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Seasonality of Viral Encephalitis and Associated Environmental Risk Factors in Son La and Thai Binh Provinces in Vietnam from 2004 to 2013

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Abstract. In Vietnam, Japanese encephalitis virus accounts for 12–71% of viral encephalitis (VE) cases followed by enteroviruses and dengue virus among identified pathogens. This study is the first attempt to evaluate the seasonality of VE and associated environmental risk factors in two provinces from 2004 to 2013 using a seasonal trend-decomposition procedure based on loess regression and negative binomial regression models. We found seasonality with a peak of VE in August and June in Son La and Thai Binh, respectively. In Son La, the model showed that for every 1°C increase in average monthly temperature, there was a 4.0% increase in monthly VE incidence. There was a gradual decline in incidence rates as the relative humidity rose to its mean value (80%) and a dramatic rise in incidence rate as the relative humidity rose past 80%. Another model found that a 100 mm rise in precipitation in the preceding and same months corresponded to an increase in VE incidence of 23% and 21%, respectively. In Thai Binh, our model showed that a 1°C increase in temperature corresponded with a 9% increase in VE incidence. Another model found that VE incidence increased as monthly precipitation rose to its mean value of 130 mm but declined gradually as precipitation levels rose beyond that. The last model showed that a monthly increase in duration of sunshine of 1 hour corresponded to a 0.6% increase in VE incidence. The findings may assist clinicians by improving the evidence for diagnosis.

INTRODUCTION

Viral encephalitis (VE) is an acute, brain inflammation caused by viruses; it has a high morbidity and mortality in humans.[1–3] The estimated incidence rates for VE are between 3.5 and 7.4 per 100,000 persons per year.[4] Remarkably, even with the latest diagnostic technology, an agent is not identified in 70% of VE cases.[5] In the United States, about 2,000 cases occur annually and it is estimated that 90% of cases are caused by herpes simplex virus 1 (HSV-1) and 10% by HSV-2.[6,7] In a California study, only 16% of VE cases had probable etiologic agents identified, and HSV-1 was the most commonly detected agent in adult patients.[8]

In a United Kingdom study, 60% of 700 cases were of unknown etiology and herpes simplex encephalitis was assumed to account for most cases of known etiology.[9] On the other hand, in Asia (including Vietnam), Japanese encephalitis (JE) is a major cause of VE in children and young adults.[10–12] The causes of other VE cases are not well identified throughout Asia.[13] In many JE-endemic countries (including Vietnam), due to a lack of diagnostic facilities, VE cases are reported and considered as a proxy for JE surveillance.[11] In Vietnam, JE virus has been considered a leading cause of VE; among identified pathogens, it accounts for 12–71% of cases with enteroviruses and dengue virus being the next most important.[11,14,15] JE vaccine was introduced in 1997 and administered in Vietnam in 2007 through the national immunization program for children aged between 1 and 5 years.

JE is transmitted by mosquitoes and has been associated temporally with wet seasons and spatially with irrigated rice paddies.[16–18] In Vietnam, pigs are considered the most important amplifying hosts for transmission to humans because they are often raised close to humans.[19–21]

The highest incidence rates of VE have been reported in the northern and the Mekong River delta regions of Vietnam.[11] Son La and Thai Binh Provinces are located in the northern region of the country. Previous studies in southeast Asia and China have described seasonality and identified environmental risk factors of VE (including JE).[22–24] A study in China found that monthly temperature, rainfall, and humidity were positively associated with the occurrence of JE whereas air pressure was negatively correlated.[24]

However, to our knowledge, no studies have been conducted to evaluate the seasonality of VE and associated environmental risk factors in Vietnam. The main objective of this study was to assess the seasonal patterns and associated environmental risk factors of VE in Vietnam from 2004 to 2013. This assessment would provide information for VE management in Vietnam.

