. In Hong Kong the mean excess numbers of deaths related to influenza annually were estimated to be 613 for pneumonia and influenza in 1999-2000 [3].In Viet Nam, the epidemiological surveillance for viral respiratory infections from 1993-1997 showed morbidity rates of 455-2,385 per 100,000 populations per year [52].

2.8 Excess Mortality and Morbidity of Influenza

The concept of excess mortality was introduced by William Farr in his description of the influenza epidemic in London in 1847. Farr defined excess mortality as the number of deaths exceeding a given norm for the given time and place in which an epidemic occurs [53]. Calculated of the excess mortality of influenza depends on estimating the number of deaths to be expected in the absence of influenza, the so-called baseline mortality [54]. In term of causal inference, assume that we could observe the number of deaths in particular population over a given time period under two settings: one with influenza circulation in the community and one without in the same community over the same time period [54]. The use of excess mortality as an index for recognizing influenza outbreaks is based primarily on the study of Dr. Selwyn Collins along with Josephine Lehmann. Collins used excess mortality to define epidemiologic characteristics of influenza epidemics [21, 55-56].

Several methods of estimating the excess deaths associated with the circulation of influenza viruses are based on a linear regression approach first developed by Serfling and published in 1963 [21]. Serfling recognized the importance of characterizing the deaths due to influenza, examining whether influenza mortality occurred among individuals with a pre-existing illness or chronic condition, or among otherwise healthy, productive individuals. The following as the source of data 1) weekly reports of deaths due to influenza and pneumonia received from the 108 cities in the United States, 2) final mortality data for specific causes of death for years up to and including 1958 and 3) the 10 percent sample of death certificates in order to obtain estimated death rates for major causes of death in 1959-1960 were used as the baseline average seasonal expected number of deaths [21].

Clifford et al. estimated excess mortality from influenza and pneumonia in England and Wales using four-weekly periods of registered deaths using data from the Office of Population Censuses and Surveys from October 1967 to April 1970 and October 1970 to April 1975 [57]. The authors incorporated into their analyses the number of years since a change in the influenza virus haemagglutin in antigen since the study period included both the pandemic influenza in the winter of 1957 (the A/Asian virus) and the winter of 1968 (the A/Hong Kong virus). They included a dummy variable in their model to allow for the increase in mortality that occurred in the period of study [57].

Recently, Simonsen et al. developed a Serfling-type linear regression model to estimate underlying pneumonia and influenza and all-cause deaths on the basis of weekly death data from 1972-1992[5]. The initial step in making estimates with models of this type involves removing the annual peaks in wintertime deaths. Then, by use of mortality statistics from several years (e.g., 5 years of data) with these seasonal peaks removed, a curve is fit to establish a sinusoidal baseline for the subsequent season. The excess deaths estimated to occur each season are defined as the numbers of deaths that exceeded a baseline or epidemic threshold value during 2 consecutive weeks [18].

In 2003, Thompson et al. further modified Serfling-type models, using Poisson regression techniques and directly incorporating influenza surveillance data, to estimate influenza-associated deaths. Using weekly death certificate data from 1976-2000 together with WHO influenza virus surveillance data, this model was fit to 3 death categories: underlying pneumonia and influenza deaths, underlying respiratory and circulatory deaths, and all-cause deaths [57]. Thompson et al. use 3 terms in the regression models to represent the percentage of specimens submitted to influenza surveillance laboratories that test positive for influenza A (H1N1), A (H3N2), or B viruses during each week for which estimates were made.

Choi and Thacker recognized the limitations of the methods for estimating excess mortality due to influenza epidemics. That Serfling's method tended to underestimate excess mortality due to the methods' omission of deaths during influenza epidemics in the calculation of baseline mortality [58]. Rather than omitting data for epidemic weeks in determining baseline mortality as Serfling did, Choi and Thacker replaced epidemic weeks with numbers of expected nonepidemic deaths using the dynamic forecasting methods (autoregressive integrated moving average (ARIMA) model) to predict the expected number of deaths for each week of the influenza epidemics from 1964-1978. The ARIMA models are based on the current value of a time series that can be explained by a function of p part values where p determines the number of steps into the past to forecast the current value [27]. Choi and Thacker estimated the expected number of deaths from the forecast was compared with the observed deaths from nonepidemic weeks, 1976-1979 [27].

The excess morbidities of seasonal influenza are calculated as the difference between thevalues obtainedfrom observationswithbaseline. There are variety of application that quantifies the burden of seasonal influenza in morbidity, for instance, Serfling, moving average, ARIMA, Poisson regression, Poisson seasonal regression. This research focuses on estimated excess morbidities of seasonal influenza using 2 methods 1) moving average and 2) Poisson seasonal regression. However, before calculate the excess morbidities of influenza; we have to calculate the baseline formulas then use it as the input to calculate the surplus (excess) of patients with influenza.

Methods for estimating excess seasonal influenza mortalities and morbidities

1. Serfling method is a cyclic regression model by assuming that the signal follows a sinusoid (a sum of sine an cosine terms) with a period of one year. The model incorporates both the sinusoidal function and the linear and quadratic function in order to describe seasonal fluctuations and to describe long-term trends, respectively. The result from the model can refer as a seasonal expectancy. Then the excess morbidity is the difference between the observed and the baseline morbidity (seasonal expectancy). Serfling method tended to underestimate excess morbidity due to the model omission of patients during influenza epidemics in the calculation of baseline [21]. Later modified versions of Serfling method have used to determine epidemic influenza activity and excess morbidity attributed to influenza. This modified version estimates the non-epidemic seasonal baseline, so weeks that typically show high influenza activity are excluded to avoid biased parameter estimates.

2. ARIMA Model applied by Choi and Thacker this model is a forecasting time series analysis called autoregressive integrated moving average model in order to estimate the expected number of influenza deaths [27]. Autoregressive models are based on the current value of a time series can be explained by a function of past values to forecast the current value. The ARIMA model has an advantage over regression models in that they capture the dynamic relation between dependent and independent variables in the model. To determine baseline mortality of influenza, instead omitting data for epidemic weeks as Serfling method, Choi and Thacker used

ARIMA model by replaced the numbers of expected non-epidemic deaths for epidemic weeks. Then the excess mortality is calculated as the difference between the observed mortality from influenza and the baseline mortality [27].

3. The moving average method is part of the ARIMA model that excluded the autoregressive integrated part from the model. Annual seasonal influenza classified 2 periods; epidemic period (May to July) and non-epidemic period (August to April). To calculated of expected baselinemorbidities by cutting out the epidemic period (May, June and July) because of assessed the trend from incidence rate of seasonal influenza from annually epidemiological surveillance ILI report during 1994-2008. The period of moving average can be any time duration that reasonable for a particular disease.For example, the 5-month moving average, which use the average of 5-month moving replace the epidemic periods. To calculated 5-month moving average the formula use:

$$\hat{Y}(t) = \frac{y(t-1) + y(t-2) + y(t-3) + y(t-4) + y(t-5)}{5}$$

When $\hat{Y}(t)$ = The average value of the forecast

y = Rate of morbidities with seasonal influenza (per 100,000 populations)

t = Timing as moving average

To estimated excess morbidities of 5-month moving average to perform: the difference between the observed and the expected 5-month moving non-epidemic period average [22]. This method will be used as a baseline value of 15 of each year

4. The Poisson seasonal regression model was fitted to seasonal influenza morbidities data available for 1994-2008. Add the represent of the seasonal; sin $(2\pi t/12)$ and $\cos(2\pi t/12)$ for baseline in Poisson seasonal regression modelin equation {1}.

$$\hat{Y}(t) = \exp\{a_0 + a_1 + a_2 t^2 + a_3 \cdot \sin(2\pi t/12) + a_4 \cdot \cos(2\pi t/12)\} \text{ ----------} \{1\}$$

where t denotes the month, $\hat{Y}(t)$ is the estimated monthly morbidities (incidence per 100,000 population),a_0, a_1, and a_2 stand for the intercept in the model,

linear time, and squared time trends, respectively, $\sin(2\pi t/12)$ and $\cos(2\pi t/12)$ represent the season. Estimates of excess monthly seasonal influenza morbidities were calculated as the difference between observed and predicted baseline morbidities during epidemic period [22].

2.9 Seasonal Influenza in Thailand

Seasonal influenza in Thailand (have classified as J09 to J11) was found slightly through the whole year, the highest number of infection was in the middle of the year. The last decade, there were 30,000-50,000 people hospitalize as infected with influenza but only 10 death were reported trough surveillance system each year. The National Health Security Office (NHSO), Thailand has taken the influenza vaccine since 2010 and the target is populationaged65 and over are at risk of chronic disease including heart disease, kidney disease, stroke, asthma, chronic obstructive pulmonary disease, cancer andundergoingchemotherapy. During July 2010-December 2012 the populations of 2-3 million people have beenvaccinated againstinfluenzaeach year. Overall national coverage rate of the influenza vaccine in patients with chronic disease, including seven chronic in 2010, 2011 and 2012 were for 31.4 percent, 24.1 and 30.5, respectively.

For countries in the tropical regions, a fairly consistent finding has found the association of influenza transmission with the rainy season with little temperature variation [59]. Complicating the role of the environment alone are those human activities that drive transmission, such as timing of opening of schools, crowing, and possibly factors such as vitamin D and melatonin levels which may modulate host susceptibility [60]. In Thailand show the superimposed on the regular seasonal variation, all-cause mortality decreased at high levels of relative humidity and increased at high temperature [25].

CHAPTER III
MATERIALS AND METHODS

3.1 Study Design

This research is a time-series study for the excess morbidities with influenza (J09 to J11) in Thailand. This study used a morbidity of seasonal influenza data during 1994-2008 to describe the excess oftheburdenofseasonal influenza in Thailand and four regions of Thailand.

3.2 Study Area

In this study, the setting areas are the whole of Thailand and four regions of Thailand (included Central, North, North-East and South) followed the categories of Ministry of Public Health, Thailand. Furthermore, for the South region there will be divided into two parts which South-East and South-West followed the categories of the Meteorology department, Thailand (Figure 3.1), as the seasons of the South-East and South-West do not at the same time.

