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Temporal and spatial analysis of hand, foot, and mouth disease in relation to climate factors: a study in the Mekong Delta region, Vietnam

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Abstract

This study examined the temporal and spatial patterns of hand, foot, and mouth disease (HFMD) in the Mekong Delta region in Viet Nam. A time-series analysis was used to examine the temporal patterns of HFMD in relation to climate factors while a retrospective space-time scan was used to detect the high-risk space-time clusters of this disease. A 1^{o}C increase in average temperature was associated with 5.6% increase in HFMD rate at lag 5 days (95% CI 0.3-10.9). A 1% increase in humidity had equal influence of 1.7% increases on HFMD rate at both lag 3 days and 6 days (95% CI 0.7-2.7 and 95% CI 0.8-2.6, respectively). An increase in 1 unit of rainfall was associated with a 0.5% increase of HFMD rate on the lag 1 and 6 days (95% CI 0.2-0.9 and 95% CI 0.1-0.8, respectively). The predictive model indicated that the peak of HFMD was from October to December – the rainy season in the Mekong Delta region. Most high-risk clusters were located in areas with high population density and close to transport routes. The findings suggest that HFMD is influenced by climate factors and is likely to increase in the future due to climate change related weather events.

Key words: Climate; Hand, foot, and mouth disease; Mekong Delta, Vietnam.

1. Introduction

Hand, foot, and mouth disease (HFMD) is a viral disease, whose incidence has increased significantly in Asian countries such as China, Japan and Vietnam over the last decade (WHO, 2011). HFMD is caused by a group of human enteroviruses species A, the main ones being Coxsackievirus A16 (CV A16) and Enterovirus 71 (EV71). This disease occurs most commonly in children under 5 years old and can be severe, even leading to death. The symptoms of HFMD range from mild symptoms of fever, skin eruptions on hand, feet and vesicles in the mouth to more severe symptoms involving the central nervous systems and/or severe respiratory symptoms (WHO, 2011). HFMD is a highly contagious disease that is transmitted from person to person by direct contact with respiratory secretions, droplets or fomites of an infected person or through faecal-oral transmission (WHO, 2011). Since there is still no specific treatment for HFMD available, and since a vaccine for EV71 has only started to be used in China since the beginning of 2016 (Knowlton et al.), preventive measures such as enhanced surveillance to provide early warning of HFMD outbreaks are essential to minimize the impacts of HFMD.

Evidence of the association between HFMD and climate factors, especially temperature, has been shown in some studies elsewhere (Hii, Rocklöv, & Ng, 2011; Huang et al., 2013; Li, Yang, Di, & Wang, 2014; Onozuka & Hashizume, 2011; Urashima, Shindo, & Okabe, 2003; J. F. Wang, Xu, Tong, Chen, & Yang, 2013; P. Wang, Goggins, & Chan, 2016; Zhu et al., 2015). However, the relationship between HFMD incidence and the ambient temperature was inconsistent for different geographical areas (Hii et al., 2011; Huang et al., 2013; Onozuka & Hashizume, 2011; Urashima et al., 2003). A study in Singapore (Hii et al., 2011) revealed that a

1^{o}C increase in maximum temperature above 32^{o}C was significantly associated with a 36% increase of HFMD incidence. Studies in other Asian cities such as Guangzhou, China (Huang et al., 2013) and Fukuoka, Japan (Onozuka & Hashizume, 2011) have also showed positive association between increasing temperature and HFMD incidence. In contrast, a study in Shandong, China (Zhu et al., 2015) identified a negative association between temperature and HFMD when the average temperature was above 21^{o}C and a study in Tokyo (Urashima et al., 2003) has also detected a negative association when the average temperatures are above 25^{o}C. The association between ambient temperature and HFMD incidence has been shown to be non-linear in studies in Tokyo (Urashima et al., 2003), Beijing (Xu et al., 2015), and Shandong (Zhu et al., 2015). Climate factors are not alone in affecting the HFMD incidence; the difference in association between climate factors and HFMD distribution in different regions suggests that other factors such as spatial factors may modify the association. Studies in some regions in China such as Liaocheng city (Zhang & Zhao, 2015), Shandong Province (Y. Liu et al., 2015), Guangdong province (Deng et al., 2013), and Sichuan province (Liu, Zhao, Yin, & Lv, 2015) have examined both spatial and temporal factors and indicated high-risk clusters of HFMD in specific periods using spatial-temporal analysis. The high-risk clusters were specific to each study region, and they tended to occur in areas that have higher population density (Deng et al., 2013; L. Liu et al., 2015) and in transit hubs of highways and railways (L. Liu et al., 2015). Understanding the existence of high-risk clusters in specific areas would enable public health planning to focus on these areas to maximize the prevention and control effects.