MATERIALS AND METHODS

Study area and data collection. Son La and Thai Binh Provinces have the highest incidence rates of VE and were thus selected for this study. Son La Province is located in northeastern Vietnam bordering Laos; it is among the five largest provinces and is characterized by rugged hills and mountains (Figure 1A). Thai Binh is a coastal northeastern province of Vietnam, situated about 110 km from Hanoi (Figure 1B). Son La and Thai Binh have total populations of 1.2 and 1.8 million and population densities of 82 and 1,139 people/km^2, respectively. In Son La, the annual temperature ranges from 10 to 38°C with an average of 21.4°C, whereas total monthly precipitation ranges from 10 to 450 mm. In Thai Binh, the annual temperature ranges from 4 to 38.1°C with an average of 23.5°C. Total monthly precipitation ranges from 1 to 718 mm.

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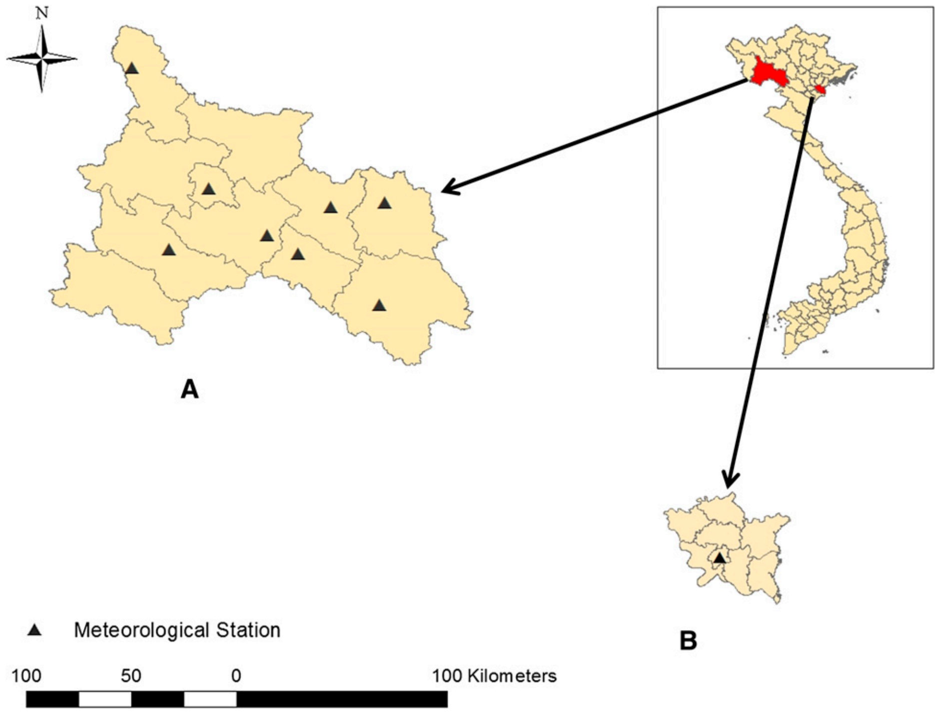

FIGURE 1. Map of the area with metrological stations in (**A**) Son La and (**B**) Thai Binh Provinces.

Under the national surveillance system of infectious diseases in Vietnam, VE is one of 28 diseases that the preventive medicine networks reported monthly. The case definition is a patient with fever (body temperature > 38°C), abnormal movements, seizures, change in mental status, and tremor, or spastic paralysis. Annually, provincial preventive medicine centers report to the regional preventive medicine institute, which in turn reports to the National Institute of Hygiene and Epidemiology, on the number of VE cases and deaths on a monthly basis at province level. We extracted data on VE cases from the annual book of communicable diseases published from 2004 to 2013; the data were then digitized in Microsoft Excel. In parallel, monthly meteorological data [total precipitation (mm), minimum/maximum/average temperature (°C), average relative humidity (%), and total duration of sunshine (hours)] for the same period were obtained from eight weather stations in Son La and one in Thai Binh (Figure 1). The collected meteorological data from eight stations were averaged and considered as representative of Son La Province for data analysis. For eight weather stations, annual temperature ranged from 19.1 to 23.6°C, precipitation from 102.9 to 150.8 mm, relative humidity from 79 to 86%, and duration of sunshine from 148.4 to 154.6 hours. Data on yearly human and pig populations were obtained from the General Statistics Office of Vietnam to calculate the monthly incidence rates ([cases/month × 100,000]/total human population) and pig population densities (per km^2) in the two provinces.[25] It was assumed that the human and pig populations were constant on a yearly basis for the period under study.