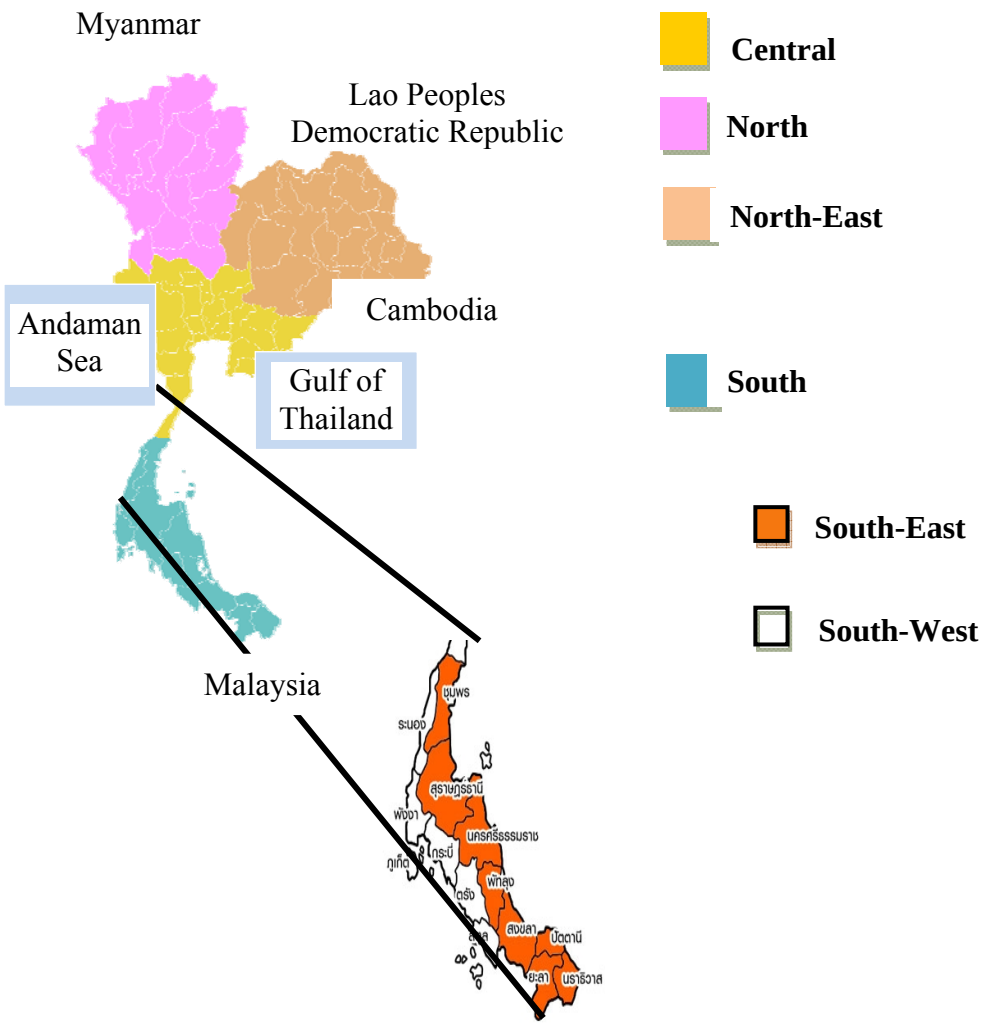


Figure 3.1 Map of the whole and the regions of Thailand

3.3 Data Collection

This study obtained all data which available for public used: 1) the monthly number of influenzamorbidities, 2) the average monthly temperature, relative humidity and rainfalls, 3) the monthly number positive of influenza viruses test, and 4) mid-year population.

3.3.1 The monthly number of seasonal influenzamorbidities (J09-11) by province from annually epidemiological surveillance report, Bureau of Epidemiology, Ministry of Public Health, Thailand during 1994-2008 [33] were aggregated to

regional level followed the categories of both Ministry of Public Health and Meteorology department, Thailand (see detail in Table 3.1).

Table 3.1 List of provinces by regions in Thailand

Regions	Sub-region	Numbers of provinces	Provinces
Central		26	Bangkok, Ang Thong, Nonthaburi, P.NakhonS.Ayutthaya, PathumThani, Chai Nat, Lop Buri, Saraburi, Sing Buri, Kanchanaburi, NakhonPathom, Ratchaburi, SuphanBuri, Phetchaburi, PrachuapKhiri Khan, SamutSakhon, SamutSongkhram, Chachoengsao, NakhonNayok, PrachinBuri, Sa Kaeo, SamutPrakan, Chanthaburi, Chon Buri, Rayong, Trat
North		17	Chiang Mai, Chiang Rai, Lampang, Lumphun, Mae Hong Son, Nan, Phayao, Phrae, Phetchabun, Phitsanulok, Sukhothai, Tak, Uttaradit, KamphaengPhet, NakhonSawan, Phichit, UthaiThani
North-East		19	Loei, NongBua Lam Phu, NongKhai,UdonThani, Kalasin, Mukdahan,NakhonPhanom, SakonNakhon, KhonKaen, MahaSarakham, Roi Et, Buri Ram**,** Chaiyaphum**,** NakhonRatchasima**,** Surin, Amnat Charoen**,** Si Sa Ket, UbonRatchathani**,** Yasothon
South	South-East	8	Chumphon, SuratThani, Nakhon Si Thammarat, Phatthalung, Narathiwat, Pattani, Yala, Songkhla
	South-West	6	Ranong, Phangnga, Phuket, Trang, Krabi, Satun

The morbidity of seasonal influenza reported in epidemiological surveillance report is the total number of influenza patients in all public health services number of who receive treatment. These individual influenza data (including ICD-10 code) collected and reported by each health services. Every hospital in each province can send the number of patients daily or weekly through two channels: 1) via thewebsite, Bureau of Epidemiology (http://164.115.25.123/ili) or send the text messages via mobile phone (send messages to1677 without any charge).When the Bureau of Epidemiology gathering those morbidity of influenza, preliminary analysis such as 1) the graphof the number of influenza patients and its moving, 2)the proportion of influenza patients compared with total number of all patients who received services- and 3) time trend of influenza.

3.3.2 Mid-year population from Bureau of Policy and Strategy during 1994-2008 [61]. This data recorded by the Survey of Population Change, National Statistical Office, Thailand.

3.4 Data Analysis

The data was analyzed by STATA Statistical Software for windows version 12 serial numbers 40120514582. The excess morbidities of seasonal influenza are calculated as the difference between the values obtained from observations with baseline. There are variety of application that quantifies the burden of seasonal influenza in morbidity, for instance, Serfling, moving average, ARIMA, Poisson regression, Poisson seasonal regression. This research focuses on estimated excess morbidities of seasonal influenza using 2 methods 1) moving average and 2) Poisson seasonal regression. However, before calculate the excess morbidities of influenza; we have to calculate the baseline formulas then use it as the input to calculate the surplus (excess) of patients with influenza.

Methods for estimating excess seasonal influenza mortalities and morbidities

1. Serfling method

Serfling method is a cyclic regression model by assuming that the signal follows a sinusoid (a sum of sine an cosine terms) with a period of one year. The model incorporates both the sinusoidal function and the linear and quadratic function in order to describe seasonal fluctuations and to describe long-term trends, respectively. The result from the model can refer as a seasonal expectancy. Then the excess morbidity is the difference between the observed and the baseline morbidity (seasonal expectancy). Serfling method tended to under estimate excess morbidity due to the model omission of patients during influenza epidemics in the calculation of baseline [21]. Later modified versions of Serfling method have used to determine epidemic influenza activity and excess morbidity attributed to influenza. This modified version estimates the non-epidemic seasonal baseline, so weeks that typically show high influenza activity are excluded to avoid biased parameter estimates.

2. The ARIMA Model

ARIMA Model applied by Choi and Thacker this model is a forecasting time series analysis called autoregressive integrated moving average model in order to estimate the expected number of influenza deaths [27]. Autoregressive models are based on the current value of a time series can be explained by a function of past values to forecast the current value. The ARIMA model has an advantage over regression models in that they capture the dynamic relation between dependent and independent variables in the model. To determine baseline mortality of influenza, instead omitting data for epidemic weeks as Serfling method, Choi and Thacker used ARIMA model by replaced the numbers of expected non-epidemic deaths for epidemic weeks. Then the excess mortality is calculated as the difference between the observed mortality from influenza and the baseline mortality [27].

3. The moving average method

Moving average is part of the ARIMA model that excluded the autoregressive integrated part from the model.

1) Expected morbidities of seasonal influenza

Annual seasonal influenza classified 2 periods; epidemic period (May to July) and non-epidemic period (August to April).To calculated of expected baselinemorbidities by cutting out the epidemic period (May, June and July) because of assessed the trend from incidence rate of seasonal influenza from annually epidemiological surveillance ILI report during 1994-2008. The period of moving average can be any time duration that reasonable for a particular disease.For example, the 5-month moving average, which use the average of 5-month moving replace the epidemic periods. To calculated 5-month moving averagethe formulause:

$$\hat{Y}(t) = \frac{y(t-1) + y(t-2) + y(t-3) + y(t-4) + y(t-5)}{5}$$

When $\hat{Y}(t)$ = The average value of the forecast

y = Rate of morbidities with seasonal influenza (per 100,000 populations)

t = Timing as moving average

2) Excess morbidities of seasonal influenza

To estimated excess morbidities of 5-month moving average to perform: the difference between the observed and the expected 5-month moving non-epidemic period average [22]. This method will be used as a baseline value of 15 of each year (show table 4.1).

4. Calculated expected and excess morbidities of seasonal influenza by Poisson seasonal regression

1) Expected morbidities of seasonal influenza

The Poisson seasonal regression model was fitted to seasonal influenza morbidities data available for 1994-2008. Add the represent of the seasonal; sin $(2\pi t/12)$ and cos$(2\pi t/12)$ for baseline in Poisson seasonal regression modelin equation {1}.

$$\hat{Y}(t) = \exp\{a_0 + a_1 + a_2 t^2 + a_3 \cdot \sin(2\pi t/12) + a_4 \cdot \cos(2\pi t/12)\} \text{----} \{1\}$$

where t denotes the month, $\hat{Y}(t)$ is the estimated monthly morbidities (incidence per 100,000 population),a_0, a_1, and a_2 stand for the intercept in the model, linear time, and squared time trends, respectively, $\sin(2\pi t/12)$ and $\cos(2\pi t/12)$ represent the season

2) Excess morbidities of seasonal influenza

Estimates of excess monthly seasonal influenza morbidities were calculated as the difference between observed and predicted baseline morbidities during epidemic period [22].

3.5 Ethical Consideration

This study have been reviewed and approved by the ethical committee for Human Research, Faculty of Public Health, Mahidol University (Appendix A). All data were obtained after accepting the authority permission from all relevant organization.

CHAPTER IV
RESULTS

The results were divided into 3 parts:

4.1 Expected and excess morbidities of seasonal influenza 1994-2008 by five-month moving average

4.2 Expected and excess morbidities of seasonal influenza 1994-2008 by Poisson seasonal regression model

4.3 Poisson seasonal regression model

4.1 Expected and Excess Morbidities of Seasonal Influenza 1994-2008 by Five-month Moving Average

Using five-month moving average by cut out the epidemic seasonal influenza, (from April to July of each year) to calculate the expected seasonal influenza. The average of expected seasonal influenzaper 100,000populations of the South of Thailand is highest expected morbidities of seasonal influenza (21.12 per 100,000 populations in 1995 period). The expected values have a high during 1994-2002 and slowly decrease after 2003 onward in overall and every region. Overall the highest average expected in 1997 was 7.25 per 100,000 populations. The mean of predicted value of South region are about 3 times of Central, North and North-East. The Central, North and North-East predicted value were 5.97, 5.99 and 5.63 per 100,000 populations in 1995, 1994 and 1997, respectively. See theaverage of expectedof seasonal influenza for overall and the each region of Thailand during 1994-2008 by five-month moving average method at the table 4.1

Divided 2 sides of the South of Thailand, the South-West expected value were more than the South-East and show graph of the excess morbidities seasonal influenza during 1994-2008 by 5-month moving average method. The average predicted value of South-West occurred about two times of the South-East during

1994-2003 and then after 2004 have an average expected of South-West decrease as same as South- East. Both sides of South, the highest average expected value of the South-East and the South-West in the same 1995 period, were 16.74 and 36.49 per 100,000 populations, respectively.

