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Spatiotemporal variation of hand-foot-mouth disease in relation to socioecological factors: A multiple-province analysis in Vietnam

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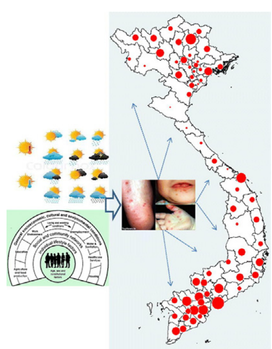
HIGHLIGHTS

- There are significant effects of breastfeeding, house condition, safe water on HFMD.
- There are significant effects of temperatures and humidity on variation of HFMD.
- Findings reflect important implications for climate change adaptation in Vietnam.
- HFMD weather-based early warning systems should be considered.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Hand-foot-and-mouth disease (HFMD) is a significant public health issue in Asia-pacific countries. Numerous studies have examined the relationship between socio-ecological factors and HFMD however the research findings were inconsistent. This study examined the association between socio-ecologic factors and HFMD in multiple provinces across Vietnam.
Methods: We applied a spatial autoregressive model using a Bayesian framework to examine the relationship between HFMD and socio-demographic factors. We used a Generalized Linear Model (GLD) with Poisson family to examine the province-specific association between monthly HFMD and climatic factors while controlling for spatial lag, seasonality and long-term trend of HFMD. Then, we used a random-effect meta-analysis to generate pooled effect size of climate-HFMD association for regional and country scale.
Results: One percent increase in newborn breastfed within 1 h of birth, households with permanent houses, and households accessed to safe water resulted in 1.57% (95% CI: −2.25, −0.93), 0.96% (−1.66, −0.23), and 1.13% (−2.16, −0.18) reduction in HFMD incidence, respectively. At the country-level, HFMD increased 7% (RR: 1.07; 95%CI: 1.052–1.088) and 3.1% (RR: 1.031, 95%CI: 1.024–1.039) for 1 °C increase in monthly temperature above 26 °C and 1% increase in monthly humidity above 76%. Whereas, HFMD decreased 3.1% associated with 1 mm increase in monthly cumulative rainfalls. The climate-HFMD relationship was varied by regions and provinces across the country.
Conclusions: The findings reflect an important implication for the climate change adaptation strategies and

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public-health decision, of which development of weather-based early warning systems should be considered to strengthen communicable disease prevention system.

1. Introduction

Hand, foot and mouth disease (HFMD), which is principally caused by Enterovirus and predominantly occurs in children < 5 year-olds, is now considered a significant public health challenge worldwide (Lee et al., 2009; Solomon et al., 2010; Cardosa et al., 2003; Sander et al., 2006). The clinical symptoms of HFMD are from minor febrile illness and rashes to severe central nervous system complications and even fatal cardiopulmonary failure (World Health Organization, 2011; Sabanathan et al., 2014). A number of HFMD outbreaks accompanied with high rates of severe and fatal cases have been reported in countries of Asia-pacific region (Chan et al., 2003; Tu et al., 2007; Zhang et al., 2010). Many epidemiological studies have been conducted to identify the potential mechanism of environmental factors in triggering the onset of HFMD in recent years (Chen et al., 2007; Ma et al., 2010; Ang et al., 2009; Nguyen et al., 2014a). Some studies indicated that seasonal variation of HFMD occurrence was sensitive to climatic factors, comprising rainfall (Xing et al., 2014; Wang et al., 2011a; Wang et al., 2011b), wind speed (Wang et al., 2011a; Bo et al., 2014), relative humidity (Wang et al., 2011a; Hu et al., 2012), temperature (Wang et al., 2011a; Wang et al., 2011b; Bo et al., 2014; Hu et al., 2012), air pressure (Xing et al., 2014; Wang et al., 2011b), and the sunshine (Xing et al., 2014). However, the relationship patterns of climate-HFMD are inconsistent from the previous studies. For instance, while significant associations between average temperatures or humidity and HFMD have reported from numerous studies (Onozuka and Hashizume, 2011; Xu et al., 2015; Yang et al., 2015; Liu et al., 2015a; Wei et al., 2015), these associations were found not significant or negative in elsewhere (Liu et al., 2015b; Urashima et al., 2003). The inconsistency in existing findings across regions may be attributed to the diversity in weather conditions, demographic characteristics and hygiene conditions in different geographical regions (Zhao et al., 2017), and these results also implies that location-specific variables such as socioecological factors might play a modification role in the association between climatic factors, especially temperature, and HFMD variation (Xiao et al., 2017). Moreover, the majority of previous studies was conducted in a single or a small group of locations and did not take into account of spatial heterogeneous relationships. Up-to-date, there is only one paper recently published by Xiao et al. (2017) examined the heterogeneity of temperature-HFMD relationship from multicity at a big scale study in mainland China. Given the non-uniform effects of climatic factors on HFMD incidence, the findings from this study might not be completely representative for other regional and less developed countries in the Asia-pacific region.