In recent decades, increased HFMD outbreaks have been reported in Vietnam (WPRO, 2016). The numbers of reported cases in 2008 and 2009 were around ten thousand, double the numbers in 2007. There was a peak of 157,654 cases in 2012 and then the incidence remained high in the following years (WPRO, 2016). Most HMFD cases in Vietnam have been reported in the South (WPRO, 2016), including the Mekong Delta Region (MDR) which is also the most vulnerable area to climate change in the South-East Asia (Yusuf & Francisco, 2009). However, no study regarding the association between HMFD and climatic factors has been conducted in this region to provide evidence for prevention measures for HFMD in the context of climate change in this highly vulnerable region. Previous studies about HFMD in Vietnam have mainly focused on virology (Khanh et al., 2012; Tan et al., 2015; Thao et al., 2010) and epidemiology characteristics of HFMD (Nguyen et al., 2014; Tu et al., 2007),

This study aims to examine the temporal and space-time clusters of HFMD in relation to climate factors in Can Tho, the central city of the MDR in Vietnam. Understanding the spatial-temporal patterns of HFMD can make a significant contribution in determining high-risk areas and periods of HFMD. The data will be useful for public health practitioners and authorities in implementing HFMD preparedness and control.

2. Methods

2.1. Research location

This study was implemented in Can Tho city, which is located in the centre of the MDR in Vietnam. Can Tho city has an area of 1409km^2 and a population of 1,237,000 people with a population density of 878 people/km^2 which is the highest population density in the MDR (Chien, 2014). There are two seasons in Can Tho city, the dry season (December-April) and the wet season (May-November). Since it is located in a complex of intertwining rivers and a vast area of orchards and rice fields, Can Tho's residential life is highly affected by hydro-meteorological factors.

2.2. Data collection

Daily HFMD cases were collected from January 2012 to December 2014 from the disease surveillance reports of Can Tho Preventive Medicine Centre (CTPMC). In Vietnam, it has been compulsory to report all HFMD cases through the health care systems from 2011 (MOH, 2010). Once a HFMD case is confirmed by a physician in a hospital or clinic, it must be reported to the local health authority, and then be reported to the higher level within 24 hours. The CTPMC is the provincial health authority responsible for collecting data of all HFMD cases in Can Tho city, and reporting them to the Ministry of Health. Thus, the data collected by CTPMC is the best available data to represent HFMD cases in Can Tho city throughout the three years from 2012 to 2014.

Daily climate factors were collected from the Southern Regional Hydro-Meteorological Centre for the period of January 2012 to December 2014. The climate factors comprise daily average temperature (^oC), relative humidity (%), and cumulative rainfall (mm).

2.3. Data analysis

2.3.1. Time-series regression analysis

Time-series regression was used to examine the temporal patterns of HFMD in relation to the climate factors, comprising average temperature, humidity and cumulative rainfall. First, seasonality and long-term trends were controlled using a flexible spline function for the three years from 2012 to 2014 using 6 degrees of freedom per year. Although there is no confirmation on how many knots are optimal, the previous study indicated that 7 knots per year can balance between providing adequate control for seasonality and other confounding factors by trend in time, while leaving sufficient information from which to estimate exposure effects (Bhaskaran, Gasparrini, Hajat, Smeeth, & Armstrong, 2013; Dominici, Samet, & Zeger, 2000). Second, for each climate factor the lag effects of up to 6 days lag were examined using a Generalized Linear Model (GLM) using linear regression with Poisson family and the distributed lag model while adjusting for spline function of time, day of the week, and the offset of population (Equation 1). We selected 6 day lags for 2 reasons. First, the usual period from infection to onset of symptoms is 3-7 days (WHO, 2012). Second, we wished to avoid enhancing the chance of statistical significance when using many lags.

$$Ln(Y) = \beta_o + \sum \beta_i T_i + \sum \beta_j H_j + \sum \beta_z R_z + s(time) + dow + Ln(pop)$$

where, Y is the daily count of HFMD cases, T_i is the average daily temperature at lag i day, H_j is the daily humidity at lag j day, R_z is the daily cumulative rainfall at lag z day, s(time) is the flexible spline function of time (6 df per year), dow is the day of the week, and pop is population. Since the research location is a tropical area which has summer only, the minimum average temperature (22^{o}C) was selected as the reference temperature to estimate the risk of HFMD associated with each increase in 1^{o}C.

