THE ASSOCIATION BETWEEN DISTRIBUTION OF INFLUENZA-LIKE ILLNESS AND CLIMATE IN EACH ZONE OF THAILAND

Suphakit Wechphanich*, Soontorn Supapong, Thanapoom Rattananupong

Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, 10330, Thailand

ABSTRACT:

Background: Influenza is a respiratory infection that commonly occurs in humans. According to the World Health Organization, the estimation of influenza-related morbidity rate was 5 - 10% in adults and 20 - 30% in children worldwide, causing 3 - 5 million people to have serious influenza-related illnesses. Climatic factors might affect both the survival and transition of influenza viruses. This study aimed to find the association between distribution of Influenza-like Illness (ILI) and climate in each zone of Thailand.

Methods: Secondary data of ILI cases and climatic factors were extracted from infectious disease surveillance report of the Bureau of Epidemiology, Thai Ministry of Public Health and from meteorological data of the Thai Meteorological Department from January 2011 to December 2015. An ecological study and generalized estimation equation was used to explore the association between Influenza-like Illness and climate in each zone of Thailand.

Results: Weekly ILI rates associated with climate and air temperature was found to have a negative association and played a major role in all zones except for Northeastern and Southwestern zones. Relative humidity was found to have a positive association with the ILI rate in Central, Bangkok, Eastern and Southwestern zones. Rainfall was found to have a positive association with ILI rates in Northern and Southwestern zones but was found to have a negative association in Southeastern zones due to its different climate. The association between rainfall and influenza outbreaks may be indirect, similar to the crowds and public spaces that contribute to increased contact time and influenza transmission.

Conclusion: Using weather information may predict influenza outbreaks and be beneficial to prevention and early preparedness for climate change.

Keywords: Influenza-like illness; Climate; Thailand; Ecological study

DOI: *Received: December 2016; Accepted: March 2017*

INTRODUCTION

Influenza is one of the most common seasonal diseases in humans caused by influenza viruses and transmitted by inhalation or contact. According to the World Health Organization, the estimated morbidity rate was 5 -10% in adults and 20 – 30% in children worldwide, causing 3 – 5 million people to have serious illnesses and 2.5 - 5 million deaths annually. Moreover, the morbidity rate was increased in vulnerable groups [1]. Between 2009 and 2013, the Bureau of Epidemiology, Department of Disease Control in Thailand reported that estimated numbers of influenza-infected patients were approximately 44,000 - 120,000 and deaths were up to 230, annually [2].

The pattern of influenza outbreaks in the equatorial regions is mostly the cyclical pattern. The period of outbreaks is between September and December. However, the longer period of outbreaks may occur in some high rainfall countries [3]. Factors affecting influenza epidemics are viral virulence, environmental and personal factors [4]. Studies in animals have shown environmental

* *Correspondence to: Suphakit Wechphanich*
E-mail: punch1234@hotmail.com

Cite this article as: Wechphanich S, Supapong S, Rattananupong T. The association between distribution of influenza-like illness and climate in each zone of Thailand. J Health Res. 2017; 31(5): 373-81. DOI:

factors, such as air temperature [5-7], humidity [5, 8-11] and ultraviolet radiation dose [12-14], affect influenza virus survival and the transmission rate in proper conditions and epidemiological studies have found an association between influenza epidemics and climate. In addition, the current global warming influences climate change; for example, researchers in the United States have found that changing weather results in the influenza epidemic [15].

Although the mortality rate of Influenza is low, its high morbidity rate and the burden of this disease affect economy in aspects of sick leave and health care resources [16]. In addition, influenza that infects an individual can spread to other people and increase severity of illness and mortality in vulnerable groups such as children, elderly people, pregnant women, chronic illness patients and immunocompromised patients [1, 17]. Therefore, this study aimed to explore the association between distribution of Influenza-like Illness (ILI) and climate in each zone of Thailand. This study will be useful to prepare and prevent the outbreak of disease which because distribution of ILI may alter due to climate change.

MATERIALS AND METHODS

Data sources

The data of ILI cases was extracted from infectious disease surveillance report of the Bureau of Epidemiology at Department of Disease Control in Thailand from 2011 to 2014 which absence any outbreaks of a new strain of influenza virus [18]. Totally, 359,766 ILI cases were diagnosed based on the clinical criteria including fever, cough, sore throat, headache, and myalgia. Annual population density data were obtained from Department of Provincial Administration.

The meteorological data were obtained from Information Center of Thai Meteorological Department. The geographical zones were classified into six similar climatic zones (Northern, Northeastern, Central, Eastern, Southeastern and Southwestern). There are three seasons in Thailand: the summer season (8^{th} to 25^{th} week), the rainy season (26^{th} to 43^{rd} week), and the winter season (44^{th} to 58^{th} week), except that the Southeastern and Southwestern zones, there is only two seasons: the summer season (8^{th} to 25^{th} week) and the rainy season (26^{th} to 43^{rd} week). The meteorological data were daily data and did not come from a normal distribution, so we transformed daily data into median weekly data.