Table 4.1 The average of expected seasonal influenza of overall and the regions of Thailand 1994-2008 by 5-month moving average method

Year	Mean of expected of seasonal influenza (per 100,000 population)						
	Thailand	**Central**	**North**	**North-East**	**South**	**South-East**	**South-West**
1994-1995	6.63	5.87	5.99	5.13	13.59	9.80	26.93
1995-1996	7.52	5.97	5.61	5.02	21.12	16.74	36.49
1996-1997	5.77	4.46	4.50	4.72	13.95	11.48	22.57
1997-1998	7.25	5.99	5.44	5.63	17.46	14.69	27.12
1998-1999	6.32	5.27	4.37	4.66	16.31	12.90	28.14
1999-2000	6.55	5.80	3.46	5.23	16.48	13.62	26.35
2000-2001	5.24	4.29	2.79	3.84	14.89	11.88	25.20
2001-2002	5.25	4.06	3.61	3.80	14.32	11.24	24.79
2002-2003	4.48	3.40	3.62	3.33	11.34	8.94	19.35
2003-2004	3.74	2.95	2.87	2.63	9.76	8.42	14.27

Table 4.1 The average of expected seasonal influenza of overall and the regions of Thailand 1994-2008 by 5-month moving average method (cont.)

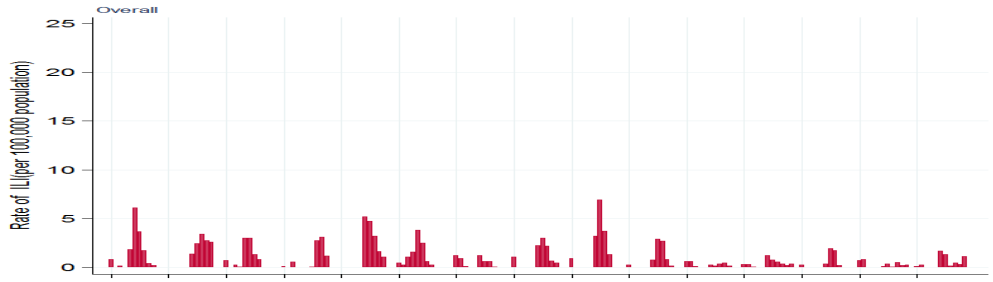
Year	Mean of expected of seasonal influenza (per 100,000 population)						
	Thailand	**Central**	**North**	**North-East**	**South**	**South-East**	**South-West**
2004-2005	2.84	2.82	2.40	1.77	6.22	5.68	8.00
2005-2006	2.64	3.07	2.05	1.44	5.42	4.99	6.84
2006-2007	2.26	2.77	1.68	1.16	4.56	4.24	5.61
2007-2008	2.39	3.36	1.58	1.29	3.87	3.36	5.53
2008-2009	2.43	3.57	1.80	1.13	3.71	3.02	5.81

Form figure 4.1 (a)-(g) presented the excess seasonal influenza by 5-month moving average method presented overall Thailand (a), Central (b), North (c), North-East (d), South (e), South-East (f) and South-West (g) during 1994-2008. The excess morbidities of seasonal influenza of overall Thailand during 1994-2008 presented a form of surplustorise and fall each year. The pattern of excess seasonal influenza morbidities during 1994-2008 in four regions had highest peak during June to July (rainy season). The level of excess morbidities of seasonal influenza the Central was the same as the North. The North-East has a lowest level of excess morbidities of seasonal influenza when compare the Central, North, and South regions. The level of excess morbidities of seasonal influenza in the Southhas about 3 times higher than the North-East in year 1996, 1999, 2007, and 2008.

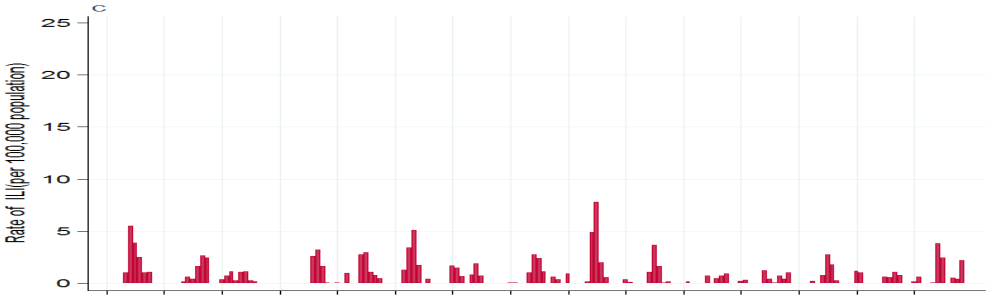
Overall the excess of seasonal influenza morbidities surplus highest in July 2002, rate of seasonal influenza was 6.95 cases per 100,000 populations, inferior to the June 1994 was 6.12 cases per 100,000 populations and 1998 was 5.19 cases per 100,000 populations, respectively (a). In the Central region pattern of the excess of

seasonal influenza was similar to overall Thailand. The excess peak in 1994 and 1999 occurred 5.49and 5.10cases per 100,000 populations, respectively (b). Excess morbidities of seasonal influenza in the North peak in June 1994 was 12.49 cases per 100, 000 populations, minor in July 2002 was5.73 cases per 100,000 populations (c). In North-East, the excess of seasonal influenza each year were similar to Central and North but the rate of excess less than Central and North. The excess morbidity of seasonal influenza was highest in July 2002 (3.18 per 100,000 populations) (d).The South region found the excess morbidities of seasonal influenza occurred almost every year in June 1998 were 24.66 cases per 100,000 populations (e). When separated into the South two sides of the South-East and South-West showed that the patterns were similar. The highest excess in1998 as well in July and June were 15.65 and 41.48 cases per 100,000 populations, respectively (f and g).

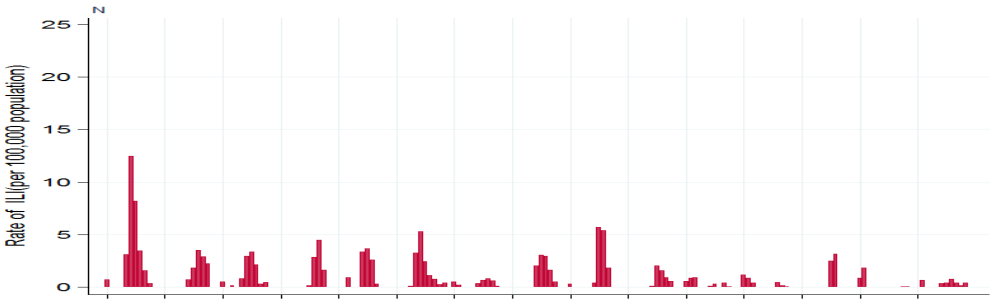
(a)


Overall
Rate of ILI(per 100,000 population)
0
5
10
15
20
25

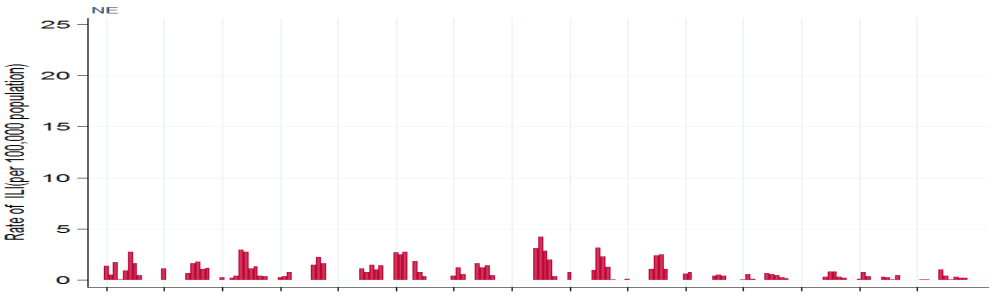
(b)


C
Rate of ILI(per 100,000 population)
0
5
10
15
20
25

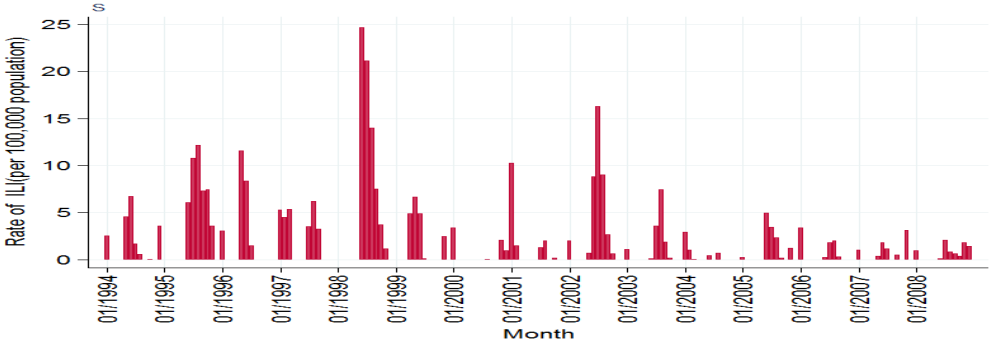
(c)


N
Rate of ILI(per 100,000 population)
0
5
10
15
20
25

(d)


NE
Rate of ILI(per 100,000 population)
0
5
10
15
20
25

(e)


S
Rate of ILI(per 100,000 population)
0
5
10
15
20
25
01/1994
01/1995
01/1996
01/1997
01/1998
01/1999
01/2000
01/2001
01/2002
01/2003
01/2004
01/2005
01/2006
01/2007
01/2008
Month

(f)

(g)