Third, the best prediction model was selected based on the lowest Akaike's information criteria (AIC) and Bayesian information criteria (BIC) to present the temporal pattern of HFMD across a year. The temporal pattern of HFMD over 52 weeks of a year was examined using the cases predicted from the best prediction model.

2.3.2. Space-time cluster analysis

A retrospective space-time statistical scan was performed to identify the presence of high-risk space-time clusters of HFMD cases using the SaTScan software. A cylindrical window with a circular geographical base and the height corresponding to time was used to scan through the space and the time statistics (L. Liu et al., 2015). Thus, the possible spatio-temporal clusters were detected by the dynamic flux of the base and the height of the cylindrical window. We used a log likelihood ratio (LLR) to test for elevated risk within the window to compare to the risk outside the window. The scanning window with the highest LLR was defined as the most-likelihood cluster. This study analysed the geographic pattern at the smallest census unit available, which is the commune. The scanning time used in this study was yearly to control for the time trend over the whole study period. For each year, we used 85 communes of the city as the spatial units, and 365/366 days from January to 31 December as the time unit. For the setting of the minimum size of the spatial cluster size, we used the value of 20% of the population for the setting of maximum size of the spatial cluster size. For each run, the number of Monte Carlo replications was set to 999 to ensure sufficient statistical power. Clusters which had statistical significance ($p \leq 0.05$) were reported.

3. Results

3.1. Descriptive analysis

The descriptive statistics of HFMD and the meteorological factors from the three years 2012, 2013, and 2014 are presented in Table 1. A total of 3,786 cases HFMD were reported in the three years from 2012 to 2014 with an average of 3 to 5 cases per day. During the study period, the average temperature ranged from 21.9^{o}C to

31^{o}C with a mean of 27^{o}C. Daily humidity ranged from 58% to 95%, and the cumulative daily rainfall ranged from 0 mm to 97.5mm.

3.2. Temporal patterns of HFMD

The factors of temperature, humidity and rainfall are all significantly associated with the changes in HFMD incidence but with different lag days over a week (Table 2.). The distributed lag model indicated that temperature at lag 5 and 6 days, humidity at lag 3 and 6 days, and rainfall at lag 1 and 6 days have a statistically significant association with HFMD changes ($p \leq 0.05$). While a 1^{o}C increase in temperature was associated with a 5.6% increase in HFMD rate at lag 5 days (95% CI 0.3-10.9), it was also associated with a 4.7% decrease in HFMD rate at lag 6 days (95% CI -9.2-0.2). A 1% increase in humidity at both lag 3 days and lag 6 days had the same influence on HFMD rate, that is a 1.7% increase (95% CI 0.7-2.7 and 95% CI 0.8-2.6, respectively). An increase in 1 unit of rainfall (mm) was associated with a 0.5% increase of HFMD rate at lag 1 day and lag 6 days (95% CI 0.2-0.9 and 95% CI 0.1-0.8, respectively). The optimal multivariable predictive model was identified, using the significant lags of these three climate factors and using the smallest AIC and BIC values, comprises temperature at lag 5 days, humidity at lag 6 days, and rainfall at lag 1 day, adjusted for seasonal and long-term trends (Table 3.) The temporal pattern of HFMD cases predicted from the model is presented in Figure 1. It shows that HFMD incidence tends to increase from September and reach a peak from week 41 to 50 of the year – corresponding to October to December, which is the rainy season in the MDR, and then gradually decreases to the lowest level from June to August.

3.3. Space-time clusters of HFMD

The spatial pattern and spatio-temporal clusters of HFMD are presented in Figure 2 and Table 4. Geographically, high incidence rates were observed in the communes of Thoi Lai, Binh Thuy and Ninh Kieu districts (Fig. 2a). The map of 2012 to 2014 (Fig. 2b) indicated that there were significant single-centre clusters and multi-centre clusters in the research locations in all three years. Most of the clusters were in communes in the Ninh Kieu district – the centre of Can Tho city and close to the main traffic running through Can Tho city, especially marked in 2013.