Methods

This is an ecological study. The dependent variable is weekly ILI rate and the independent variables that we interested are average of air temperature, relative humidity, and rainfall. Meanwhile, population density may influence on ILI epidemics [19, 20], so annual population density data were include in this study in order to control for the effects. All data were transformed as weekly format which starts from Sundays to Saturdays. Bangkok was separated from the central zone because it is the capital city and its population density is very high.

Data analysis

The association between weekly ILI rate and climate were explored by the Generalized Estimation Equation (GEE) Model which estimated the population-averaged effects, may have within-subject covariance structure and repeated measurement, and can be used in any distribution of data [21]. We examined on ILI data and found that the data were negative binomial distribution. We use log link function with exchangeable correlation structure to write a linear function as follows [22]:

$$Log(\lambda) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4$$

λ = weekly ILI rate (per 100,000 population)
X_1 = median weekly average air temperature (°C)
X_2 = median weekly relative humidity (%)
X_3 = median weekly rainfall (mm)
X_4 = annual population density (people/km^2)

RESULTS

During the 5-year study period, 359,766 cases of ILI were reported. Classified into vulnerable aged-group, the age group under 5 year-old group was the highest ILI rate, followed by the age group between 5 - 64 years old and the age group from 65 years old (Table 1). Considering each zone, the ILI rate was highest in Bangkok, median was 5.73 (Q_1 2.14, Q_3 7.30) cases per 100,000 population, followed by Northern, Southeastern, Eastern, Central, Southeastern and Northeastern zones.

Trends of ILI rates in Northern, Northeastern, Central, Bangkok and Eastern zones were similar (Figure 1). There were two peaks of outbreaks in a year: first peak was between 2^{nd} and 12^{th} week (the winter season) and second peak was between 28^{th} and 42^{nd} week (the rainy season). The magnitude of the first peak was higher than the second peak in 2011 and 2012 but the magnitude of the second peak

Table 1 Descriptive statistics for climate and influenza-like illness cases data in 2011 – 2015

	Northern	**Northeastern**	**Central**	**Bangkok**	**Eastern**	**Southeastern**	**Southwestern**
Weekly ILI* rate, per 100,000 population	2.49	0.94	1.64	5.73	1.94	1.10	2.07
(Q_1, Q_3)	(0.58, 3.04)	(0.15, 1.08)	(0.39, 1.92)	(2.14, 7.30)	(0.21, 1.95)	(0.22, 1.40)	(0.33, 2.68)
Age group under 5 year-old	14.26	4.17	6.29	21.10	5.53	2.98	5.36
(Q_1, Q_3)	(0.01, 16.87)	(0.01, 4.84)	(0.01, 7.99)	(7.78, 26.73)	(0.01, 6.98)	(0.01, 4.05)	(0.01, 6.93)
Age group between 5 -64 year-old	2.06	0.69	1.26	5.17	1.70	0.94	1.72
(Q_1, Q_3)	(0.47, 2.36)	(0.10, 0.84)	(0.37, 1.67)	(1.89, 6.75)	(0.22, 1.66)	(0.24, 1.27)	(0.29, 2.31)
Age group from 65 year-old	1.02	0.78	0.67	2.50	0.84	0.65	1.00
(Q_1, Q_3)	(0.01, 1.66)	(0.01, 0.92)	(0.01, 1.13)	(0.63, 3.35)	(0.01, 1.05)	(0.01, 1.08)	(0.01, 1.04)
Average climate data							
Median of air temperature, °C	27.50	27.60	28.54	29.39	28.11	27.50	27.60
(Q_1, Q_3)	(25.84, 28.63)	(26.18, 28.79)	(27.69, 29.46)	(28.40, 30.40)	(27.21, 29.03)	(26.73, 28.26)	(26.86, 28.28)
Median of relative humidity,%	76.57	72.43	75.14	72.43	78.57	80.57	81.86
(Q_1, Q_3)	(69.43, 81.57)	(66.296, 79.29)	(70.49, 78.80)	(66.43, 77.00)	(73.31, 83.29)	(77.43, 83.86)	(77.14, 85.29)
Median of rainfall, mm	1.21	1.22	1.27	2.17	2.60	2.47	5.33
(Q_1, Q_3)	(0.01, 5.54)	(0.01, 5.83)	(0.01 4.29)	(0.01 6.86)	(0.13, 8.67)	(0.31, 6.75)	(0.97, 13.6)
Population density, people/km^2	66	128	170	3,516	129	124	108
Age group under 5 year-old, %	5.12	5.68	5.44	4.61	6.26	7.03	7.17
Age group between 5 - 64 year-old, %	83.90	84.94	83.95	84.55	84.48	83.20	84.64
Age group from 65 year-old , %	10.98	9.38	10.61	10.83	9.27	9.76	8.19

*ILI - Influenza-like illness

was high in 2013 to 2015. In 2015, there was the different pattern in the Central zone, Bangkok and the Eastern zone, high ILI rate without peak throughout the year. The trends of the ILI rate in Southeastern and Southwestern zones was different from others, there was only one peak of ILI rate between 32nd and 62th in the Southeastern zone and between 27th and 62th in the Southwestern zone. The lowest magnitude of the ILI rates occurred between 14th and 24th (the summer season) in all zones of Thailand.