Vietnam, a tropical and less developed country, is one of the countries in Asia-pacific region mostly vulnerable to climate change related hazards such as flooding, extreme temperatures, and sea level rise (Yusuf and Francisco, 2009). For example, the annual average temperature in Vietnam is predicted to increase from 1.1–1.9 °C to 2.1–3.6 °C by the end of the 21st century (Monhaz, 2010), and temperature of over 40 °C have been reported in the majority of areas in Vietnam recently (Yang et al., 2012). The previous studies indicated that the extreme weathers associated with an increase in the risk of water- and vector-borne infectious diseases (Phung et al., 2015a; Phung et al., 2016; Phung et al., 2014; Phung et al., 2015b). HFMD, which is considered as a notifiable communicable disease in the disease surveillance system, has been reported as an epidemic disease recently in Vietnam. There was a peak of >150,000 cases recorded in 2012 and then the incidence remained high in the following years (WPRO, 2016). The previous studies in HFMD in Vietnam mainly focused on the viral, clinical and epidemiological characteristics of HFMD cases (Khanh et al., 2012; Tan et al., 2015; Thao et al., 2010; Nguyen et al., 2014b) but there is lacking evidence on the relationship between socioecological factors and HFMD variation. To the best of our knowledge, there is only one study conducted by Nguyen et al. (2017) to investigate climate-HFMD relationship. However, this study was conducted in a single city in the Mekong Delta region which might not reflect the spatial variation of climate-HFMD association in different ecological regions across Vietnam.

This study aims to examine the spatiotemporal relationship between socio-ecological factors, comprising socio-demographic and climatic factors, and the variation of HFMD incidence in multiple provinces across Vietnam.

2. Methods

2.1. Data collection

Monthly counts of reported clinical HFMD across 63 provinces between June 2011 and December 2014 were obtained from the disease surveillance report of the Division of Infectious Disease Control (DIDC), General Department of Preventive Medicine (GDPM), Vietnam Ministry of Health (MOH). A clinical HFMD case is characterized by a brief febrile illness in a patient with popular or vesicular rashes on hands, feet, mouth or buttocks, knees or elbows, especially in younger children and infants (WHO, 2011). According to the Law on Prevention and Control of Infectious Disease (LPCID), HFMD is one of 28 notifiable communicable diseases for which physicians in hospitals and clinics must report to the local health authorities (i.e. commune health clinic). The local health authorities must then report these cases to the next level of health agencies (i.e. district and provincial preventive medicine) within 24 h. Finally, provincial preventive medicine centres will analyse the reported data (i.e. weekly counts of HFMD) to report to GDMP that is the leading agency responsible for infectious disease control entire the country (Yamamura and Amachi, 2014; Ministry of Health, 2015). Therefore, it is believed that the monthly counts of diarrhoea are consistent and representative for the provinces/cities over the study period.

Daily meteorological data (ambient temperature and humidity) were obtained from the provincial hydro-meteorological stations or from the closest airport weather stations from 1st January 2000 to 31st December 2015, and then these daily data were collapsed into monthly average values for data analysis. The provincial/city populations were obtained from Vietnam General Statistics Office (GSO, 2010) and Health Statistic Yearbook (ATSDR, 2007).