Data analysis. Monthly incidence rates (per 100,000) were calculated for the period under study. Seasonal trend-decomposition procedure based on loess regression (STL) was used to evaluate the seasonality of VE. This method decomposes a time series dataset into three parts: trend, seasonal, and remainder components on a 12-month basis.[26]

In addition, a seasonal cycle subseries plot and an unconditional negative binomial regression (NBR) model were used to evaluate the monthly variations.[26,27] In the seasonal cycle subseries plot, the horizontal line displays the average for each month from January to December, whereas the vertical line displays the individual pattern for the same months in each year. To statistically compare average monthly incidence rates, an unconditional NBR model was fit, with the number of cases as the outcome, month as the sole predictor (with January as the baseline), and the log of the population as an offset.

Several multivariable NBR models were used to investigate the association between VE and environmental variables. Although Poisson models are frequently used for the analysis of count data, monthly counts of cases showed evidence of overdispersion (variance greater than the mean) so NBR models that incorporated an overdispersion term (alpha [α]) were preferred to Poisson models.[28,29] A likelihood ratio test confirmed that α was not zero and the NBR is more appropriate than the Poisson model ($P < 0.001$).

In addition to the environmental values recorded in the month in which the VE cases were counted, values from the preceding month (one lag) were also obtained. For the variable screening, the linearity of effect of environmental variables on VE incidence was investigated using loess smoothed curves. If there was evidence of nonlinearity, a quadratic function of the predictor was evaluated and retained if $P < 0.05$. The quadratic terms for relative humidity and precipitation were included for Son La and Thai Binh, respectively, since the effects were not linear.

Correlations among all predictors were investigated and preceding month values also considered in models if collinearity was less than 0.70. Because of the strong correlations between total monthly temperature and precipitation or duration of sunshine in each province, we developed two and three models for Son La and Thai Binh, respectively—one including temperature along with other variables and one with precipitation replacing temperature. For Thai Binh, an additional model with duration of sunshine and other variables (excluding temperature) was developed.

A random effect for year was included to account for unmeasured yearly predictor in the model. Variables with $P < 0.05$ were considered to be significant in the final models. The results for the NBR were expressed as incidence rate ratio and 95% confidence interval (CI). All data were entered into Microsoft Excel 2010 and analyzed using R version 3.2.2 and STATA version 14.0 (StataCorp, College Station, TX). ArcGIS version 10.3 ArcMap (ESRI, Redlands, CA) was used to create the map (Figure 1). This study was approved by the Hanoi Medical University Institutional Review Board (HMU IRB: no. 00003121), Vietnam.

RESULTS

Son La province. A total of 1,133 cases were reported between January 1, 2004 and December 31, 2013. The annual incidence rate was highest in 2009 (22.42 per 100,000; 95% CI: 22.34–22.50), whereas the lowest rate (5.71 per 100,000; 95% CI: 5.67–5.75) was reported in 2013 (data not shown). Monthly incidence rates (per 100,000) (Figure 2A) showed cyclic peaks between July and September in most years with relatively higher incidence rates between March 2008 and March 2010.

The STL plot (Figure 3A) showed the seasonal patterns with a strong peak in the middle of each year (July–August) and a smaller peak in March (Figure 3A: second plot). The trend plot indicated mild fluctuations until 2008 and dramatically increasing incidence between 2008 and 2010 (Figure 3A: first plot). The remainder component showed varying residuals with intermittently large values. The seasonal cycle subseries plot (Figure 4A) confirmed the patterns noted above and showed that the lowest incidence rates were in February.

An unconditional NBR model (Table 1) showed that, compared with January, there were significantly higher occurrences of diseases in March and June through November, whereas February, April, May, and December were not statistically significantly different from January.