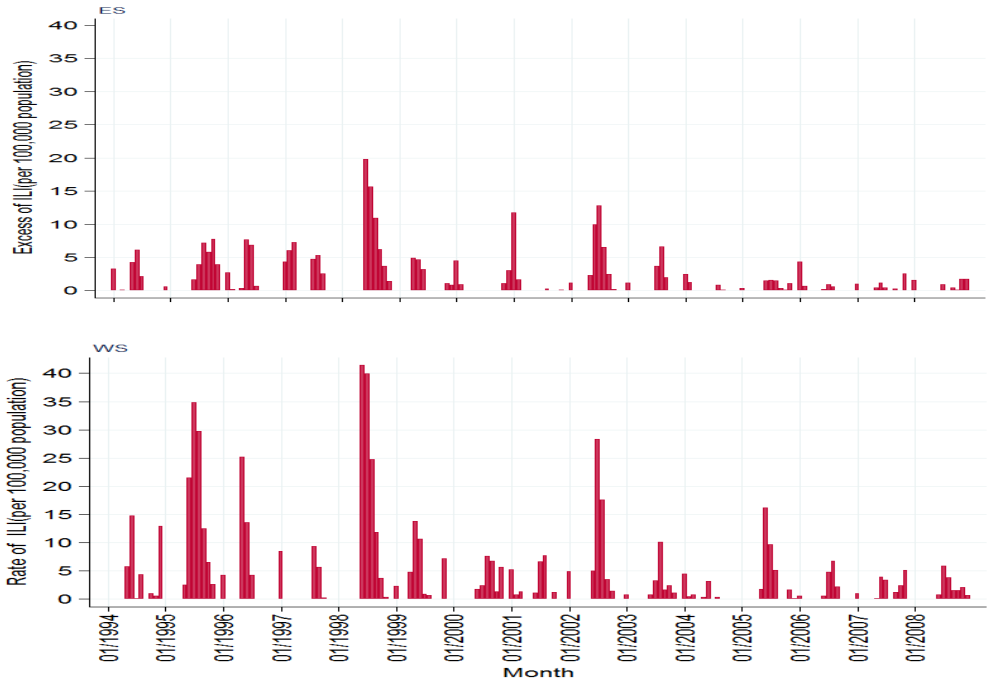


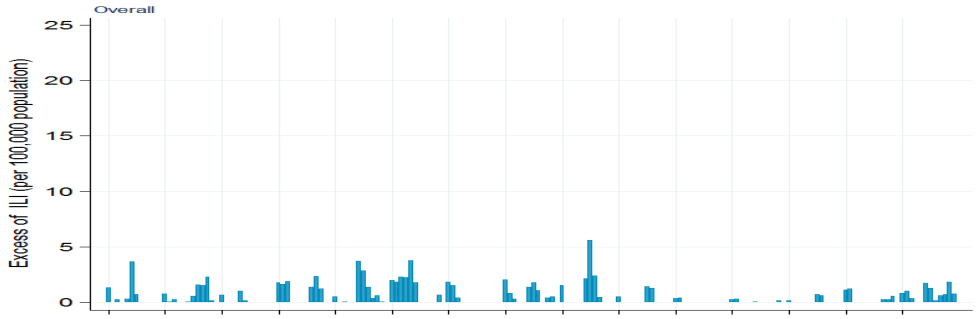
Figure 4.1 Excess seasonal morbidities influenza as baseline 5-month moving during 1994-2008 (red bar). (a- Overall, b- Central, c- North, d- North-East, e- South, f- South-East and g- South-West)

4.2 Expected and Excess Morbidities of Seasonal Influenza 1994-2008 by Poisson Seasonal Regression Model

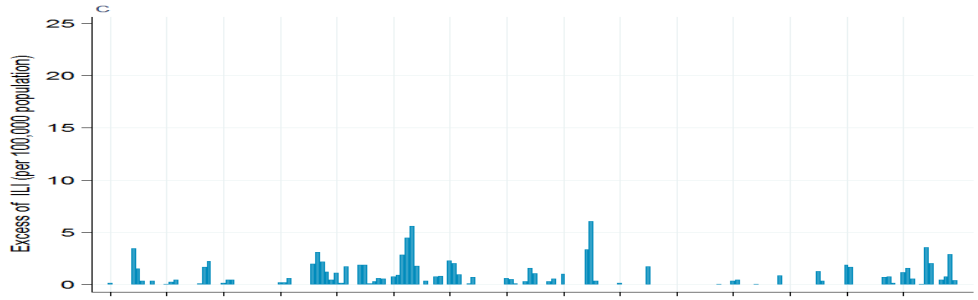
Figure 4.2 (h)-(n) presented the observed of seasonal influenza and a baseline of Poisson seasonal regression method presented overall Thailand (h), Central (i), North (j), North-East (k), South (l) South-East (m) and South-West (n) during 1994-2008. The excess morbidities of seasonal influenza of overall Thailand during 1994-2008 presented the patient had a rise and fall pattern every year, especially were highest during rainy season. Overall the patient surplus highest in July 2002, rate of excess was 5.60 cases per 100,000 populations (h). In the Central region pattern of the excess of seasonal influenza was similar to overall Thailand, the excess peak in 2002 occurred 6.09 cases per 100,000 populations (i). Excess of seasonal influenza the North peak in June 1994 was 9.51 cases per 100,000 populations, minor in July 2002 was 5.08 cases per 100,000 populations (j). In the North-East, the excess morbidity of

seasonal influenza was highest in July 2001 (3.35 per 100,000 populations). The excess of seasonal influenza each yearis less than other region compared to the four regions (k). For the South region the excess morbidities of seasonal influenza occurred almost every year, peak in June1998 was 21.41cases per 100,000 populations (l). When separated into the Southside of the South-East and South-West showed that the patterns were similar excess of South found that the highest rate of excess 1998 as well in June were 17.41 and 35.13 cases per 100,000 populations, respectively (m and n).

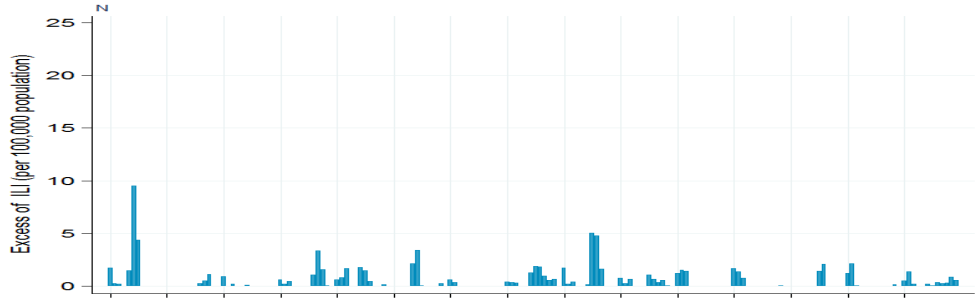
(h)


Overall
Excess of ILI (per 100,000 population)
25
20
15
10
5
0

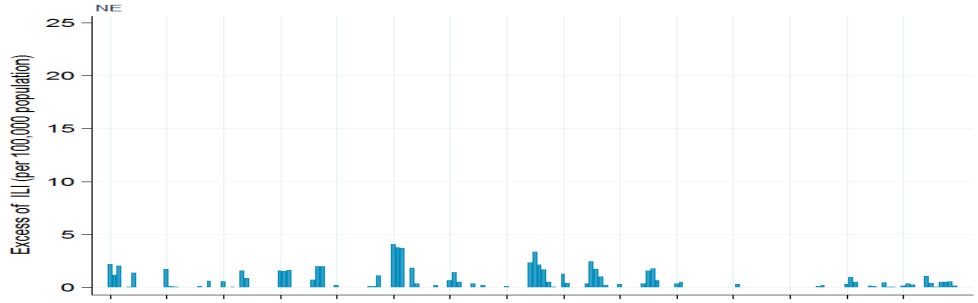
(i)


C
Excess of ILI (per 100,000 population)
25
20
15
10
5
0

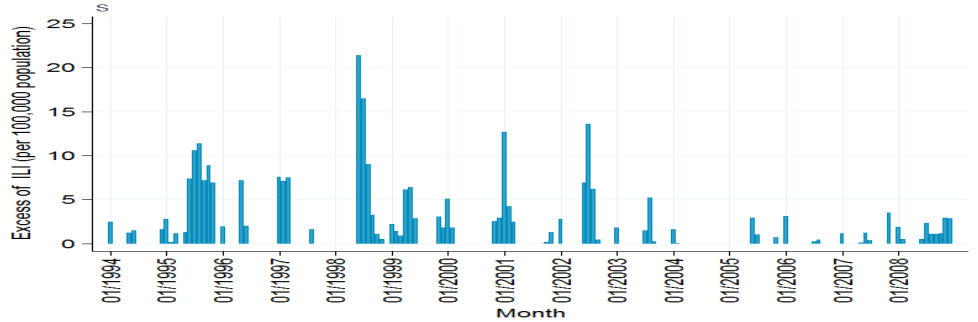
(j)


N
Excess of ILI (per 100,000 population)
25
20
15
10
5
0

(k)


NE
Excess of ILI (per 100,000 population)
25
20
15
10
5
0

(l)


S
Excess of ILI (per 100,000 population)
25
20
15
10
5
0
01/1994
01/1995
01/1996
01/1997
01/1998
01/1999
01/2000
01/2001
01/2002
01/2003
01/2004
01/2005
01/2006
01/2007
01/2008
Month

(m)

(n)

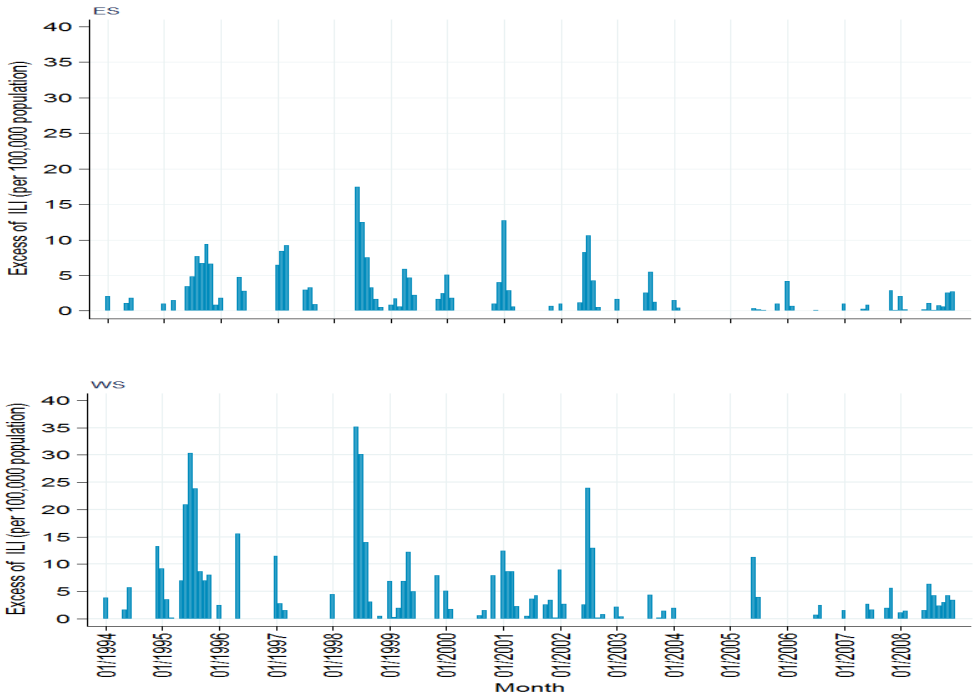


Figure 4.2 Excess seasonal morbidities influenza as baseline Poisson seasonal regression method during 1994-2008 (blue bar). (h-Overall, i-Central, j-North, k-North-East, l-South, m-South-East and n-South-West).

Table 4.2 Compare the total of excess seasonal influenza morbidities 1994-2008 during baseline using 5-month moving average method and Poisson seasonal regression method

	Total of excess seasonal influenza morbidities 1994-2008					
	5-month moving average			**Poisson seasonal regression**		
	Total	**Standard error**	**95% CI**	**Total**	**Standard error**	**95% CI**
Thailand	155.73	14.51	(126.95,184.50)	93.96	9.11	(75.83-112.09)
Central	125.16	13.37	(98.60,151.71)	95.66	11.04	(73.70-117.62)
North	137.03	18.08	(101.08,172.99)	89.55	12.56	(64.54-114.56)
North-East	99.19	8.85	(81.62,116.77)	72.27	8.35	(55.65-88.89)
South	328.37	42.29	(244.29,412.45)	278.61	278.61	(208.24-348.97)
South-East	270.56	33.37	(203.63,337.48)	239.92	239.92	(180.03-299.80)
South-West	601.92	83.82	(435.42,768.43)	491.29	491.29	(362.61-619.96)

Within period 15 years (during 1994-2008), the excess morbidities seasonal influenza overall and four regions, the South has a highest whole baseline five-month moving average and Poisson seasonal regression. Using a Poisson seasonal regression baseline the total excess morbidities due to seasonal influenza was less than using five-month moving average baseline. Comparing between two regions in the South, the excess seasonal influenza morbidities in the South-West was higher than the South-East.