Besides the meteorological factors, which have been illustrated to be associated with HFMD incidence from previous studies (e.g. (Huang et al., 2013; Nguyen et al., 2017)., the socio-demographic and health characteristic factors were selected based on two justifications. The factors are revealed to be associated with oral-transmission communicable diseases including HFMD (e.g. population density, income, households accessed to safe water, etc.), and the data of the factors are available in published data sources. We collect data on socio-demographic and health characteristics for each of 63 provinces from the Health Statistic Year Book (HSY, 2013), Statistic Year Book of Vietnam (SYV, 2014), and the National Census (GSO, 2009). The indicators included: population density (persons/km^2), monthly average income per capita (*1000 VND), communes in each province reached national criteria for a commune health (%), newborn breastfed within 1 h of birth (%), number of kindergarten schools, households have permanent houses (%), number of livestock farms, households accessed to safe water (%), and households accessed to hygiene toilets (%).

2.2. Data analysis

Three steps involve in data analysis. First, we applied a spatial autoregressive model using the Bayesian framework to examine the relationship between HFMD and socio-demographic and health factors (Eq. (1)), in which we created a spatial-weighting matrix and generated a spatial lag that is a weighted average of observations on the HFMD variable over neighbouring units. The spatial lag was then inputted into the model to adjust for the spatial variation of HFMD while evaluating the influence of multiple socio-demographic variables on the distribution of HFMD incidences. For the Bayesian framework, we used non-informative prior with mean zero and variance δ^2 for all examined parameters. We run an initial burn-in of 2500 iterations as the default. Convergence was assessed by visual inspection of posterior density plots, autocorrelation of selected parameters, efficiency and acceptance rate. The local Moran's I statistic to examine the potential spatial clusters of HFMD across the country.

$$y_i = \gamma \sum_{j=1}^{n} w_{ij} y_j + S_i + \varepsilon_i \quad (1)$$

where, y_i denotes the incidence rate of HFMD (/per person-year) in Province I; $\sum_{j=1}^{n} w_{ij} y_j$ is a spatial lag, and the w_{ij} are the spatial weights; S_i is socio-demographic values in Province I; and ε_i is a disturbance term. We calculated incidence rate for each province using the formula below:

$$\text{Total incidence cases from 2011 to 2014}/\\(\text{average population from 2011 to 2014} * 4 \text{ years})$$

Second, a Generalized Linear Model (GLD) with Poisson family was used to examine the province-specific association between monthly count of HFMD and monthly average temperatures, relative humidity and rainfall while controlling for spatial lag of HFMD, seasonality and long-term trend using a spline function of time with 3° of freedom for each province (Eq. (2)). We used one-month lag data to examine the relationship between meteorological factors and HFMD for 2 reasons. First, The previous study (Huang et al., 2013) indicated that hand, foot, and mouth (HFMD) are better explained when meteorological variables are used with week lag because it probably matches the incubation period of enteroviruses and the potential delay in parental awareness of and response to clinical symptoms of children. Second, the availability of HFMD monthly data collected from the surveillance system was monthly only. Temperature and humidity were centred at the mean value of each ecological region where provinces locate in

$$Y_t \sim Poisson(\mu_t)$$

$$Ln(\mu_t) = \alpha + \beta_1 T_t + \beta_2 H_t + \beta_3 R_t + s(time) \quad (2)$$

where, Y_t is the monthly count of HFMD on month t; α is the intercept; T_t is the monthly temperature on month t; H_t is the monthly humidity; and R_t is monthly cumulative rainfall; s is the natural cubic spline function of time with 3° of freedom for each province.

Finally, a random-effect meta-analysis was applied to compute within- and between-province variation and generate pooled effect size (relative risk, RR) for the country- and regional-level effect of climatic factors on HFMD variation. The ecological regions used for regional effect comprise North-East, North-West, Red River Delta, North-Central Coast, South-Central Coast, South-East, Mekong Delta, and Highland region. Heterogeneity between provinces was quantified by the coefficient of inconsistency (*I-squared*) which describes the percentage of total variation across provinces that are due to heterogeneity (Higgins et al., 2003).