The two models were developed to avoid collinearity issues between temperature and precipitation ($r = 0.72$, $P < 0.001$, Table 2). The NBR model predicted that for a 1°C increase in temperature, we expect a 4.0% increase in monthly VE incidence rate (Table 3). In addition, there was a gradual decline in incidence rate as the average relative humidity rose to its mean value (80%), and a dramatic rise in incidence rate as relative humidity rose

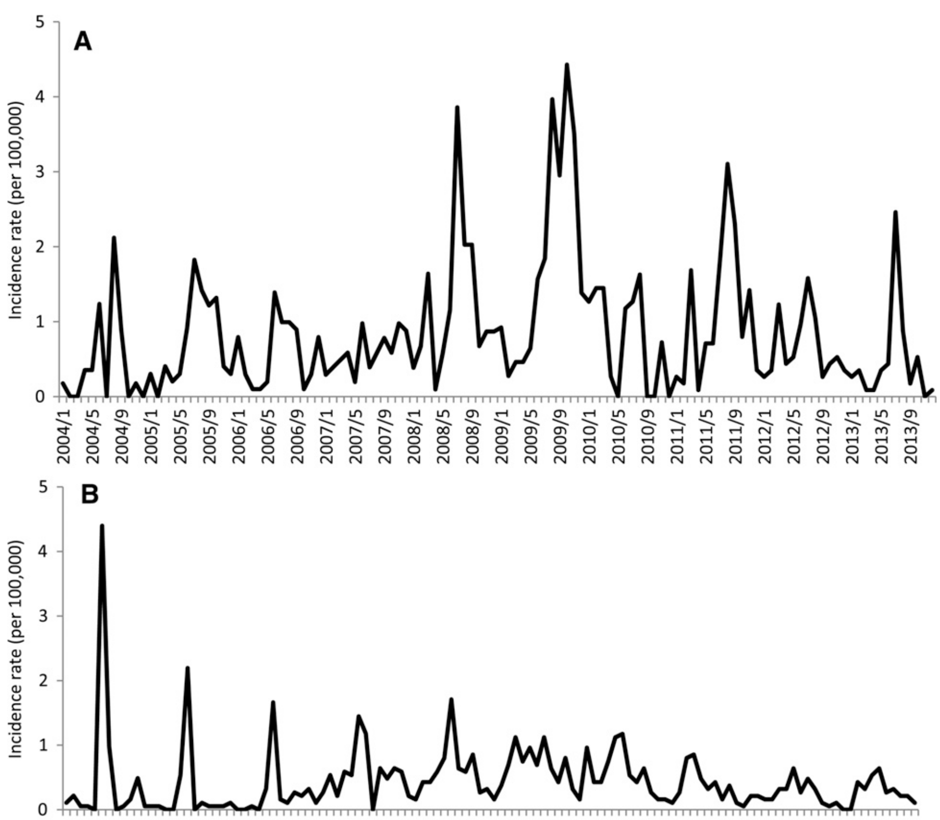

FIGURE 2. Monthly incidence rates of viral encephalitis in (**A**) Son La and (**B**) Thai Binh Provinces from 2004 to 2013.