There were two familiar weather patterns. The first weather pattern was in Northern, Northeastern, Central, Bangkok and Eastern zones, which the peak of air temperature in these zones occurred between 12th and 25th week and the bottom of temperature occurred between 49th and 57th week. Ranges of air temperature in Northern and Northeastern zones were higher than the other zones, which ranges were greater than 14 °C. These zones have higher relative humidity and rainfall between 31st and 41st week. From 2010 to 2011, there was lower air temperature in all zones and longer period of high rainfall only in Central, Bangkok, and Eastern zones. The second weather pattern was in Southeastern and Southwestern zones, which the peaks of air temperature were in the same period but there were higher rainfall and relative humidity. The peak of higher rainfall occurred between 42nd and 53rd week in the Southeastern zone and between 20th and 42nd week in the Southwestern zone.

The GEE method is used to measure the correlation in longitudinal studies and interpreted as beta coefficients, so we converted beta coefficients to incidence rate ratios (IRRs) and the results showed that there was a significant association between the ILI rate and climate in each zone (Table 2). Air temperature also played a major role, in combination with relative humidity or rainfall in most zones. After controlling other variables, air temperature was negatively associated with the ILI rate in all areas except for Northeastern and Southwestern zones. Relative humidity was positively associated with the ILI rate in Central, Bangkok, Eastern and Southwestern zone. Rainfall was positively associated with the ILI rate in Northern and Southwestern zones but there was negatively associated in the Southeastern zone. Population density was positively associated with the ILI rate in Southwestern zone but there was negatively associated in Bangkok and Southeastern zone. The Relative risk of the ILI rate was increased when air or relative humidity was increased (Figure 2), the highest effect was in Bangkok. The association between the ILI rate and climate in Bangkok and the central zone was accordant but the magnitude of the association in Bangkok was higher than that of the central zone.