3. Results

A total number of 418,546 cases of hand-foot-and-mouth disease (HFMD) were reported over 42 months (from June 2011 to December 2014) from 63 provinces across Vietnam. The average monthly counts of HFMD was 9734 cases (Sd: 5073), of which the Southern areas had a significantly higher number of cases (monthly mean: 7391 cases) than the Northern areas (monthly mean: 2344 cases). Among eight ecological regions, the Mekong Delta region contributed the biggest proportion of the total HFMD cases with a monthly average of 3269 cases (Sd: 1839), and the Noth-West region contributed the least proportion of HFMD (monthly mean: 205; Sd: 191) (Table 1). The monthly temperatures during the study period ranged from 19.9 °C to 29.7 °C (mean: 26.0; Sd: 3.2). The monthly relative humidity ranged from 70.7% to 83.6% (mean: 76.9; Sd: 2.9) while the average monthly cumulative rainfall ranged from 0.06 to 6.3 mm (mean: 2.37; Sd: 1.87). In terms of socio-economic factors, the population density ranged from 45 to 3731 people per km^2 across the provinces/cities, and the monthly average income per capita ranged from 50 to 250 USD (mean: 114 USD; Sd: 39.8 USD). Percents of communes reached to national criteria for commune health in each province were from 3.8 to 96.6% (mean: 39.6%; Sd: 21.4%), and the percents of newborn breastfed within 1 h of birth were from 43.5 to 100% (mean: 83.9; Sd: 12.9%). The households which had permanent houses proportioned from 3.1 to 98.4% (mean: 43.7%; Sd: 33.4%). The number of kindergarten schools and sanitation factors such as a number of livestock farms, % of households accessed to safe water, and % of household accessed to hygienic toilets which may influence on the transmission of HFMD is also reported in Table 1.

The spatiotemporal patterns of HFMD were presented in Figs. 1 and 2. The incidence rates of HFMD varied across the country and ranged from 15 to 528 cases per 100,000 person-years (mean: 142, Sd: 106). In overall, the provinces with higher incidence rates were seen more spatially frequent in the South-East (mean: 247, Sd: 157), Mekong Delta (mean: 230, Sd: 94), South Central Coast (mean: 148, Sd: 71), and Red River Delta (mean: 112, Sd: 80) in comparison with the rest of regions (Fig. 2A). The results of Local Moran's I indicated that two significant high-high risk clusters of HFMD, where the provinces with high incidences of HFMD were clustered, were found in the Mekong Delta (Long An, Dong Thap, and Vinh Long Province) and the South-East (Dong Nai, and Vung Tau Province); whereas, a nearby low-high risk cluster, where the low-incidence provinces neighboured with high-incidence provinces, was found in the South-East region (Binh Thuan province). A high-low risk cluster, where high-incidence provinces neighboured with low-incidence provinces, was identified in Da Nang city in the start-point of South Central Coast. In the contrary to the south, two low-low risk clusters of HFMD, where low-incidence provinces were clustered, was found in North Central Coast (Ha Tinh Province) and Red River Delta (Ha Noi City) (Fig. 2B). In terms of the temporal pattern of HFMD, a likely two-peak seasonal pattern was observed in most of the regions except the Mekong Delta (Fig. 1). One peak was seen in the middle of the cold for the North (November to April) and the wet season for the South (October to April), and the other peak was found in the middle or late in the hot season for the North (May to October) and the dry season for the South (May to October); whereas, the longer-distance peak (once a year) was observed in the Mekong Delta. The temporal down-trend of HFMD was observed in all the regions and the entire country, especially from the middle of the year 2013.

The association between the variation of HFMD incidence and socio-demographic factors were found statistically significant with three indicators. One percent increase in newborn breastfed within 1 h of birth, households with permanent houses, and households accessed to safe water resulted in 1.57% (95% CI: −2.25, −0.93), 0.96% (−1.66, −0.23), and 1.13% (−2.16, −0.18) reduction in HFMD incidence rates, respectively. All other indicators listed in Methods section were none statistically significant associated with HFMD incidence rates

Table 1
Descriptive statistics of hand-foot-mouth diseases and socio-ecological factors.