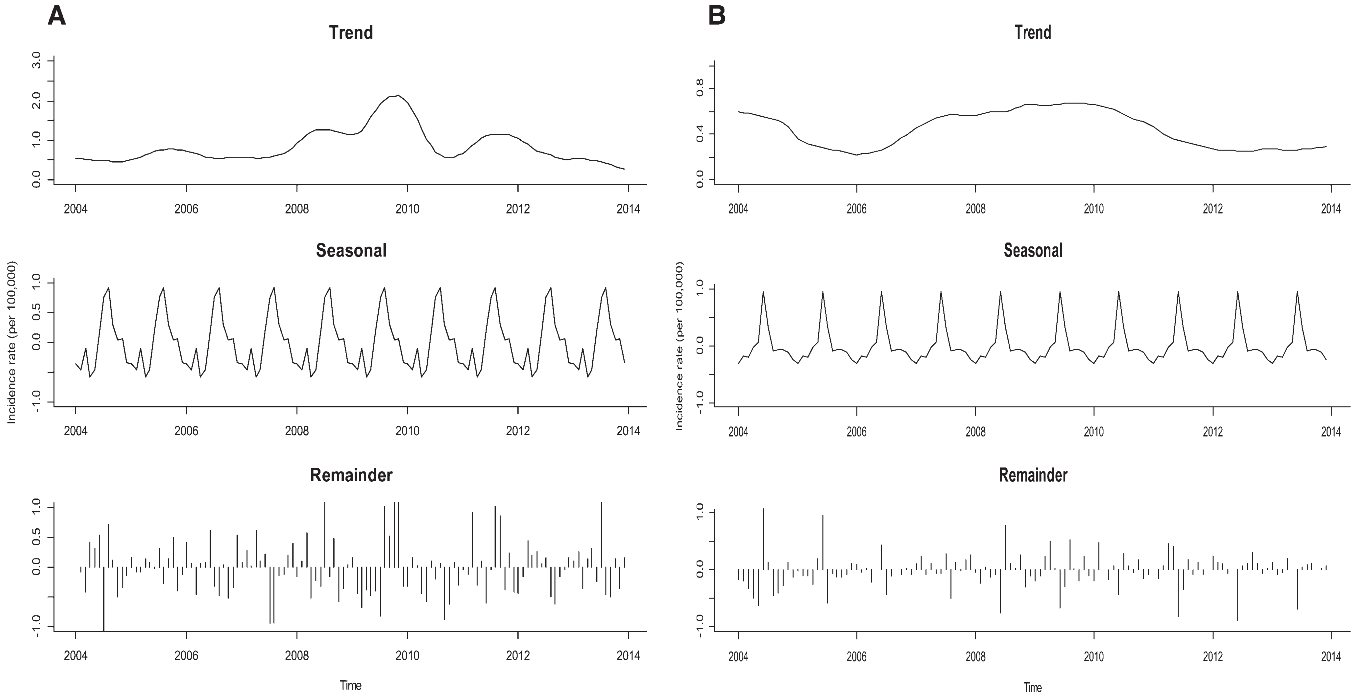

FIGURE 3. Seasonal trend decomposition of the monthly incidence rates of viral encephalitis in (**A**) Son La and (**B**) Thai Binh Provinces from 2004 to 2013.

past 80%. The preceding month temperature and relative humidity were not significant in the model. Another NBR model showed that a 100 mm increase in precipitation in the preceding and same months corresponded to a 23% and 21% increase, respectively, in monthly incidence rate of VE. Neither of the models found that pig density was significantly associated with VE incidence rate.

Thai Binh province. A total of 1,487 VE cases were reported from January 1, 2004 to December 31, 2013. The annual incidence rate was highest in 2009 (8.46 per 100,000; 95% CI: 8.42–8.50), whereas the lowest rate was in 2006 (3.11 per 100,000; 95% CI: 3.09–3.14). Monthly incidence rates (per 100,000) showed some cyclic peaks while the highest value was detected in June 2004 (Figure 2B). The trend plot showed minimal fluctuation with an apparent overall increase and decrease between 2007 and 2012 (Figure 3B: first plot), whereas the STL plot had one peak with a seasonal pattern (Figure 3B: second plot). In the remainder component, large residuals were observed throughout the period under study.

The seasonal cycle subseries plot showed that the average incidence rate was highest in June and lowest in January