4.3 Poisson Seasonal Regression Model

This section would explain the result of the equations from Poisson seasonal regression models:

$$Y(t) = \exp\{a_0 + a_1 t + a_2 t^2 + a_3 \sin(2\pi t/12) + a_4 \cos(2\pi t/12)$$

The coefficient of variables in equation as well as the value likelihood ratio test presented in table 4.2

Table 4.3 Summarize the morbidities based Poisson seasonal regression model 1994-2008

$\hat{Y}$ (t)	Coefficient of variables	Log-likelihood	p-value	Pseudo R^2	AIC	Model
rili	$\exp\{-4.17 + 0.03t - t^2$ $-0.06\sin(2\pi t/12)$ $-0.23\cos(2\pi t/12)\}$	-332.86	<0.001	0.193	675.723	T1

Model T1 is a baseline model that captures only the seasonal trend by using the Poisson seasonal regression methodduring 1994-2008. Log-likelihood was -332.86, p-value < 0.001 were the significant statistical.

CHAPTER V
DISCUSSION

5.1 The Estimation of Excess Morbidities of Seasonal Influenza

This study estimated the excess morbidities of influenza in Thailand for four regions and the whole country. The baseline morbidity of influenza was calculated using two methods: moving average model and Poisson seasonal regression model. The moving average method estimated baseline followed method published by Thomas A. Reichert et.al [26] cutting out the epidemic seasonal influenza from April to April of each year in Thailand. Using moving average model, it was found that the excess morbidities in the South of Thailand were higher than in other regions. The rate in the South region was approximately 3 times higher than the North-East region. Each year, the levels of excess morbidities of seasonal influenza were different. In the South part, the excess peak was 24.66 cases per 100,000 populations in June 1998. The patterns of excess seasonal influenza morbidities during 1994-2008 were varied among four regions. The overall Thailand found that the excess morbidities influenza highest was 6.95 per 100,000 populations in July 2002. While C.K.Li et.al. [3] found that the bi-annual peaks of influenza in Hong Kong and the excess rate of hospitalizations attributable to influenza were estimated to be 62.10 and 38.29 per 100,000 populations in 1999 and 2000 respectively.

In followed work Poisson seasonal regression model was published by Chung-Min Liao et. al. [22]. This work the pattern of excess morbidities of seasonal influenza among four regions during 1994-2008 had a rise and fall, with the highest peak in June to July (rainy season). However in the study of Chit Ming Wong et.al. [12] in Hong Kong during 1996-2000, the estimated hospitalization of influenza was 29.3 per 100,000 populations. When comparing with this study, the highest rate of excess morbidities of seasonal influenza was 5.60 cases per 100,000 populations during 1994-2008 in Thailand.

A geographical variation resulted in the disease burden of influenza especially in sub-tropical and tropic cities. Different locations in each region also resulted in excess morbidities due to different climate landscapes in the country. It was found in this study that the different seasons in the north and in the south region affected in the differences of excess morbidities of seasonal influenza. Moreover the different climates resulted in a survival of influenza viruses spread in each area in a different way [30]. In Taiwan, the excess morbidities in three regions varied on a weekly basis found that the northern region (the higher latitude region) had the highest excess morbidities per 100,000 populations, while subordinate central region and southern region. In details, the capital Taipei located in the north had the highest peak of excess morbidity, while Taichung in the central region and Kaohsiung in the south showed less disease burden than in Taipei [62].

5.2 Data Report of Surveillance Data of Seasonal Influenza

In this study, the data of seasonal influenza was used in monthly basis from R506 surveillance. The results showed that the excess morbidities seasonal influenza was increased during 1994-2002 and decreased in 2003 onwards. More importantly, it was beneficial that to the management of avian influenza outbreaks in 2004 resulted in decreasing the seasonal influenza. As a consequence, the National Institute of Health established surveillance sites to monitor frequency of influenza, identifying new strains and describing seasonality. Due to the surveillance system establishment, the preventive and control policy resulted in better management of the disease. Additionally, Malinee et al. detected influenza viruses on monthly basis throughout the year during 2004-2010 in Thailand, especially in the southern part of Thailand. The better data collection system can be very useful as its can be applied upon request in order to bring the benefits for the country. Although the study of Malinee et al. did not explain the difference in seasonality between the north and the south of Thailand, there were many factors such as climates, viral re-introduction and tourist differences contributing to viral persistence [30].

5.3 Accessibility and Availability of a Long-term Data Set

C.K.Li et.al showed uncertainty of applicable local data on health burden of influenza [3] likewise, there were restrictions of the data in Thailand in accessing seasonal influenza from the annual epidemiological surveillance report by Bureau of Epidemiology, Ministry of Public Health. This study was in need of additional information such as data on daily and weekly basis; however, the data was not publicly circulated in Thailand. The government plan to obtain efficiently created long-term access to data and the information systems would benefit to Thailand.

5.4 Variation of Excess Morbidities Based on Difference Baselines and Others Factors

There was a limit for baseline the excess of influenza morbidity studies if baseline data inadequate were used to evaluate the burden of attribute to influenza was inadequate. This contributed to limitations in the tropical and sub-tropical regions, including Thailand, in order to find a definite for reasonable baseline. This study selected the baseline using 5-month moving average method by cutting out the epidemic seasonal influenza from July to April of each year during 1994-2008. Five-month period was calculated the expected seasonal influenza. While a considerable number of deaths attributable to influenza in United States occurring in November, it excluded the epidemic month from calculation of the baseline [26]. However, it was not considered that the observed trends resulted in increased influenza mortality risk with age. In this study age was not considered as a factor contributed to influenza morbidity. Secondly the moving averages did not adjust for the increased frequency with A (H3N2) viruses dominated influenza seasons in the 1990s [7]. In Hong Kong, the method of baseline comparison and influenza predominance periods was that the periods being compared may differ because of seasonal and other factors that may contribute to mortality [12].

5.5 Environmental Factors and Virus Circulation Related to Seasonal Influenza

Meteorological factors may contribute to the seasonal influenza at vary influence such as temperature, relative humidity and rainfalls are also critical for survival and transmission of influenza viruses [22]. This study also Radina P. Soebiyanto et.al. [63] used the weekly proportion of laboratory-confirmed influenza positive samples and taking into account meteorological data (rainfalls and humidity) for Thailand (see appendix B). However, the limitation of the climate data and the surveillance influenza viruses in Thailand were not recorded in every station and influenza viruses recorded in 2005 onwards leading to difficulty analyze with the other factors related the seasonal influenza in Thailand.

Information from the Meteorology Department, Thailand [64] are collected data of climates from 106 stations: Central 33 stations (included Bangkok), North 15 stations (8 provinces), North-East 27 stations (16 provinces) and South 31 stations (16 provinces). However, there were only 18 sites that had a complete data during study period 1994-2008. The reason of incomplete data was either did not record completely of each station or the monitoring site was set up after 1994. For this reason most of regions climate data were calculate as average values from at least 5 stations, except the North-East region. For the the monthly number positive of influenza viruses, this part of analysis the test from throat swabs from patients with influenza from 11 sentinel sites during 2005-2008 and viruses were tested from the National Science Department, National Institute of Health (Thai NIH), Ministry of Public Health were used [30].

The limitation in this study due to the limited data of climate data and influenza viruses. The results using both moving average models and Poisson seasonal regression models to estimate the excess morbidity due to seasonal influenza in Thailand by adding climate and viruses data were not significant statistical (p-value < 0.05).

5.6 The Difference of Moving Average Method with the Poisson Seasonal Regression Method

The analysis of excess morbidities of seasonal influenza in Thailand during 1994-2008 using the moving average methods and the Poisson seasonal regression method found that the pattern of excess morbidities from two methods were similarly. The level of excess morbidities of seasonal influenza calculated by Poisson seasonal regression method lower than the moving average method. First, the moving average method used five months moving average as baseline by cutting out the epidemic period of seasonal influenza. Second, the Poisson seasonal regression method was utilized by adding the seasonal sinusoidal (sin and cos), this method included the epidemic period of seasonal influenza. The result of two methods in overall Thailand and four regions (Central, North, North-East, and South) found that the excess morbidities of seasonal influenza were highest during June to July (rainy season).

The resulted of the Poisson seasonal regression method presented lower level of the excess morbidities of seasonal influenza compare to the moving average method. This indicated that the burden of seasonal influenza using the Poisson seasonal regression method will provided the less burden due to influenza than the moving average method. However, assessing the burden of influenza epidemics on morbidity is difficult. Influenza diagnoses are generally not laboratory confirmed, and illness related to influenza are often attributed to pneumonia and other secondary complications that occur well after the influenza virus infection.

5.7 Limitations of This Study

1. The availability of weekly seasonal influenza from the Bureau of Epidemiology, Ministry of Public Health was very limited. Subsequently, in this study had to utilize the available data which was monthly data.

2. The collection of information is not exhaustive of the factors of temperature, relative humidity, and rainfall in various stations of the sentinel site and the number of influenza viruses in Thailand that were not enough. The data did not use to represent each region.

5.8 Strengths of This Study

1. The number of patients in excess seasonal influenza will indicate the impacts of overall seasonal influenza epidemic in Thailand. Therefore the government needs to prepare for medical personnel, vaccinations, and other essential resources in combatting seasonal influenza in Thailand.

2. The excess morbidities of seasonal influenza using two methods found that the peak of excess morbidities of seasonal influenza occurred during rainy season but the level of excess morbidities of seasonal influenza had different. However, the selection of the method for the excess morbidities of seasonal influenza in Thailand would be realized every time to use the practices.

CHAPTER VI
CONCLUSION AND RECOMMENDATION

6.1 Conclusion

The study was carried out using the information obtained from secondary data, the monthly number of seasonal influenza morbidities (J09 to J11). Estimated of excess monthly seasonal influenza morbidities was calculated as the difference between observed and predicted baseline morbidities during epidemic period. The baselines were calculated using two methods: using moving average method and Poisson seasonal regression method.

Overall Thailand, the excess morbidities of seasonal influenza using the moving average method and the Poisson seasonal regression method found that the peak of level of the excess morbidities of seasonal influenza occurred rainy season (June to July). The excess peaked for moving average method and Poisson seasonal regression method in year 2002 were 6.95 and 5.60 cases per 100,000 populations, respectively.