Using the setting of 20% of the total population, the most-likely cluster of HFMD in CanTho city in three years from 2012 to 2014 were detected in this study. They are listed in Table 4. In 2012, two most-likely clusters were recorded. The spatio-temporal cluster with highest LLR was located at 10.03^{o}N by 105.51^{o}E, and the cluster radius was 10.38 km; it occurred from 30 October to 28 December. The annual incidence rate within this window was 806.5/100,000 with relative risk of 5.73 ($p \leq 0.01$). This cluster was repeated in 2013 with the same centre but an earlier time period, which was from 6 September to 23 December, and a lower incidence rate of 289.6/100,000. Another cluster was also detected in 2013, which lasted longer, from 1 January to 8 June, in Long Tuyen commune, which is near the centre of Can Tho city. Three spatio-temporal clusters were recorded in 2014 with cluster centres in Truong Thanh commune, Thoi An Dong commune, and Truong Xuan commune. Most of the clusters were located along the main roads crossing Can Tho city, and close to the centre of Can Tho city.

4. Discussion

This study has explored the association between hydro-meteorological factors and the distribution of HFMD in Vietnam. Time-series analysis was used to examine the short-term effects of climate factors including the temperature, humidity, and rainfall on HFMD. This study has created a predictive model for HFMD incidence by analysing multiple distributed lag models. Spatio-temporal analysis was used to describe the spatial patterns and spatial-time clusters of HFMD in Can Tho city of the MDR.

All three hydro-meteorological factors including temperature, humidity, and rainfall were found to be statistically significantly associated with HFMD cases. The positive association between temperature and humidity factors and HFMD found in this study is consistent with previous studies in Asian countries, in particular, China (Huang et al., 2013), Hong Kong (P. Wang et al., 2016), Japan (Onozuka & Hashizume, 2011), and Singapore (Hii et al., 2011). However, the positive association between rainfall and HFMD in this study is different to the finding of the study in Guangzhou, China (Huang et al., 2013) which showed no statistically significant association between rainfall and HFMD. The best predictive model of HFMD in this study consists of lag 5 days for temperature, lag 6 days for humidity and lag 1 day for rainfall. This lag time is different to the lag time shown in the study in Guangzhou, China (Huang et al., 2013), which used weekly data and indicated that the best model to predict HFMD was lag one week in the effects of both temperature and humidity. The difference between the two studies could be explained by the data collection in these studies, i.e. our study used daily data for both HFMD cases and hydro-meteorological factors while the study in Guangzhou only used weekly data. Thus, it is suggested that the predictive model in this study can produce more specific prediction and it is useful for public health practitioners in early detecting HFMD outbreaks.

For the temporal pattern of HFMD over the year, this study found one single peak from October to December which was different to the “double peaks” recorded in other studies in China (Deng et al., 2013; Li et al., 2014; L. Liu et al., 2015). This difference may be explained by the difference in climate regions. The climate in studies in China is Warm Temperature Climate (category C) while the climate of the MDR is Equatorial Climate (category A), according to the Köppen-Geiger Climate Classification (Kottek, Grieser, Beck, Rudolf, & Rubel, 2006). The Warm Temperature Climate is the climate that has the minimum temperature ranging from -3^{o}C to 18^{o}C; which means it actually has a cool winter, either with dry or humid – depending on particular subregions. Hence, the explanation for the double peaks of studies in this climate category may be that the viruses tend to develop in early summer (Li et al., 2014) and early autumn (Onozuka & Hashizume, 2011). The Equatorial Climate is described as having minimum temperature equal to or above 18^{o}C, thus it does not actually have a cool winter. The weather is warm through the year, and the yearly seasons are divided into dry and wet seasons. Hence, there is only one peak of HFMD during the wet season due to the positive association of HFMD with higher humidity and rainfall.

The biological mechanism of the association between climate factors (temperature, humidity and rainfall) remains unclear even though the positive association found between weather factors and HFMD has been consistently reported from previous studies (Hii et al., 2011; Huang et al., 2013; Onozuka & Hashizume, 2011). The possible underlying mechanism of HFMD can be explained by interactions of pathogens, host population structure, and environmental factors (Barrett, Charles, & Temte, 2015; Khasnis & Nettleman, 2005). Environmental factors such as warm weather and high humidity can facilitate the transmission of enteroviruses as they survive well in a watery environment (Rajtar, Majek, Polański, & Polz-Dacewicz, 2008). This interaction between environmental factors and pathogens can explain the peak of HFMD in warm temperature and wet season in the MDR. Moreover, temperature can also affect the behaviour patterns of host population. For instance, warm weather may encourage children more often to go out to public entertainment areas, so increasing the contact frequencies among them, leading to more exposure to pathogens (W. Liu et al., 2015).