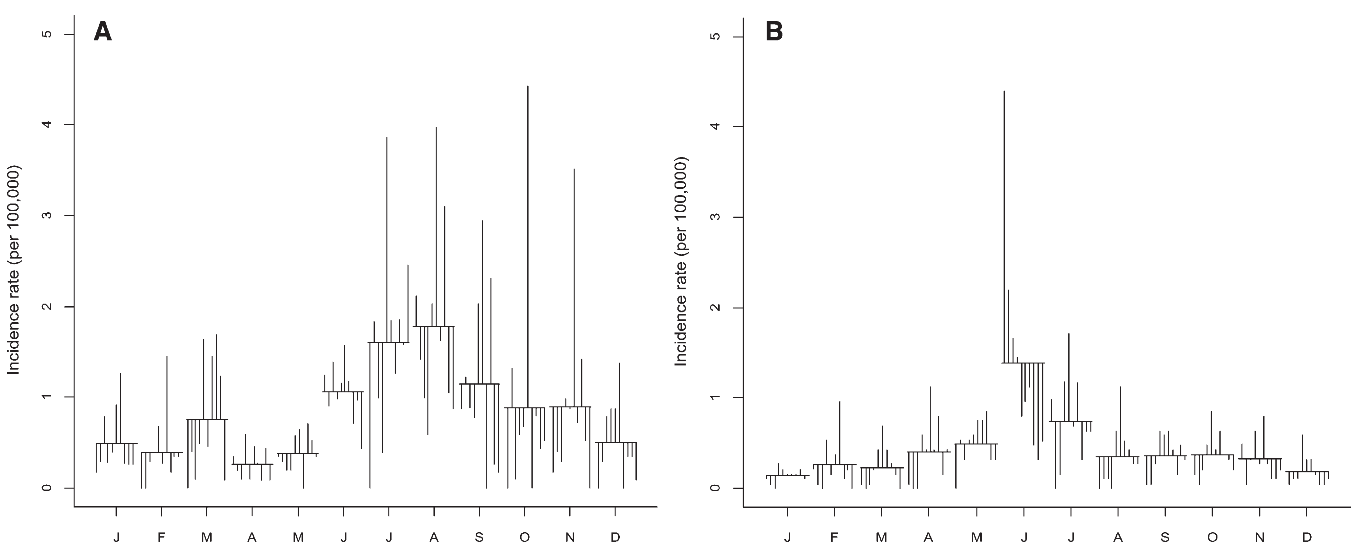

FIGURE 4. Seasonal cycle subseries plot of the monthly incidence rates of viral encephalitis in (**A**) Son La and (**B**) Thai Binh Provinces from 2004 to 2013.

Table 1
Unconditional negative binomial regression results for the viral encephalitis incidence rates by month with IRR and 95% CI.

Month	IRR: Son La	IRR: Thai Binh
January	Reference: 1	Reference: 1
February	0.80 (0.54–1.19)	1.81 (1.13–2.90)*
March	1.62 (1.16–2.27)*	1.59 (0.98–2.58)
April	0.54 (0.34–0.83)	2.78 (1.79–4.31)*
May	0.84 (0.57–1.24)	3.44 (2.24–5.29)*
June	2.05 (1.49–2.83)*	9.59 (6.45–14.26)*
July	3.29 (2.44–4.43)*	5.19 (3.43–7.82)*
August	3.25 (2.41–4.38)*	2.41 (1.54–3.77)*
September	2.18 (1.59–2.99)*	2.52 (1.62–3.93)*
October	1.88 (1.36–2.59)*	2.59 (1.66–4.04)*
November	1.82 (1.31–2.52)*	2.26 (1.44–3.55)*
December	0.96 (0.66–1.40)	1.30 (0.78–2.14)

CI = confidence interval; IRR = incidence rate ratio.
*Statistically significant at $P < 0.05$.

(Figure 4B). The unconditional NBR showed that, compared with January, VE incidence was significantly higher in February and April through November, but not statistically significantly different from that in March or December.

The three models were explored to avoid collinearity among temperature, precipitation, and duration of sunshine ($r = 0.589$, $P < 0.001$ and $r = 0.788$, $P < 0.001$; Table 2). The NBR model showed that a 1°C increase in temperature in the same month corresponded to a 9% increase in VE incidence rate, whereas temperature in the preceding month was not significant (Table 3). Another NBR model predicted that VE incidence rate increased as monthly precipitation rose to its mean value of 130 mm but declined gradually as precipitation levels rose beyond that. The last model showed that a 1-hour increase in duration of sunshine corresponded to a 0.6% increase in VE incidence rate. Precipitation and duration of sunshine in the preceding months were not significant in the models. None of the models showed that pig density was significantly associated with VE incidence rate.