For four regions of Thailand, the moving average method found the South region highest of excess morbidities influenza as same as the Poisson seasonal regression method. Using the moving average method, the excess morbidities influenza in the South, North, and Central region were 24.66, 12.49, and 5.49 per 100,000 populations, respectively. When separated into the South region two sides of the South-East and South-West the patterns of excess morbidities of seasonal influenza were similar and the peak occurred during June to July. Using the Poisson seasonal regression method presented the excess peaked in the South, North, and Central region were 21.41, 9.51, and 6.09 per 100,000 populations, respectively. There was no difference pattern between the South-East and South-West, however the excess morbidities rate in the South-West was higher than the South-East.

6.2 Recommendations and Suggestions

1. For reporting surveillance systems of influenza more information and complete details, will be used in forecasting, policy formulation and evaluation of prevention and control of diseases.

2. The improvements to the current influenza surveillance systems will provide increasingly accurate estimates of the burden of influenza and help the Thailand to better prepare for future.

3. The selection of the best method for the burden diseases of seasonal influenza to use the true impact of seasonal influenza in Thailand.

6.3 Recommendations for Further Study

1. Weekly data collection is highly recommended for analysis of excess seasonal influenza morbidity in Thailand.

2. The length of the available data was limited so it would be an opportunity if the analysis of the influenza excess morbidities covered longer period of time. The factor of weather condition-associated to influenza should be more complete better, to obtain better analysis results.

3. Age specific analysis of the influenza excess morbidity is highly recommended in order to better estimation burden of disease.

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APPENDICES

APPENDIX A
ALL COMMANDS FOR EXCESS MORBIDITIES
SEASONAL INFLUENZA

1. Set time before run model

```
gen t = tm(1994m1)+_n-1
format t %tm
tsset t
```

2. Command for moving average

```
gen tt=t
tsset  t
gen moveave2 = (F1. rili+F2. rili + rili+L2. rili + L1. rili) / 5
gen r_excess = rili-  avemoving
```

3. Command for Poisson regression

```
gen rili =(ili*100000)/ pop
gen t = tm(1994m1)+_n-1
format t %tm
tsset t
gen sin1=sin(2*_pi*t/12)
gen cos1=cos(2*_pi*t/12)
gen tt=t^2
```

4. Command for making Poisson regression and excess

```
poisson rili  t tt sin1 cos1
predict pr_c
gen excess_rili= rili- pr_c
```

5. Command for making the graph

- graph twoway (line avemoving rili t), ytitle("Rate of ILI(per 100,000 population)") xtitle("Month")
- graph twoway (bar r_excess t), ytitle("Rate of ILI(per 100,000 population)")
- graph twoway (line pr_c rili t), ytitle("Rate of ILI(per 100,000 population)") xtitle("Month")

APPENDIX B
EXCESS MORBIDITIES OF SEASONAL INFLUENZA IN EACH REGION OF THAILAND

In the figures B1-B7, the symbol used to describe the picture (a) blue solid line is the observed of rate of seasonal influenza, red dash line is Poisson seasonal regression baseline. In this figure in appendix B, showed that the detail from the observed and the expected number of seasonal influenza of Thailand and each region of Thailand by Poisson seasonal regression method.

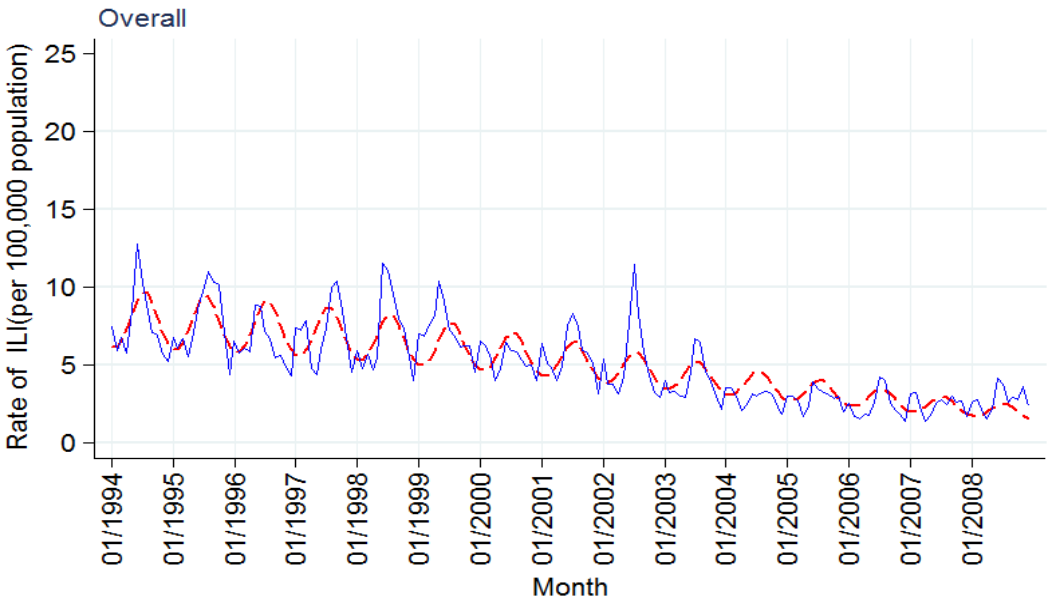

Figure B1 Excess seasonal morbidities influenza as baseline Poisson seasonal regression, Thailand, 1994-2008

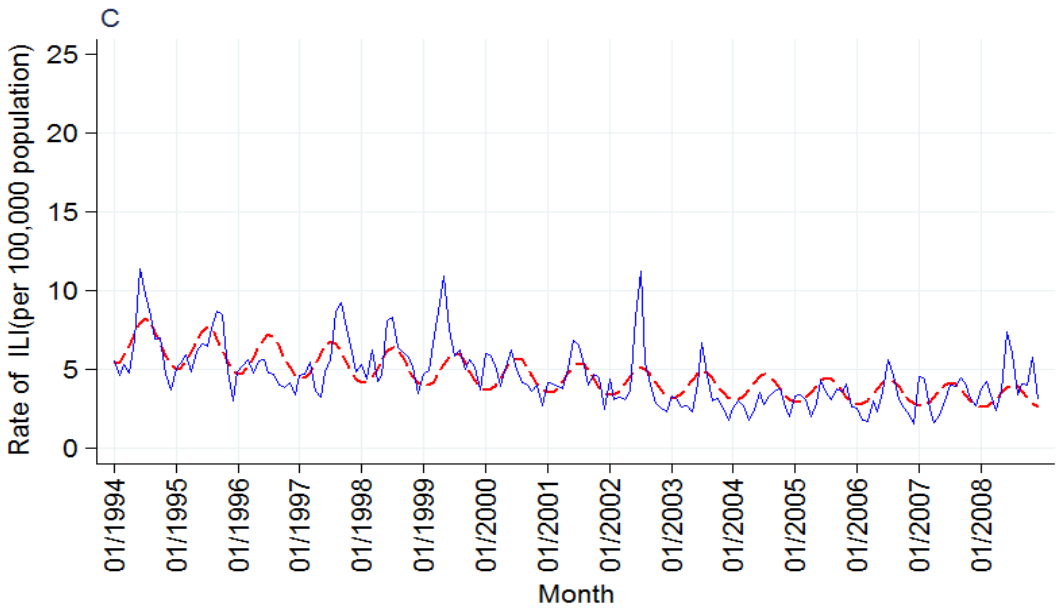

Figure B2 Excess seasonal morbidities influenza as baseline Poisson seasonal regression, Central, 1994-2008

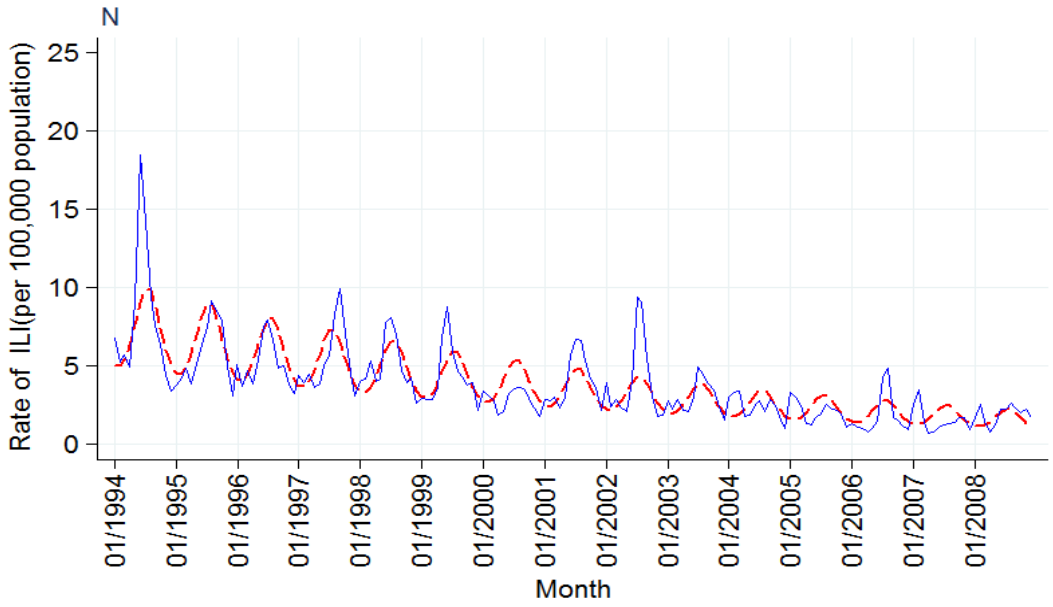

Figure B3 Excess seasonal morbidities influenza as baseline Poisson seasonal regression, North, 1994-2008

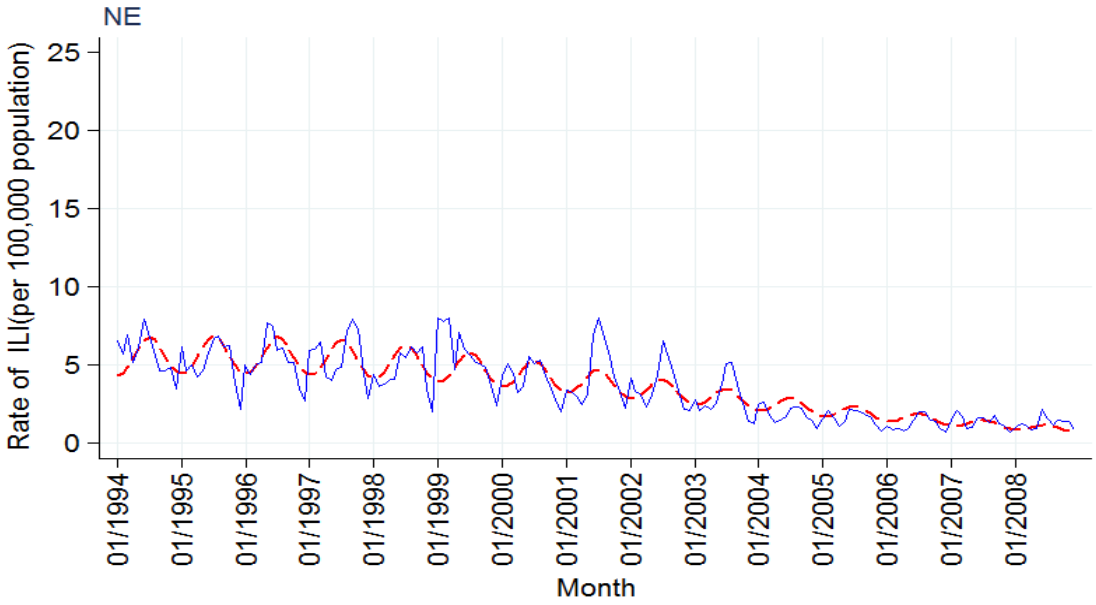

Figure B4 Excess seasonal morbidities influenza as baseline Poisson seasonal regression, North-East 1994-2008