The spatial scan results (Table 4) show that the centres of HFMD clusters were mostly located at the centre of Can Tho city, namely Ninh Kieu district, which has the highest population density. Higher population density and high frequency contact may help the HFM viruses to spread. This finding was consistent with those from previous studies in Sichuan province (L. Liu et al., 2015) and Hong Kong (Ma, Lam, Chan, Wong, & Chuang, 2010). In the context of climate change, the MDR is the region that will be affected by sea level rise (Yusuf & Francisco, 2009), which will reduce land area, and thus cause population to gather. This will result in higher population density and more frequent contacts among population. For this reason, HFMD may tend to increase in the future in the MDR.

There are some limitations in this study. First, as HFMD has only recently appeared in the MDR and reporting of HFMD was only made compulsory in Vietnam from 2011, there were only three years data available for this study. Personal information of HFMD patients, and virus types were not included in this study. Other factors such as economic status and behaviour, in particular, exposure behaviour may be factors that influence the HFMD transmission. However, those factors are long-term factors, hence; they would not affect the results of this study which focuses on short-term effect on HMFD. Another limitation is that this study was conducted in the central city of the MDR which may not represent the whole MDR. Future studies should utilize longer periods and broader areas in the whole MDR for more accuracy and validity, and should involve long-term factors such as behaviour and economic status to provide more comprehensive and extensive evidence for preventive and control programmes for HFMD in MDR – a region that is very sensitive to climate change. Those studies should also determine appropriate and practical prevention measures that best fit the local context of the MDR. Furthermore, understanding the social and economic effects of HFMD outbreaks is needed in order to raise awareness and to promote more actions to prevent and control HFMD.

5. Conclusion

This study reveals the significant relationship between HFMD and climate factors including temperature, humidity and rainfall in Can Tho city. A predictive model of HFMD was created and high-risk areas of HFMD were determined, and these can support the development of an early warning system for HFMD in the MDR. As both high temperature and high population density are associated with elevated risk of HFMD, this disease is likely to increase in the future in the MDR due to projected increases of climate change in the MDR. Further studies should be conducted about factors influencing HFMD which focus on both ecological factors and behaviour factors, social and economic effects of HMFD, and prevention measures in the whole MDR to provide more comprehensive understanding of the interaction between climate change related factors and other factors related to HFMD.

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Conflict of interest None

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Table1. *Descriptive statistics of HFMD and meteorological factors*

	Percentile			Minimum	Maximum	Mean (SD)
	25th	50th	75th			
Hand-Foot-Mouth (daily counts of cases)						
2012	2	4	7	0	30	5(4)
2013	1	2	4	0	16	3(2)
2014	1	3	5	0	30	4(3)
Temperature (^{O}C)	26.6	27.6	28.5	21.9	31	27(1.3)
Humidity (%)	77	81	84	58	95	80.8(5.2)
Cumulative rainfall (mm)	0	0	2.6	0	97.5	3.9(9.7)

Table2. *The lag effects of climate factors on the rates of HFMD (Distributed Lag Model)*

Lag (days)	**Temperature** (^{o}C)		**Humidity** (%)		**Rainfall** (mm)	
	Change, %	95%CI	Change, %	95%CI	Change, %	95%CI
0	3.2	-1.3-0.08	-0.9	-1.8-0.003	0.03	-0.3-0.4
1	-4.3	-9.5-0.9	0.2	-0.7-1.2	**0.5***	0.2-0.9
2	3.3	-2-8.5	-0.1	-1.1-0.9	-0.09	-0.4-0.3
3	0.3	-5-5.5	**1.7***	0.7-2.7	-0.3	-0.6-0.09
4	-3.8	-9-1.4	-0.8	-1.8-0.2	-0.5	-0.9-(-0.1)
5	**5.6***	0.3-10.9	-1.8	-1.2-0.8	-0.4	-0.8-(-0.03)
6	**-4.7**	-9.2-0.2	**1.7***	0.8-2.6	**0.5***	0.1-0.8

CI, Confidence Interval
*Statistically significant (P<0.05)
The models adjusted seasonal and long-term trends using a flexible spline function of time (6 D.F. per year), and day of a week.