DISCUSSION

This study evaluated the association of VE and seasonal and environmental factors in two provinces of Vietnam, Son La and Thai Binh, from 2004 to 2013. We found seasonality with a peak of VE in August in Son La and June in Thai Binh, coinciding with the rainy summer season. Meteorological factors (temperature, humidity, and precipitation) were significantly associated with VE in the more mountainous Son La Province, whereas temperature, precipitation, and duration of sunshine were associated with increased risk of VE in coastal Thai Binh. High temperature, precipitation, humidity, and duration of sunshine provide favorable conditions for breeding of mosquitoes that transmit JE virus and this may explain our results.[30–32]

For Son La, we found that the incidence rate of VE declined when the relative humidity was below 80%; above this level, the incidence rate began to increase, producing a U-shaped curve. In addition, VE incidence rate had a significant relationship with the level of precipitation in the preceding month, which might be a potential predictor in that region in an early warning system to prevent the spread of disease. For Thai Binh, VE incidence rate increased when the level of precipitation was below 130 mm then gradually decreased at precipitation levels higher than 130 mm, resulting in a reverse U-shaped curve. It is possible that heavy rains or typhoons may wash away mosquito larvae, thereby reducing the mosquito population.[33,34] Both provinces are affected by typhoons annually; the wet season is between May and October. Thai Binh is more prone to floods and heavy rainfall (Vietnam Meteorological Agency) and we found that average precipitation here was approximately 150 mm (maximum 300 mm) higher than in Son La. In addition, JE cases were positively correlated with duration of sunshine in other studies, which was consistent with our result.[29,35]

We were not able to identify the main causes of VE in contrast to previous studies.[11,14,15] However, it is likely that

Table 2
Pearson's correlation coefficient (r) among environmental variables with lag 1 in Son La and Thai Binh Provinces, 2004–2013

Province/variable	Monthly temperature (°C)	Monthly temperature (°C) (lag 1)	Monthly precipitation (100 mm)	Monthly precipitation (100 mm) (lag 1)	Monthly humidity (%)	Monthly humidity (%) (lag 1)	Monthly sunshine (hour)	Monthly sunshine (hour) (lag 1)	Pig density (per km^2)
Son La									
Temperature	1.000								
Temperature (lag 1)	0.782	1.000							
Precipitation	0.724	0.651	1.000						
Precipitation (lag 1)	0.648	0.730	0.687	1.000					
Humidity	0.405	0.561	0.472	0.553	1.000				
Humidity (lag 1)	0.148	0.401	0.129	0.467	0.720	1.000			
Sunshine	0.515	0.360	0.155	0.169	0.109	0.178	1.000		
Sunshine (lag 1)	0.323	0.532	0.156	0.159	0.268	0.101	0.1213	1.000	
Pig density (per km^2)	−0.134	−0.1271	−0.046	−0.051	−0.3748	−0.366	−0.160	−0.147	1.000
Thai Binh									
Temperature	1.000								
Temperature (lag 1)	0.803	1.000							
Precipitation	0.586	0.639	1.000						
Precipitation (lag 1)	0.411	0.587	0.402	1.000					
Humidity	0.071	−0.236	0.099	−0.075	1.000				
Humidity (lag 1)	0.250	0.051	0.007	0.090	0.339	1.000			
Sunshine	0.788	0.751	0.434	0.329	−0.165	0.110	1.000		
Sunshine (lag 1)	0.587	0.819	0.530	0.448	−0.288	−0.158	0.574	1.000	
Pig density	−0.003	0.002	0.088	0.082	0.331	0.023	−0.033	0.027	1.000

lag 1 = preceding month.

TABLE 3
Final NBR models with associated risk factors of viral encephalitis incidence rates in Son La and Thai Binh Provinces, 2004–2013.