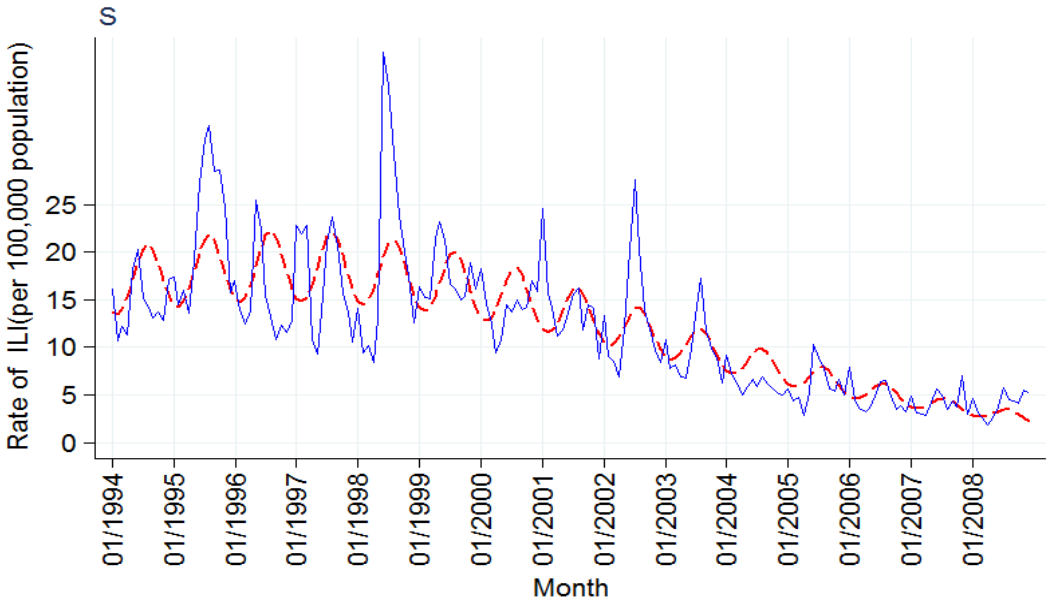

Figure B5 Excess seasonal morbidities influenza as baseline Poisson seasonal regression, South, 1994-2008

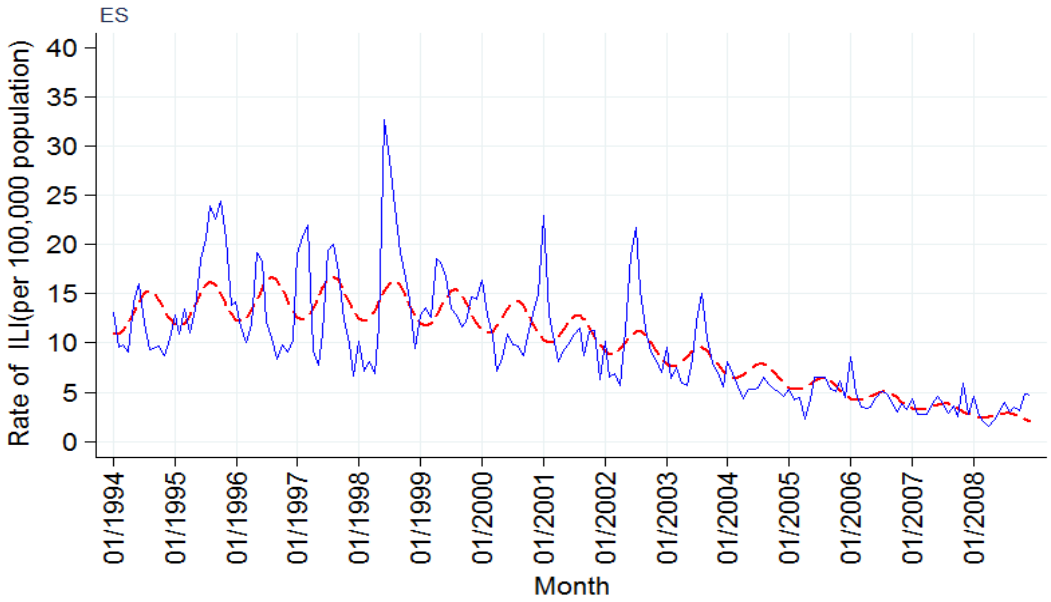

Figure B6 Excess seasonal morbidities influenza as baseline Poisson seasonal regression, South-East, 1994-2008

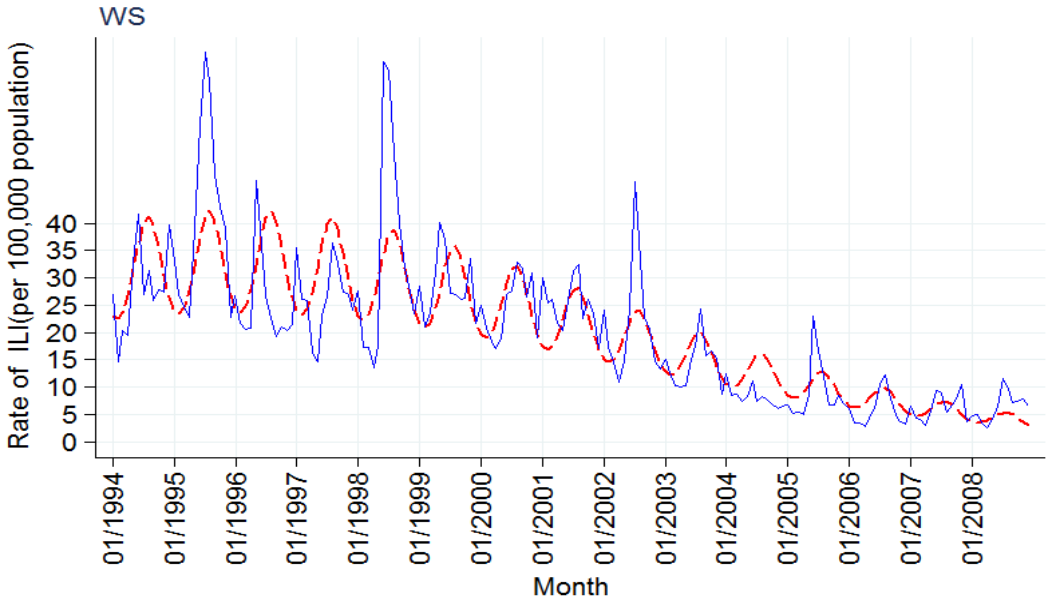

Figure B7 Excess seasonal morbidities influenza as baseline Poisson seasonal regression, South-West, 1994-2008

APPENDIX C
ENVIRONMENTAL FACTORS AND VIRUS CIRCULATION RELATED TO SEASONAL INFLUENZA

1. Literature reviews for environmental factors related to seasonal influenza

Liao CM et.al. applied a Poisson seasonal regression models to evaluate the impact of epidemic influenza on morbidity for 1999-2006, used the environment data (average weekly temperature and monthly relative humidity) into for 3 cities: Taipei city is located in the north, Taichung is located in the central and Kaohsiung is located south. An evidence indicated that temperature had a higher negative correlation (r^2 = 0.23-0.51) with morbidity than relative humidity in three major cities of Taiwan (r^2< 0.07). There was a statistically that the effect of temperature on morbidity was not the same for the three cities but there was no difference in the effect of relative humidity on morbidity in three cities [1]. This study indicates that different non-epidemic periods indeed affect the results obtained from the Poisson seasonal regression model. But this study could not implicate explicitly the relationship of the well-defined non-epidemic periods among the different characteristics of weather, population density, medical resources and the dominant influenza subtypes and could not provide a comparative analysis with other research on annual influenza-associated deaths. However, this study could not implicate explicitly the relationship of the well-defined non-epidemic periods among the different characteristics of weather, population density, medical resources and the dominant influenza subtypes [1].

Radina P. Soebiyanto et.al. used influenza surveillance data collected from 11 departments or provinces in 3 Central America countries. These included 4 departments in Guatemala: San Marcos, Quetzaltenango, Guatemala and Santa Rosa, 5 departments in El Salvador: Santa Ana, La Libertad, Cuscatlán, San Salvador and San Miguel and 2 provinces in Panama: Chiriquí and Panama. This work used logistic regression to model the weekly proportion of laboratory-confirmed influenza positive samples (excluding pandemic year 2009) and meteorological data (rainfalls and

humidity) for Guatemala, EI Savador and Panama during 2008-2013. They founded a positive association between humidity and influenza in EI Savador and Panama but found negative association in Guatemala. This work was not account for the difference in time spent in air-conditioned environments, other social and economic parameters. Those may contribute to biased results and difficulties for generalization and used influenza positive proportion as a proxy of influenza activity, although it was not a direct measure of influenza morbidity or mortality [2].

2. Data report of climate and surveillance influenza viruses

2.1 Climate data in Thailand

Table C1 Sites for climate data in Thailand [3]

Region	Sites
Central	- Bangkok (Bangkok station, Klong Toey station, Bang Na station and Donmuang station - Chanthaburi province (Chanthaburi station and Phriu agromet station) - Trat province (Khlong Yai station)
North	- Tak province (Tak station, Mae Sot station, Bhumibol Dam station, Doi Muser agromet station and Umphang station)
North-East	- Nong Khai province (Nong Khai station)
South	- Suratthani province (Suratthani station, Phunphin airport station, Koh Samui station, Suratthani agromet station and Phra Sang station)

2.2 Sentinel sites for influenza viruses in Thailand

Table C2 Sentinel sites for influenza viruses in Thailand [4]

Region	Sentinel sites
Central	- Bangkok (Prachaniwet Health Center) - Chanthaburi province (Prapokklao hospital) - Trat province (Chang-Island hospital)
North	- Tak province (Mae Sot hospital Chiang Rai province (Chiang San hospital and Mae-jun hospital)
North-East	- Nong Khai province (Nong Khai hospital).
South	- Suratthani province (Koh Samui hospital and Bangkok Samui hospita l) - Songkhla province (Hatyai hospital)

3. Descriptive statistic

Environmental variables used in the research are monthly average temperature, relative humidity and rainfalls data, acquired a separate monthly data collected by location. The monthly data of each station (most provinces have one station, the province has more than one station, it will mean in the first) and bring together the stations of each sector and then calculated the mean of the temperature, relative humidity and rainfalls of each stations in Thailand.

Influenza viruses data from the specimen and case sampling from 9 hospitals and 1 health care in Bangkok as the sentinel site in Thailand by National Science Institute, Ministry of Public Health. Then the proportions of positive influenza viruses A, A (H1N1), A (H3N2) and B during 2005-2008 were calculated.