Table3. *Identification of the optimal multiple distributed lag model*

Model	% change in rate of FHM	95%CI	AIC	BIC	Model	% change in rate of FHM	95%CI	AIC	BIC
Model 1			5367	5502	*Model 9*			5362	5496
Lag 5: Temperature	1	-2.8-4.7			Lag 6: Temperature	-2.7	-6.4-1		
Lag 3: Humidity	1.3	4.7-2.0			Lag 3: Humidity	1.3	0.5-2		
Lag 1: Rainfall	0.5	0.2-0.8			Lag 1: Rainfall	0.5	0.2-0.8		
Model 2			5362	5497	*Model 10*			5357	5492
Lag 5: Temperature	0.7	-3-4.4			Lag 6: Temperature	-2.5	-6.2-1.2		
Lag 3: Humidity	1.5	0.7-2.3			Lag 3: Humidity	1.5	0.7-2.3		
Lag 4: Rainfall	-0.7	-1.1-0.3			Lag 4: Rainfall	-0.7	-1.1-(-0.3)		
Model 3			5370	5505	*Model 11*			5364	5499
Lag 5: Temperature	-0.7	-4.7-3.3			Lag 6: Temperature	-2.7	-6.4-0.9		
Lag 3: Humidity	1.3	0.5-2.1			Lag 3: Humidity	1.3	0.5-2.1		
Lag 5: Rainfall	-0.5	-0.9-(-0.06)			Lag 5: Rainfall	-0.5	-0.9-(-0.08)		
Model 4			5366	5501	*Model 12*			5367	5502
Lag 5: Temperature	2.1	-1.7-5.9			Lag 6: Temperature	-1	-5-2.9		
Lag 3: Humidity	1.3	0.5-2			Lag 3: Humidity	1.3	0.5-2.0		
Lag 6: Rainfall	0.4	0.09-0.8			Lag 6: Rainfall	0.4	-0.008-0.7		
Model 5*			**5355**	**5490**	*Model 13*				
Lag 5: Temperature	2.1	-1.6-5.9			Lag 6: Temperature	-0.1	-4-3.8	5357	5491
Lag 6: Humidity	1.7	0.9-2.6			Lag 6: Humidity	1.7	0.8-2.5		
Lag 1: Rainfall	0.5	0.2-0.9			Lag 1: Rainfall	0.6	0.2-0.9		
Model 6					*Model 14*			5356	5491
Lag 5: Temperature	1.9	-1.8-5.7	5535	5490	Lag 6: Temperature	0.08	-3.8-3.9		
Lag 6: Humidity	1.7	0.9-2.5			Lag 6: Humidity	1.6	0.8-2.5		
Lag 4: Rainfall	-0.6	-1-(-0.2)			Lag 4: Rainfall	-0.6	-1-(-0.2)		
Model 7			5360	5495	*Model 15*			5360	5495
Lag 5: Temperature	0.4	-3.6-4.5			Lag 6: Temperature	-0.1	-4-3.8		
Lag 6: Humidity	1.7	0.9-2.5			Lag 6: Humidity	1.7	0.8-2.5		
Lag 5: Rainfall	-0.5	-0.9-(-0.05)			Lag 5: Rainfall	-0.5	-0.9-(-0.1)		
Model 8			5363	5497	*Model 16*				
Lag 5: Temperature	2.8	-1-6.7			Lag 6: Temperature	1	-3-5.2	5364	5499
Lag 6: Humidity	1.5	0.7-2.4			Lag 6: Humidity	1.5	0.6-2.3		
Lag 6: Rainfall	0.3	-0.04-0.7			Lag 5: Rainfall	0.3	-0.08-0.7		

*The best model has the lowest values of AIC and BIC

The models adjusted seasonal and long-term trends using a flexible spline function of time (6 D.F. per year) as well as day of a week.

Table 4. *The most-likely cluster of HFMD in Can Tho City, 2012-2014, setting 20% as the maximum cluster size*

Scan timeframe	**Cluster time**	**Cluster centre/radius**	**Annual Cases** (/100,000)	**LLR**	**RR**	**P**
1 Jan. 2012-31 Dec. 2012	30 Oct. 2012-28 Dec. 2012	(10.03^{o}N, 105.51^{o}E)/10.38 km	806.5	164.2	5.73	<0.01
	4 Jan. 2012-28 Feb. 2012	(10.21^{o}N, 105.58^{o}E)/9.91km	364.4	35.5	2.47	<0.01
1 Jan. 2013-31 Dec. 2013	6 Sept. 2013-23 Dec. 2013	(10.03^{o}N, 105.51^{o}E)/8.54 km	289.6	59.3	3.97	<0.01
	1 Jan. 2013-8 Jun. 2013	(10.03^{o}N, 105.7^{o}E)/4.97 km	139.1	17.6	1.87	<0.01
1 Jan. 2014-31 Dec. 2014	18 May. 2014-3 Nov. 2014	(10.02^{o}N, 105.6^{o}E)/9.60 km	178.1	36.5	2.32	<0.01
	15 Mar. 2014-9 Jun. 2014	(10.06^{o}N, 105.7^{o}E)/6.99 km	188.7	22.0	2.36	<0.01
	1 Jan. 2014-18 Jan. 2014	(9.99^{o}N, 105.5^{o}E)/8.81km	476.4	21	5.79	<0.01