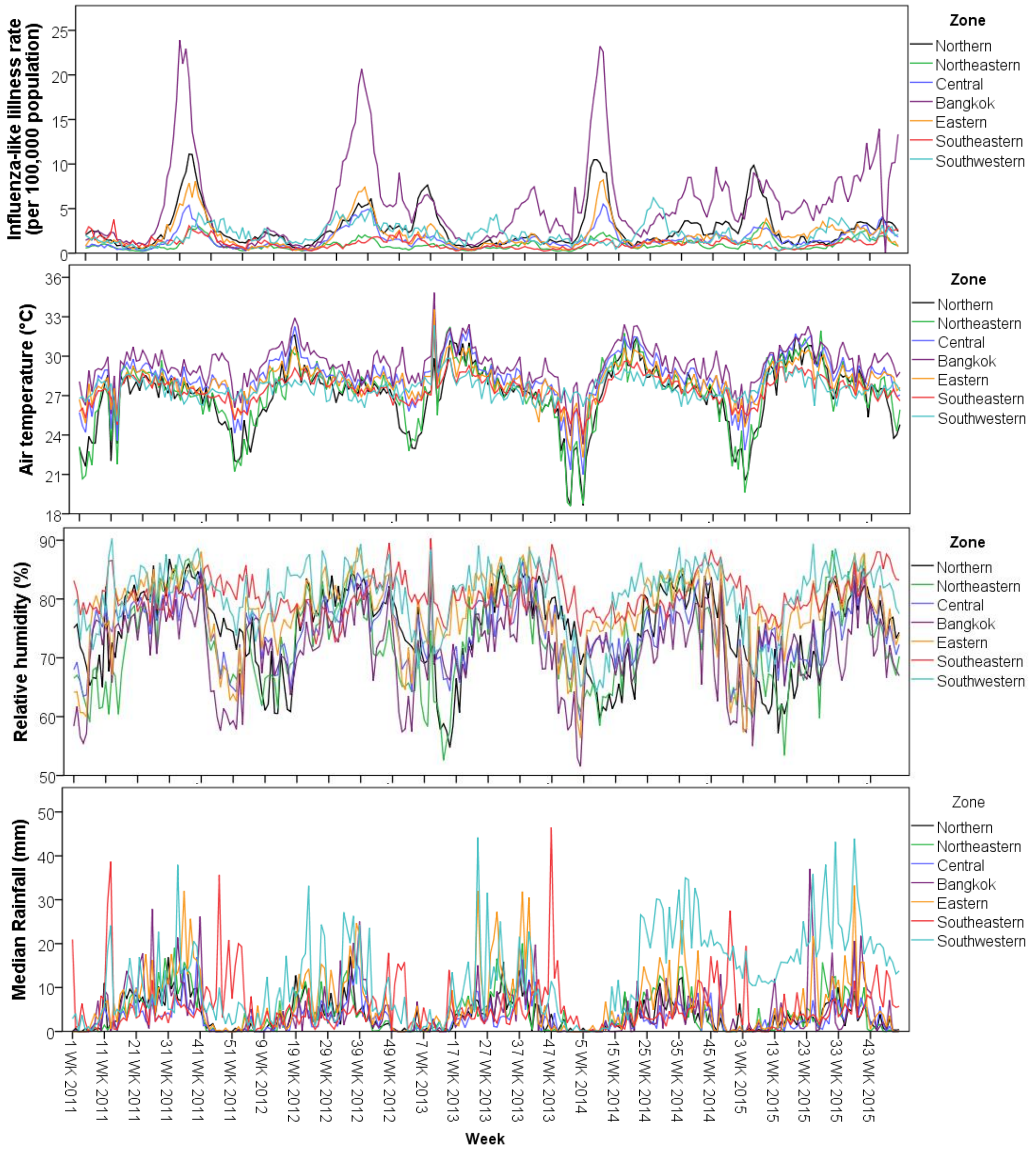

Figure 1 Weekly influenza-like illness rate and climate parameters in each zone

DISCUSSION

Although the ILI data from the surveillance system is not real data of influenza cases, studies in Thailand from 2004 to 2010 found the patients who had ILI symptoms were proportionally correlated with influenza cases by the Hemagglutination inhibition method [18]. Variable groups were classified by age into 2 groups: age group under 5 years old and age group from 65 years old [23].This study found the ILI rate of age group under 5 years old was highest as expected. However, the ILI rate of age group over 65 years old was lowest. The elderly may have more comorbidity illnesses that were reported as other diseases as a result of complications of influenza including pneumonia or often associated with other diseases, such as asthma or heart failure that might be triggered by influenza virus infection [17]. These may brought the ILI rate in the elderly lower than actual rates [24] and the ILI rate in this study was not affected by vaccination. To exemplify, Thai Ministry of Public Health had provided Influenza vaccines for variable groups including the elderly since 2009 but the ILI rate was still lowest in the elderly since 2013, when the infectious diseases surveillance system was established.

Table 2 Multivariable analysis of climate factors associated with influenza-like illness

	Incidence rate ratios (IRRs)[a]			
	Unadjusted	**(95% CI)**	**Adjusted**	**(95% CI)**
Northern				
Air temperature	0.9245	(0.8979, 0.9520)***	0.9218	(0.8892, 0.9557)***
Relative humidity	1.0033	(0.9901, 1.0167)	0.999	(0.9839, 1.0149)
Rainfall	1.0037	(0.9989, 1.0166)	1.0109	(1.0012, 1.0206)*
Population density	0.9983	(0.9855, 1.0113)	1.0014	(0.9877, 1.0153)
Northeastern				
Air temperature	1.0321	(1.0136, 1.0510)**	1.0128	(0.9971, 1.0287)
Relative humidity	1.0147	(1.0028, 1.0268)*	1.0115	(0.9980, 1.0252)
Rainfall	1.0160	(1.0067, 1.025)**	1.0048	(0.9954, 1.0142)
Population density	0.9990	(0.9879, 1.0103)	1.0018	(0.9900, 1.0138)
Central				
Air temperature	0.9802	(0.9728, 0.9876)***	0.9734	(0.9596, 0.9872)***
Relative humidity	1.2080	(1.0187, 1.0373)***	1.0263	(1.0167, 1.0359)***
Rainfall	1.0281	(1.0190, 1.0373)***	1.0082	(0.9946, 1.2019)
Population density	0.9997	(0.9991, 1.0005)	0.9997	(0.9988, 1.0006)
Bangkok				
Air temperature	0.8949	(0.8807, 0.9093)***	0.8815	(0.8673, 0.8959)***
Relative humidity	1.0341	(1.0256, 1.0426)***	1.0367	(1.0240, 1.0495)***
Rainfall	1.0221	(1.0164, 1.0279)***	1.0004	(0.9908, 1.0101)
Population density	1.0005	(1.0005, 1.0005)***	0.9468	(0.9411, 0.9527)***
Eastern				
Air temperature	0.9615	(0.9351, 0.9885)**	0.9444	(0.9022, 0.9885)**
Relative humidity	1.0376	(1.0327, 1.0425)***	1.0364	(1.0258, 1.0473)***
Rainfall	1.0192	(1.0129, 1.0255)***	1.0051	(0.9985, 1.0117)
Population density	1.0004	(0.9895, 1.0112)	1.0060	(0.9954, 1.0168)
Southeastern				
Air temperature	0.8973	(0.8386, 0.9599)**	0.9144	(0.8610, 0.9712)**
Relative humidity	1.0270	(1.0079, 1.0464)**	1.0272	(0.9991, 1.0499)
Rainfall	1.0035	(1.0013, 1.0057)**	0.9931	(0.9873, 0.9990)*
Population density	0.9969	(0.9964, 0.9974)***	0.9971	(0.9965, 0.9977)***
Southwestern				
Air temperature	0.9447	(0.8831, 1.0105)	1.0097	(0.9534, 1.0692)
Relative humidity	1.0275	(1.0183, 1.0368)***	1.0264	(1.0162, 1.0367)***
Rainfall	1.0075	(1.0060, 1.0090)***	1.0043	(1.0017, 1.0068)**
Population density	1.0021	(1.0012, 1.0031)***	1.0024	(1.0014, 1.0033)***