Variable	Minimum	25th	50th	Mean (Sd)	75th	Maximum
Hand-foot-mouth cases (average monthly counts)						
Entire country	3107	6035	7757	9734 (5073)	13,237	23,763
Mekong Delta	1529	1994	2582	3269 (1839)	3897	9195
Red River Delta	58	383	698	1022 (908)	1681	3726
North East	56	285	520	711 (717)	982	3700
North East of the South	796	1449	2030	2442 (1435)	2771	6978
North Central Coast	39	149	244	406 (392)	548	1596
South Central Coast	225	507	869	1057 (711)	1575	2857
North West	29	77	134	205 (191)	234	842
Highland	138	311	444	623 (526)	690	2292
Meteorological factors (average monthly values)						
Ambient temperature (°C)	19.9	23.6	27.1	26.0 (3.2)	28.9	29.7
Relative humidity (%)	70.7	74.9	76.6	76.9 (2.9)	78.6	83.6
Cumulative rainfall (mm)	0.06	0.62	1.83	2.37 (1.87)	3.77	6.3
Socio-economic factors						
Population density (persons/km^2)	45	129	272	476 (581)	669	3731
Monthly average income per capita (*1000 VND)	987	1673	2174	2268 (796)	2642	4893
% of communes reached national criteria for commune health	3.8	23.3	33.3	39.6 (21.4)	57.6	96.6
% of newborn breastfed within 1 h of birth	43.5	76.1	85.2	83.9 (12.9)	95.6	100
Number of schools of kindergarten	78	143	186	225 (162)	252	960
% of permanent houses	3.1	12.5	29.8	43.7 (33.4)	80.1	98.4
Number of livestock farms	0	17	72	201 (338)	306	2099
% of households accessed to safe water	17.2	68.8	88.2	79.8 (22)	96.7	98.5
% of household accessed to hygienic toilet	14.3	30.9	42.1	46.2 (20.5)	59.1	98.5

(Table 2). The positive association between monthly average temperatures was observed in almost all the provinces from North to South of Vietnam, in which the strong associations, which report an over 25% increase in HFMD corresponding to a 1 °C increase in monthly temperature above the mean, were found mostly in Northern provinces (Fig. 3A). It is interesting that the negative associations between monthly temperatures and HFMD were found in most of Mekong delta provinces where the incidence rates were recorded as highest across the country. The variation in temperature-HFMD relationship in the Mekong Delta region in compared with other regions is still unclear, and we may