LLR, Log likelihood ratio; RR, relative risk

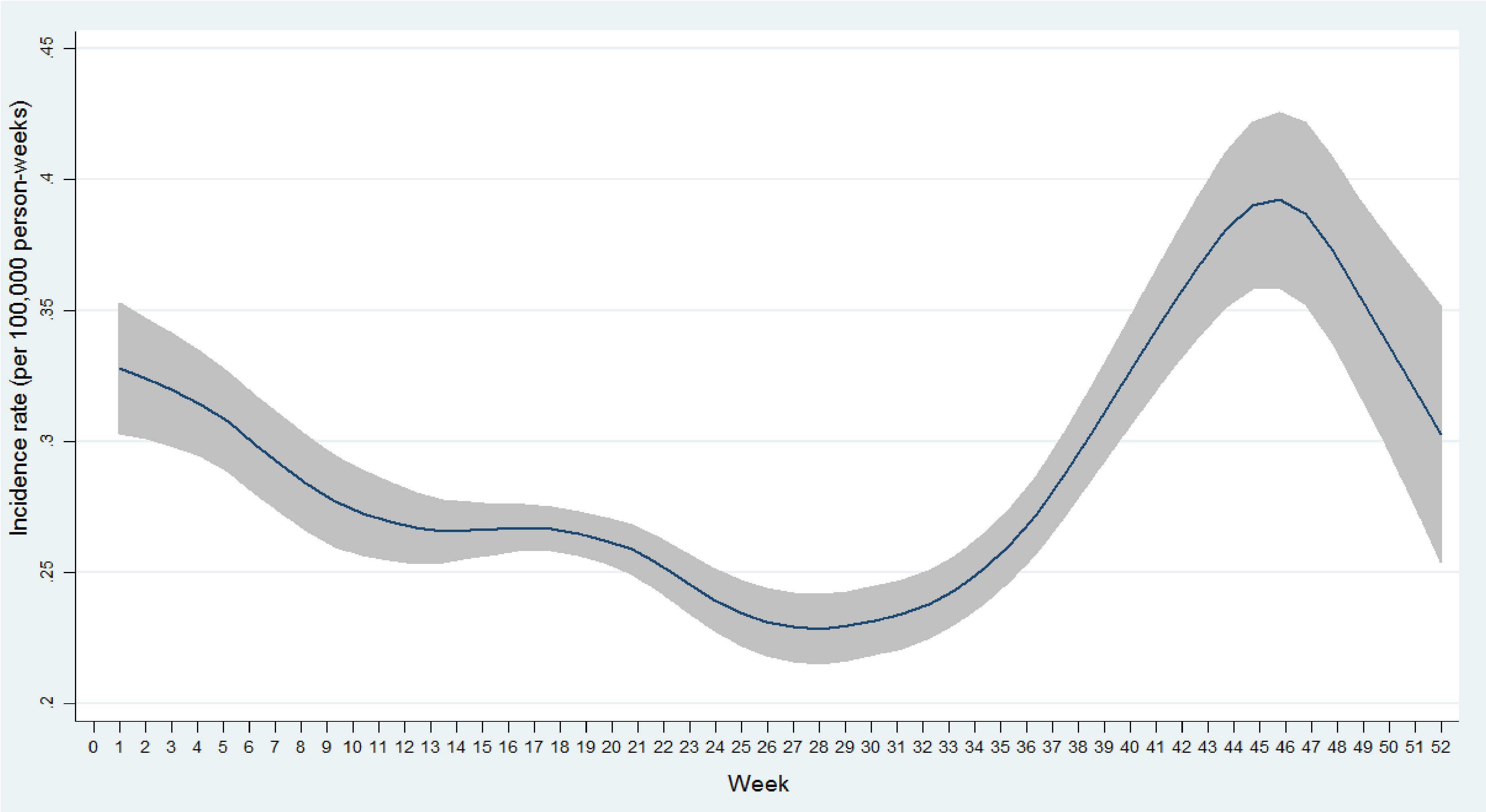

Figure 1. Temporal pattern of HFMD across 52 weeks of a year. Incidence rate (per 100,000 person-weeks) is predicted by Model 5 in Table 3 (lag-6 humidity, lag-5 temperature, and lag-1 cumulative rainfall)