[a] Generalized Estimating Equation (GEE), family negative binomial
*** *p*-value <0.001, ** *p*-value < 0.01, * *p*-value < 0.001

Our finding on the association between the ILI rate and climate, all zones except for Northeastern and Southwestern zones were showed that the ILI rate was high in lower–air temperature period, occurring from 49th to 56th week. The highest peak of ILI cases occurred between 1st and 5th of week in 2014 which there was the lowest air temperature in this 5-year study and the ILI rate was low when air temperature was increased. These associations supported results from experimental studies, demonstrating that lower air temperature was efficient airborne transmission and good virus survival in such environment [5, 6], and from epidemiology studies in subtropical countries [25] and tropical countries [4]. In contrast, we found that relative humidity was positively associated with the ILI rate in all zones except for the Northern zone which contrary to other studies, the experimental studies demonstrated airborne transmission was decreased when relative humidity over 80% [5, 10]. However, epidemiological studies in Hong Kong found that high relative humidity in summer while Vancouver has high relative humidity in winter has increased outbreaks of influenza infection [4]. People who spend a longer time indoors, causing increased contact rates via inhalation or contact, are important in influenza virus transmission [26]. This study found correlation between relative humidity

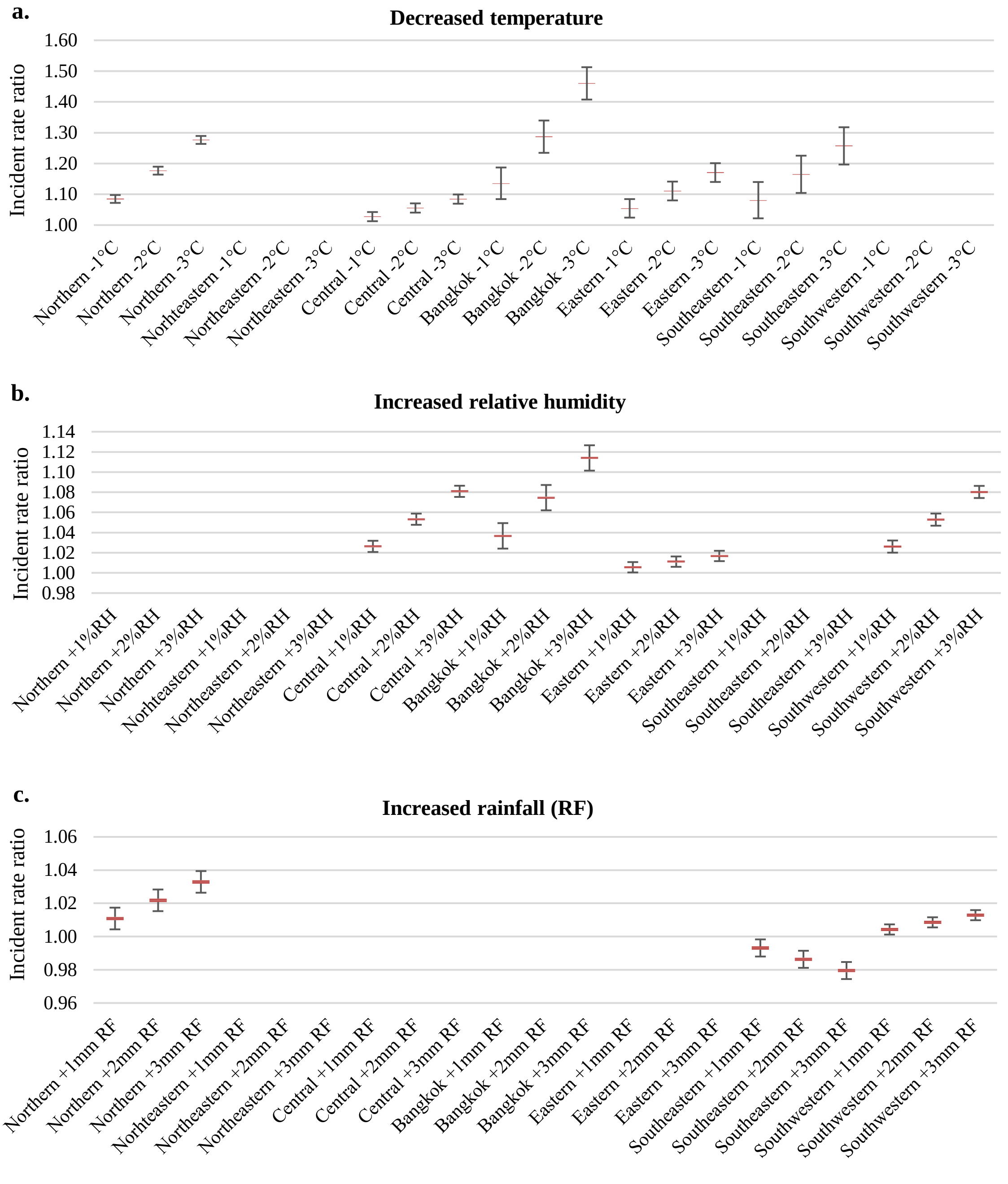

Figure 2 Incident rate ratio with 95% confidential interval of ILI rate when climate was changed

and rainfall (Pearson correlation = 0.4719). The rainy season in Thailand is between 25th and 42nd week and the peak of ILI occurred between 33rd and 42nd in all zones while statistic found positive association between rainfall and the ILI rate only in Northern and Southwestern zones but negative association in the Southeastern zone. A recent study indicated that in locations with high specific humidity and temperature, influenza epidemics were characterized by months with humidity and rainfall [4]. As previously mentioned, the association between rainfall and the ILI rate is likely to be indirect. Rainfall may lead to indoor crowding, which consequently increase contact rates.

In addition, Thailand was impacted by La Niña phenomenon in 2015 causing longer period of rainfall and decreased air temperature especially in Central, Bangkok, and Eastern zones. This phenomenon may explain the changing pattern of ILI rates. Other important phenomenon was the biggest forest fire in the last 15 years in Indonesia. Impact of smoke in the Southeastern zone, occurred between 26th and 50th week in 2015, made people need to spend more time indoors. The outdoor air quality was better, if there was more rainfall that may explain the paradoxical association in the Southeastern zone.