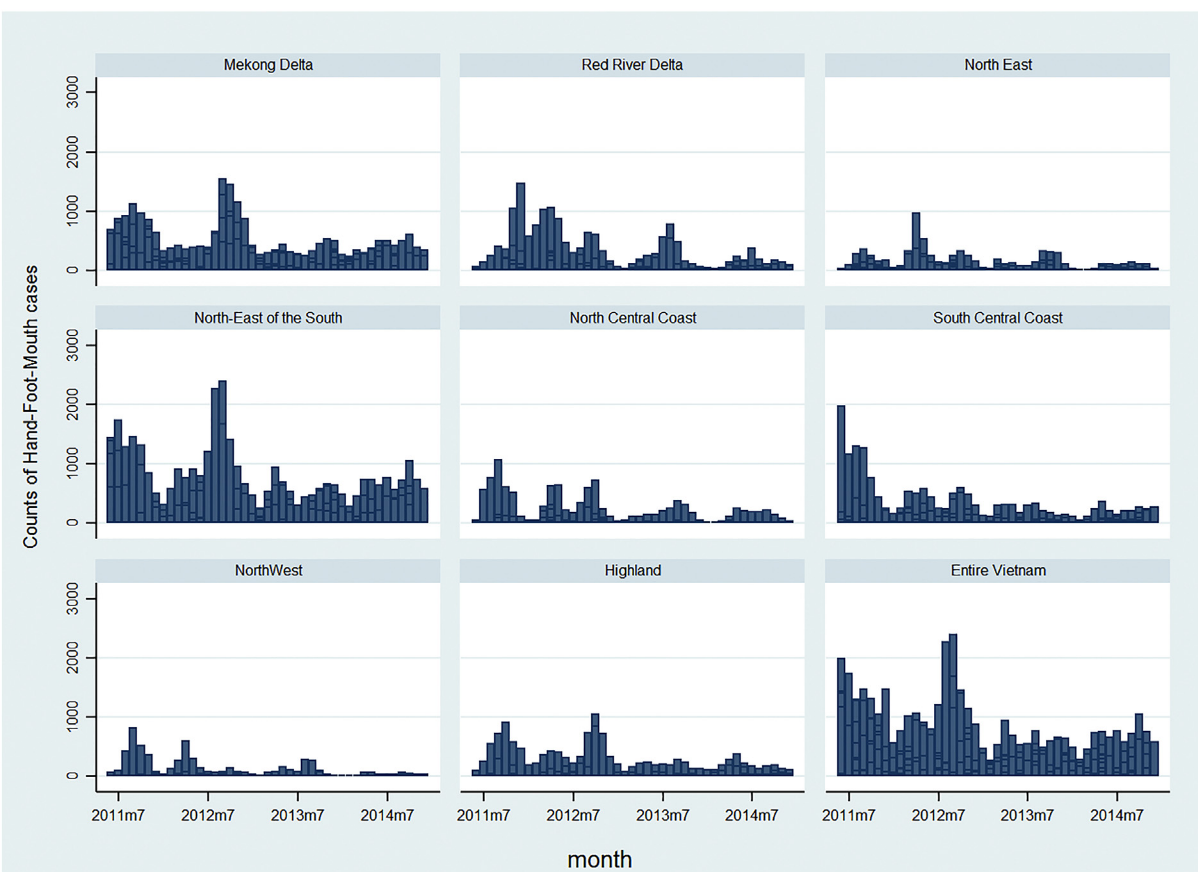

Fig. 1. Monthly counts of Hand-Foot-and-Mouth Disease (HFMD) by ecological regions of Vietnam.