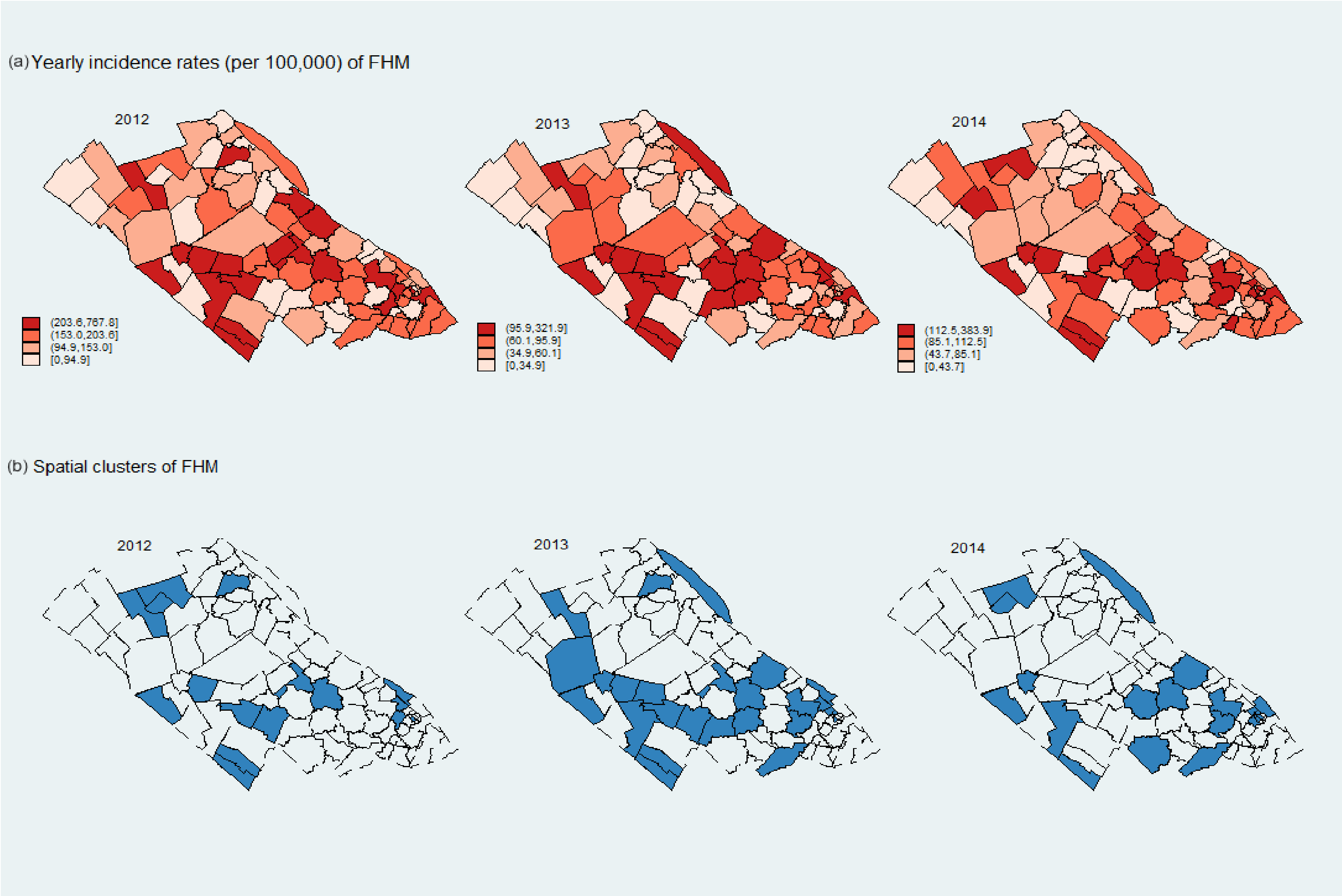

Figure 2. Incidence rate and spatial clusters of HFMD in Can Tho city, 2012-2014, setting 20% as the maximum cluster size