Population density was positively associated with the ILI rate in Southeastern according to studies in America [19] and India [20]. In contrast to Bangkok and the Southeastern zone, population density was negatively associated with the ILI rate. The population density data extracted from the civil registration database did not reflect true population density. The non-registered citizens, individuals moved to other residences without changing their civil registration, were highest in Bangkok (2.49 million people or 43.83% of Bangkok citizens) which immigrated in order to get jobs or study while the lowest non-registered citizen occurred in the Northeastern zone (0.45 million people or 2.18% of Northeastern citizens). Despite population increased from the civil registration in the Northeastern zone, but the ILI rates was decrease. And vice versa, the highest rate of ILI in Bangkok may be influenced by non-registered citizens from the Northeastern zone which increase population density higher than the civil registration database.

Human behaviors may increase the outbreak of influenza. The longer time in crowded area massively increased influenza transition [27, 28], studies in the US found that raining days resulting in cold weather influenced people to spend–average 1- 2 more hours indoors which potentially increases contact rates [26, 29]. Another study found influenza can be transmitted to passengers in long-haul flights [30].

Additionally, influenza transmission frequently occurred among children in school due to increasing change of exposure with sick children [31, 32]. Behaviors that reduce influenza transmission are good hand hygiene after contact infected person [33], while influenza vaccination is the best way to prevent the influenza infection [34].

The limitation of study was that this study was an ecological study using population data to reflect the association between distribution of ILI and climate only. These can't be implied as individual causation of influenza infection due to lacking other factors which affect transmission, such as contact time, personal hygiene, indoor air quality, and personal immunity. Although ILI cases from surveillance system reflected data of influenza outbreaks, these data are not the true number of cases because the surveillance system does not cover other health providers outside the Ministry of Public Health sector.

Human behaviors may increase the outbreak of influenza. The longer time in crowded area massively increased influenza transition [27, 28]. Studies in the US found that raining days resulting in cold weather influenced people to spend-average 1- 2 more hours indoors which potentially increases contact rates [26, 29]. Another study found influenza can be transmitted to passengers in long-haul flights [30].