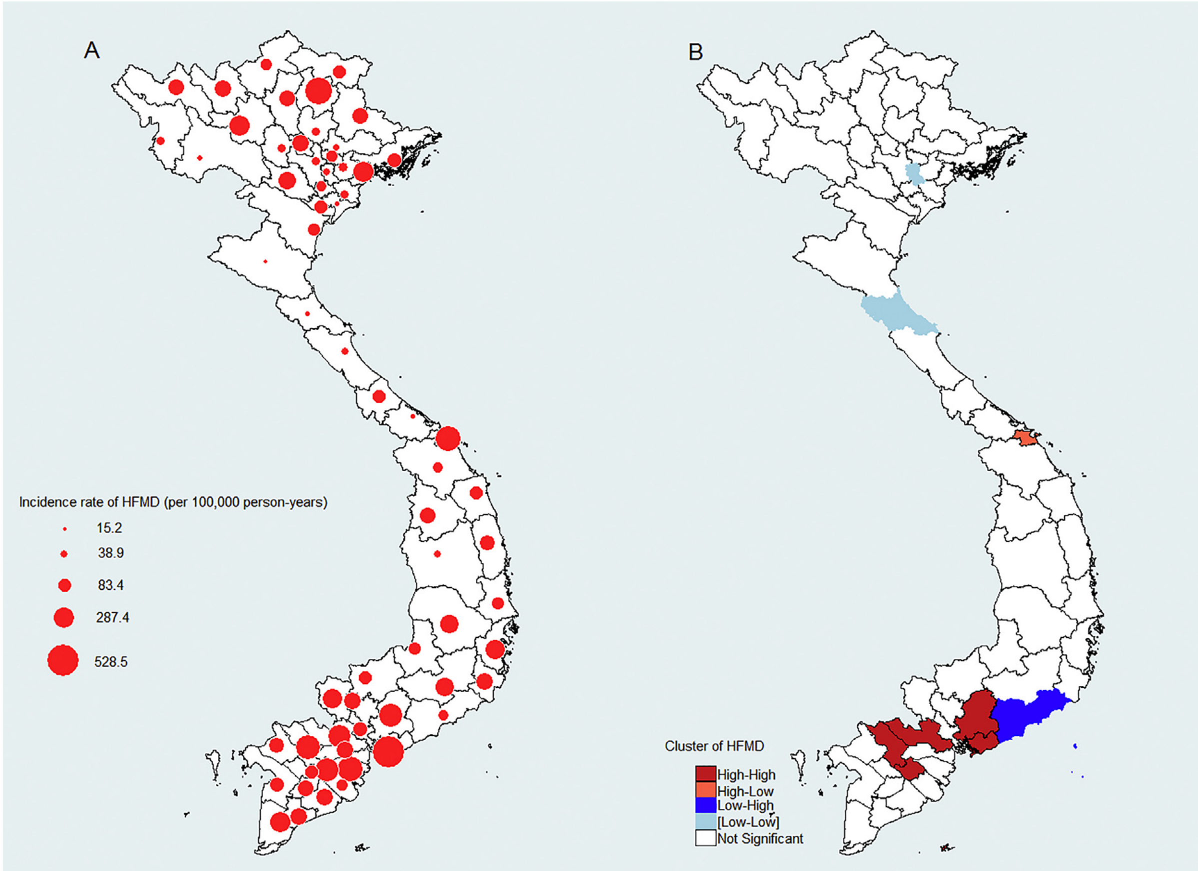

Fig. 2. (A) Yearly incidence rates (per 100,000 person-years) of Hand-Foot-and-Mouth Disease (HFMD) by provinces. (B) the spatial clusters of HFMD across Vietnam.

need further study to examine this phenomenon. However, it may be attributed to the differences in climate (e.g. Mekong region has 2 seasons, comprising dry and wet while northern regions have four seasons, comprising summer, winter, autumn and spring) and the interaction between socio-demographic factors with climatic factors in facilitating communicable diseases. For humidity, the month average humidity was strongly positively associated with HFMD in North Central Coast provinces, and this is corresponding to the findings found in the temperature-HFMD relationship in this region. However, the negative associations between HFMD and humidity were found in most of the North-East provinces; whereas, the rest of provinces had a minor or moderate positive change in HFMD for 1% increase in humidity above the mean (Fig. 3B). Unlike from temperature and humidity, the strong positive associations, which reported over 10% increase in HFMD corresponding to 1 mm increase in monthly rainfall above the mean, were observed in High-land and South Central Coast provinces but not in North Central Coast. The strongest negative association between rainfall and HFMD was found in Red River Delta and part of North-West with the direction from East to West of the up North region. The inconsistent relationship, which shows "*tiger skin*" distributions comprising positive, negative and non-significant associations, between rainfall and HFMD was observed in all regions across Vietnam (Fig. 3C).

At the country-level, the results of meta-analysis indicated that HFMD increased 7% (RR: 1.07; 95%CI: 1.052–1.088) and 3.1% (RR: 1.031, 95%CI: 1.024–1.039) for a 1 °C increase in monthly temperature above 26 °C and 1% increase in monthly humidity above 76%. In the contrary, HFMD decreased 3.1% associated with 1 mm increase in the monthly cumulative rainfall. At the regional level, positive association between temperatures and HFMD was observed in all regions except the Mekong Delta. The magnitudes of increases in HFMD associated with a 1 °C increase from the regional mean of temperature ranged from 2.5% to 52.5% (Fig. 4). The positive association between humidity

Table 2
Estimated mean of % change in the incidence rate of hand-foot-mouth disease per unit change in socio-economic factors.