4. Influenza-associated morbidity effects of meteorological factors and virus circulation

Regression model approach can use for estimating morbidity and mortality attributable to influenza. This was implemented by Thompson et al [5], by fit a regression model to death time series that combined a sinusoidal function with weekly

virologic surveillance data. The work by Thompson et al. represents an advance over baseline methods, because it quantifies the relation between deaths attributed to influenza infection and virologic surveillance data.

This work considered the impact of influenza on morbidities in Thailand, taking into account seasonal patterns and climate for influenza associated with the co-circulation of influenza viruses.

The influenza virus model in equation {2} was used as a baseline model. This model is a Poisson seasonal regression model that was used to estimate the morbidities attributable to influenza and climate conditions:

$$\hat{Y}(t) = \exp\{a_0 + a_1 + a_2 t^2 + a_3 \cdot \sin(2\pi t/12) + a_4 \cdot \cos(2\pi t/12) + \underbrace{a_5 \cdot tem_t + a_6 \cdot rh_t + a_7 \cdot rain_t}_{\text{Climate condition}} \quad \text{--}\{2\}$$

Where tem_t is the average monthly temperature, rh_t is the average monthly relative humidity and $rain_t$ is average monthly rainfall. To examine further the relationships between proportion of morbidities and the respiratory viruses, i.e., influenza A (H1N1) virus, influenza A (H3N2) virus and influenza B, the model equation {2} was extended to estimate influenza-associated morbidities attributable to influenza virus circulation associated with seasonality and climate factors. The detail of model is in equation {3} which adding the laboratory surveillance data for 2005-2008 influenza virus circulation.

$$\hat{Y}(t) = \exp\{a_0 + a_1 + a_2 t^2 + a_3 \cdot \sin(2\pi t/12) + a_4 \cdot \cos(2\pi t/12) + a_5 \cdot tem_t + a_6 \cdot rh_t + \underbrace{a_7[A(H1N1)]_t + a_8[A(H3N2)_t] + a_9[B_t]}_{\text{Laboratory surveillance data}}\} \text{----------}\{3\}$$

Where a_7 through a_9 represent coefficients associated with the monthly proportion of specimens testing positive.

A full model with all variables was built, and then forward one by one step, those variables that did not significantly contribute to the model were removed to derive a final model containing only significant variables. To explore the climate factors including virus pattern associated with the influenza-associated morbidities, the correlations between influenza virus circulation, temperature, and relative humidity were examined.

The results would explain the result of the equations from Poisson seasonal regression models:

Table C3 Summary of Poisson seasonal regression models

Poisson seasonal regression models	Model
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3\sin(2\pi t/12) + a_4\cos(2\pi t/12)$	T1
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3\sin(2\pi t/12) + a_4\cos(2\pi t/12) + a_5tem_t$	T2
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3\sin(2\pi t/12) + a_4\cos(2\pi t/12) + a_6rh_t$	T3
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3\sin(2\pi t/12) + a_4\cos(2\pi t/12) + a_7rain_t$	T4
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3\sin(2\pi t/12) + a_4\cos(2\pi t/12) + a_5tem_t + a_6rh_t$	T5
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3\sin(2\pi t/12) + a_4\cos(2\pi t/12) + a_5tem_t + a_7rain_t$	T6
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3\sin(2\pi t/12) + a_4\cos(2\pi t/12) + a_6rh + a_7rain_t$	T7
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3\sin(2\pi t/12) + a_4\cos(2\pi t/12) + a_5tem_t + a_6rh_t + a_8[A_t] + A_9[B_t]$	T8
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3\sin(2\pi t/12) + a_4\cos(2\pi t/12) + a_5tem_t + a_6rh_t + a_{10}[H1N1_t] + A_{11}[H3N2_t] + A_9[B_t]$	T9

Note: tem= temperature, rh= relative humidity, rain= rainfalls, a = influenza A virus, b= influenza B virus, H1N1= influenza A (H1N1) subtypes virus, H3N2 = influenza A (H3N2) subtypes virus

Model T1 is a baseline model that capture only the seasonal trend (by using the Poisson seasonal regression model) during 1994-2008, compare with the model T2, T3 and T4 (add the temperature, relative humidity and rainfalls, respectively), the result show significant of the temperature, relative humidity and rainfalls only (p-value <0.001). Compare T2, T3 and T4 found that log-likelihood of

model T2 is the highest, AIC of model T2 is the lowest. When T1 compare with T5, T6 and T7 add two climate conditions (temperature and relative humidity, temperature and rainfalls and relative humidity and rainfalls, respectively), the result show a significant of two variables in each model (p-value <0.001). Compare T5, T6 and T7 found that log-likelihood of model T5 is the highest; AIC of model T6 is the lowest. Adding the three weather condition variables (temperature, relative humidity and rainfalls) into the models, the colinearity between all pair among those variables were checked using r^2. The r^2 between relative humidity-rainfalls was 0.92, temperature-rainfalls was 0.45, and temperature-relative humidity was0.26. The colinearity between relative humidity-rainfalls was very high (0.92). The rainfalls level data have high variation. Therefore the rainfalls variable was excluded from the model analysis.

Model T1** is a baseline model that capture only the seasonal trend (by using the Poisson seasonal regression) during 2005-2008, to investigate the relationship between monthly morbidities and each virus (sub) types (Model T8, T9). The result show that the seasonal influenza A(H1N1) and A(H3N2) viruses had no significant (all p-value > 0.05, see Table 4.9) effects on monthly morbidities from 2005-2008 in the Thailand.

Form Poisson seasonal regression total model (T1 to T9), T1 and T1** model were the baseline model during 1994-2008 and 2005-2008, respectively. T2 to T4 are the models that added one weather condition variables (temperature, relative humidity, and rainfalls). T5 to T7 are the models that added two weather condition variables. Once considered the reliable for each weather condition, the rainfalls have high variation (i.e. some stations had zero rainfall level, some stations had highly rainfall level). Moreover, adding three weather conditions variables into the models, the colinearity between relative humidity and rainfalls were founded (r^2= 0.92). Therefore, the rainfalls variable was excluded from the model analysis.

The criteria selection of best model was the maximum log-likelihood of each model, as well as the lowest AIC (AIC= -2 x ln (likelihood) +2 x k). Model T2 to T7 were all significant. However, model T5 to T7 had more variable than model T2 to T4 but the log-likelihood were not significant improve the model. Meanwhile, model T8 and T9 were added both viruses influenza variables (A(H1N1), A(H3N2) and B) and two weather condition variables (temperature and relative humidity). Model T8

and T9 (included viruses influenza) were not significant statistical. The best fit Poisson seasonal regression model that used to estimate the morbidities attributable to influenza could be the model as followed:

$$\hat{Y}(t) = \exp\{a_0+a_1+a_2t^2+ a_3\cdot \sin(2\pi t/12)+a_4\cdot\cos(2\pi t/12)+a_5\cdot tem_t \text{--}\textbf{Model T2}$$

$$\hat{Y}(t) = \exp\{a_0+a_1+a_2t^2+ a_3\cdot \sin(2\pi t/12)+a_4\cdot\cos(2\pi t/12) + a_6\cdot rh_t \text{---}\textbf{Model T3}$$

Table C4 Show the coefficient for the best fit model T2

Variables	Coefficient (β)	p-value	95% CI
t	1.04	0.02	1.01-1.07
t^2	0.99	0.004	0.99-0.99
sin	1.01	0.93	0.89-1.13
cos	0.73	0.00	0.64-0.84
temperature	0.95	0.11	0.88-1.01

Table C5 Show the coefficient for the best fit model T3

Variables	Coefficient (β)	p-value	95% CI
t	1.03	0.03	1.00-1.06
t^2	0.99	0.006	0.99-0.99
sin	1.00	0.95	0.87-1.14
cos	0.85	0.07	0.72-1.01
Relative humidity	1.01	0.34	0.99-1.04

The coefficient for the temperature in model T2 (Table 4.10) was 0.95 (95% CI, 0.88, 1.01) and for the relative humidity in model T3 (Table 4.11) was 1.01 (95% CI, 0.99, 1.04). Those coefficients of temperature and relative humidity from models T2 and T3 had not statistical significant (p-value > 0.01). Therefore, the model added the weather condition variable was not present any significant affected the seasonal influenza morbidities.

APPENDIX D

คณะกรรมการจริยธรรมการวิจัยในมนุษย์
คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล
มอบประกาศนียบัตรฉบับนี้เพื่อแสดงว่า

นางสาวธารทิพย์ สังข์สิงห์

เข้ารับการอบรม เรื่อง จริยธรรมการวิจัยในมนุษย์
วันที่ ๒๔ มีนาคม ๒๕๕๔
ณ ห้องประชุม อาคารสาธารณสุขตามรอยพระบาทพระบิดา

(รองศาสตราจารย์สุนีย์ ละกำปั่น)
ประธานคณะกรรมการจริยธรรมการวิจัยในมนุษย์

(รองศาสตราจารย์ นายแพทย์พิทยา จารุพูนผล)
คณบดีคณะสาธารณสุขศาสตร์

คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

ประกาศนียบัตรฉบับนี้มอบไว้เพื่อแสดงว่า

ธารทิพย์ สังข์สิงห์

ได้นำเสนอผลงานวิจัยแบบโปสเตอร์เรื่อง

การป่วยส่วนเกินเนื่องจากไข้หวัดใหญ่ตามฤดูกาลในประเทศไทย ระหว่างปี พ.ศ. 2538-2550

ในการประชุมวิชาการสาธารณสุขแห่งชาติ ครั้งที่ ๑๔

เรื่อง "มุมมองเชิงนิเวศน์ในงานสาธารณสุขเพื่อการพัฒนาอย่างยั่งยืน:

การเปลี่ยนแปลง ความเสี่ยง และความท้าทาย"

ระหว่างวันที่ ๑๕ – ๑๖ สิงหาคม ๒๕๕๖ ณ โรงแรมมิราเคิล แกรนด์ คอนเวนชั่น กรุงเทพมหานคร

(รองศาสตราจารย์พักตร์พิมล มหรรณพ)
ประธานคณะกรรมการพิจารณาผลงานวิชาการ
และจัดทำ Proceedings

(รองศาสตราจารย์ นายแพทย์พิทยา จารุพูนผล)
คณบดี
คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

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BIOGRAPHY

NAME	Miss Thanthip Sungsing
DATE OF BIRTH	25 May 1985
PLACE OF BIRTH	Nakhon Sri Thammarat, Thailand
INSTITUTIONS ATTENDED	Rangsit University, 2004-2007 Bachelor of Nursing Science
HOME ADDRESS	55/331 Moo 3 Bang Pud sub-district, Pakkret District, Nonthaburi, 11120 Tel. 094-478-2612 E-mail: rainbow_fhon3@hotmail.com
EMPLOYMENT ADDRESS	Thai Red Cross AIDS Research Center **Position:** Study nurse E-mail: thanthip@trcarc.org
PUBLICATION / PRESENTATION	3rd Thailand Human Influenza Research Meeting: Oral presentation The 6th International Public Health Conference: Poster presentation