Additionally, influenza transmission frequently occurred among children in school due to increasing change of exposure with sick children [31, 32]. Behaviors that reduce influenza transmission are good hand hygiene after contact infected person [30], while influenza vaccination is the best way to prevent the influenza infection [34].

The limitation of study was that this study was an ecological study using population data to reflect the association between distribution of ILI and climate only. These can't be implied as individual causation of influenza infection due to lacking other factors which affect transmission, such as contact time, personal hygiene, indoor air quality, and personal immunity. Although ILI cases from surveillance system reflected data of influenza outbreaks, these data are not the true number of cases because the surveillance system does not cover other health providers outside the Ministry of Public Health sector.

CONCLUSION

Although there are limitations of other factors affecting influenza transmission, the study showed that weekly ILI rates associated with climate, air temperature was found the negative association and played a major role in most zones. Central, Bangkok, Eastern and Southwestern zone were found the positive association between ILI rate and relative humidity. Rainfall was found the positive association with ILI rate in Northern and Southwestern zones but was found the negative association in Southeastern zone due to different climate. The association between rainfall and influenza outbreaks may be indirect, similar to the crowding effect that contributes to increased contact time and influenza transmission. Using weather information may predict the influenza outbreaks and be beneficial to prevention and early preparedness for climate change.

ACKNOWLADGEMENTS

We would like to thank Mr. Samarn Sayumpurujinan and member staff of Bureau of Epidemiology, Department of Disease Control, Thai Ministry of Public Health for their assistance in ILI case data extraction. We also appreciate the staff of Thai Metrological Department for their contributions to climate data.

REFERENCES

1. World Health Organization [WHO]. Fact sheets: influenza (Seasonal). [updated: 2014 March 1; cited 2015 November 6]. Available from: http://www.who.int/mediacentre/factsheets/fs211/en/
2. Bureau of Epidemiology Thailand. Weekly epidemiological surveillance report: Influenza. Bangkok: Department of disease control, Ministry of public health; 2015.
3. Tamerius JD, Shaman J, Alonso WJ, Bloom-Feshbach K, Uejio CK, Comrie A, et al. Environmental predictors of seasonal influenza epidemics across temperate and tropical climates. PLoS Pathog. 2013 Mar; 9(3): e1003194. doi: 10.1371/journal.ppat.1003194
4. Tamerius J, Nelson MI, Zhou SZ, Viboud C, Miller MA, Alonso WJ. Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environ Health Perspect. 2011 Apr; 119(4): 439-45. doi: 10.1289/ehp.1002383
5. Lowen AC, Mubareka S, Steel J, Palese P. Influenza virus transmission is dependent on relative humidity and temperature. PLoS Pathog. 2007 Oct; 3(10): 1470-6. doi: 10.1371/journal.ppat.0030151
6. Lowen AC, Steel J, Mubareka S, Palese P. High temperature (30 degrees C) blocks aerosol but not contact transmission of influenza virus. J Virol. 2008 Jun; 82(11): 5650-2. doi: 10.1128/JVI.00325-08
7. Polozov IV, Bezrukov L, Gawrisch K, Zimmerberg J. Progressive ordering with decreasing temperature of the phospholipids of influenza virus. Nat Chem Biol. 2008 Apr; 4(4): 248-55. doi: 10.1038/nchembio.77
8. Harper GJ. Airborne micro-organisms: survival tests with four viruses. J Hyg (Lond). 1961 Dec; 59: 479-86.
9. Hemmes JH, Winkler KC, Kool SM. Virus survival as a seasonal factor in influenza and poliomylitis. Antonie Van Leeuwenhoek. 1962; 28: 221-33.
10. Hood AM. Infectivity of Influenza Virus Aerosols. J Hyg (Lond). 1963 Sep; 61: 331-5.
11. Schaffer FL, Soergel ME, Straube DC. Survival of airborne influenza virus: effects of propagating host, relative humidity, and composition of spray fluids. Arch Virol. 1976; 51(4): 263-73.
12. Jensen MM. Inactivation of Airborne Viruses by Ultraviolet Irradiation. Appl Microbiol. 1964 Sep; 12: 418-20.
13. Powell WF, Setlow RB. The effect of monochromatic ultraviolet radiation on the interfering property of influenza virus. Virology. 1956 Jun; 2(3): 337-43.
14. Tamm I, Fluke DJ. The effect of monochromatic ultraviolet radiation on the infectivity and hemagglutinating ability of the influenza virus type A strain PR-8. J Bacteriol. 1950 Apr; 59(4): 449-61.
15. Towers S, Chowell G, Hameed R, Jastrebski M, Khan M, Meeks J, et al. Climate change and influenza: the likelihood of early and severe influenza seasons following warmer than average winters. PLoS Curr. 2013 Jan; 5. doi: 10.1371/currents.flu.3679b56a3a5313dc7c043fb944c6f138
16. CDC Foundation. Flu prevention. [updated: 2015 December; cited 2016 May 9]. Available from: http://www.cdcfoundation.org/businesspulse/flu-prevention-infographic
17. Centers for Disease Control and Prevention. Seasonal influenza: flu basics. [updated 2014 August 5; cited 2016 January 8]. Available from: http://www.cdc.gov/flu/about/disease/index.htm
18. Chittaganpitch M, Supawat K, Olsen SJ, Waicharoen S, Patthamadilok S, Yingyong T, et al. Influenza viruses in Thailand: 7 years of sentinel surveillance data, 2004-2010. Influenza Other Respir Viruses. 2012 Jul; 6(4): 276-83. doi: 10.1111/j.1750-2659.2011.00302.x
19. Chandra S, Kassens-Noor E, Kuljanin G, Vertalka J. A geographic analysis of population density thresholds in the influenza pandemic of 1918-19. Int J Health Geogr. 2013 Feb; 12: 9. doi: 10.1186/1476-072X-12-9
20. Kumar S, Piper K, Galloway DD, Hadler JL, Grefenstette JJ. Is population structure sufficient to generate area-level inequalities in influenza rates? An examination using agent-based models. BMC Public Health. 2015; 15: 947. doi: 10.1186/s12889-015-2284-2
21. Gibbons RD, Hedeker D, DuToit S. Advances in analysis of longitudinal data. Annu Rev Clin Psychol 2010;6:79-107. doi: 10.1146/annurev.clinpsy.032408.153550.
22. Ballinger GA. Using Generalized Estimating Equations for Longitudinal Data Analysis. Organizational Research Methods 2004;7:127-50. doi: 10.1177/1094428104263672
23. Centers for Disease Control and Prevention. People at high risk of developing flu–related complications. [updated 2016 August 25; cited 2016 August 30]. Available from: http://www.cdc.gov/flu/about/disease/high_risk.htm
24. Centers for Disease Control and Prevention. Seasonal influenza: estimating seasonal influenza-associated deaths in the United States: CDC study confirms variability of flu. [updated 2016 May 9; cited 2016 October 1]. Available from: http://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm
25. Soebiyanto RP, Clara W, Jara J, Castillo L, Sorto OR, Marinero S, et al. The role of temperature and humidity on seasonal influenza in tropical areas: Guatemala, El Salvador and Panama, 2008-2013. PLoS One. 2014; 9(6): e100659. doi: 10.1371/journal.pone.0100659
26. Lofgren E, Fefferman NH, Naumov YN, Gorski J, Naumova EN. Influenza seasonality: underlying causes and modeling theories. J Virol. 2007 Jun; 81(11): 5429-