Province/variable	Adjusted IRRs	95% CI	*P* value
Son La Province			
NBR 1			
Monthly average temperature (°C)	1.04	1.00–1.08	0.043
Monthly average humidity (%)	1.07	1.03–1.10	0.001
Monthly average humidity (%) (quadratic term)	1.01	1.00–1.01	0.002
NBR 2			
Monthly total precipitation (100 mm) in the preceding month	1.23	1.06–1.41	0.005
Monthly total precipitation (100 mm) in the same month	1.21	1.04–1.41	0.013
Thai Binh Province			
NBR 1			
Monthly average temperature (°C)	1.12	1.08–1.16	< 0.001
NBR 2			
Monthly total precipitation (100 mm)	1.14	1.00–.29	0.043
Monthly total precipitation (100 mm) (quadratic term)	0.90	0.83–0.98	0.011
NBR 3			
Monthly during of sunshine (hour)	1.006	1.003–1.008	< 0.001

CI = confidence interval; IRR = incidence rate ratio; NBR = negative binomial regression.

JE is the most important cause of VE in Vietnam among identified pathogens. This is based on recent studies conducted in 2004 and from 1996 to 2008 in southern Vietnam, and others from 1998 to 2007 across the country.[11,14,15] Pigs act as important amplifying hosts of the JE virus because they have high viral load viremias that infect mosquito vectors.[36] However, we were not able to identify an association between VE and pig density in either province. Possible explanations are that JE was mainly acquired from other hosts (such as water birds) or JE was not a leading cause of VE in the two provinces.

Another study in Vietnam demonstrated seasonality and identified climate risk factors for dengue fever (also mosquito transmitted); disease peaks were seen between June and November.[37,38] In addition, seasonality of enteroviruses with peaks during summer has been described in Korea, Taiwan, and the United States.[39–41] The Taiwan study found that enterovirus infection was significantly associated with increasing temperature and humidity, which was consistent with our study.

Therefore, from a preventive point of view, it is crucial to increase public awareness between June and September. For vector-borne diseases (such as JE and dengue), public awareness campaigns should address the following: vaccination against JE and dengue (commercially available in some countries); protection by wearing long-sleeved shirts, long pants, and hats; and sleeping under a mosquito net. In parallel, it is important to eliminate mosquito larval habitats such as standing water and swamps and to kill adult mosquitoes by insecticides or other means.[40] Human enteroviruses are transmitted from person to person via direct contact with saliva, mucus, fluid from blisters, or stools of infected people.[41] To prevent the disease, it is very important to raise public awareness between June and November on good personal hygiene including frequent hand washing with soap.[42] At present, EV71 vaccine is available in some Asian countries, but it is not approved in Vietnam.

This study had several limitations. First, due to lack of medical facilities in rural communities and lack of capacity in the health system, VE cases are less likely to be reported in rural areas; also, due to diagnostic limitations, not all clinical cases are confirmed. It is recommended that an independent surveillance system for subclinical diseases at district/provincial level be established. Second, climate data may not be representative of the entire area for which diseases were reported. In particular, for Son La Province, climate variations may be high due to the hilly terrain. Third, we only evaluated the impact of climate conditions and pig density; other factors (environmental and socioeconomic) should not be overlooked. Further studies will be needed to investigate more deeply the relationship between risk factors and each disease (JE, dengue, and enterovirus infection) identified among VE cases through laboratory confirmation at provincial/regional level. Fourth, JE vaccine was introduced in 1997 and administered in Vietnam in 2007 through the national immunization program for children aged between 1 and 5 years. Multiple vaccine doses are required for prevention, but one study demonstrated that only 19.5% of VE child patients had received at least one dose of JE vaccine, perhaps because of high costs.[1] However, it is difficult to determine whether the JE national vaccination program has reduced the number of JE cases since the national surveillance program does not collect information on age, gender, and vaccination records. Finally, we assumed that human population was constant on a yearly basis, whereas not accurate, this was considered to result in a nondifferential bias because the relatively large denominators had minimal impact on monthly incidence rate. The mean incidence rates (horizontal line) of seasonal cycle subseries plots could be influenced by large values, but these were easily identified by plotted vertical lines.

This study provides valuable information for determining the temporal pattern of VE. It is the first to attempt to investigate seasonality of VE and environmental risk factors in Vietnam. The findings may assist clinicians by providing information on seasonality and can inform public health policy that interfaces with livestock development as well as agricultural and environmental policy.

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