36. doi: 10.1128/JVI.01680-06

27. Ahmed QA, Arabi YM, Memish ZA. Health risks at the Hajj. Lancet. 2006 Mar; 367(9515): 1008-15. doi: 10.1016/S0140-6736(06)68429-8
28. Dushoff J, Plotkin JB, Levin SA, Earn DJ. Dynamical resonance can account for seasonality of influenza epidemics. Proc Natl Acad Sci USA. 2004 Nov; 101(48): 16915-6. doi: 10.1073/pnas.0407293101
29. Graham SE, McCurdy T. Developing meaningful cohorts for human exposure models. J Expo Anal Environ Epidemiol. 2004 Jan; 14(1): 23-43. doi: 10.1038/sj.jea.7500293
30. Brownstein JS, Wolfe CJ, Mandl KD. Empirical evidence for the effect of airline travel on inter-regional influenza spread in the United States. PLoS Med. 2006 Sep; 3(10): e401. doi: 10.1371/journal.pmed.0030401
31. Cauchemez S, Valleron AJ, Boelle PY, Flahault A, Ferguson NM. Estimating the impact of school closure on influenza transmission from Sentinel data. Nature. 2008 Apr; 452(7188): 750-4. doi: 10.1038/nature06732
32. Lipsitch M, Viboud C. Influenza seasonality: lifting the fog. Proc Natl Acad Sci USA. 2009 Mar; 106(10): 3645-6. doi: 10.1073/pnas.0900933106
33. Remschmidt C, Stocker P, an der Heiden M, Suess T, Luchtenberg M, Schink SB, et al. Preventable and non-preventable risk factors for influenza transmission and hygiene behavior in German influenza households, pandemic season (H1N1) 2009/2010. Influenza Other Respir Viruses. 2013 May; 7(3): 418-25. doi: 10.1111/j.1750-2659.2012.00407.x
34. Centers for Disease Control and Prevention. Vaccine effectiveness - how well does the flu vaccine work? [updated 2016 November 17; cited 2016 November 30]. Available from: https://www.cdc.gov/flu/about/qa/vaccineeffect.htm