Variable	Unit change in predictor	% change in incidence rate of hand-foot-mouth disease	95% Credible Interval
Population density	persons/km^2	−0.021	−0.074, 0.031
Monthly average income per capita	10,000 VND	0.043	−0.012, 10.1
% of communes reached national criteria for commune health	1%	0.15	−0.39, 0.69
% of newborn breastfed within 1 h of birth	1%	−1.57[a]	−2.25, −0.93
Number of schools of kindergarten	1 school	−0.12	−0.27, 0.021
% of permanent houses	1%	−0.96[a]	−1.66, −0.23
Number of livestock farms	1 farm	0.048	−0.009, 0.106
% of households accessed to safe water	1%	−1.13[a]	−2.16, −0.18
% of household accessed to hygienic toilet	1%	0.32	−1.15, 1.90

[a] Statistically significant (p ≤ 0.05).

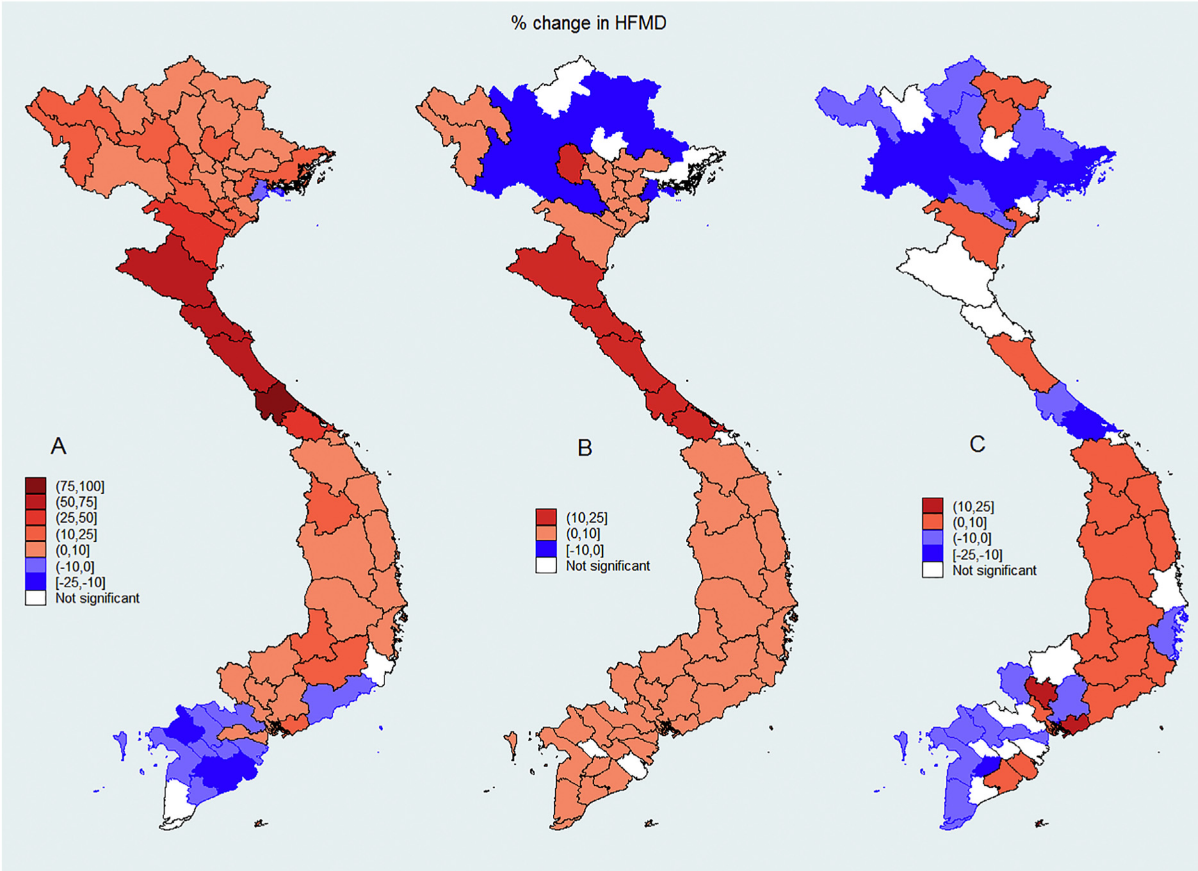

Fig. 3. (A) % changes in HFMD for a 1 °C increase above the regional monthly average temperature. (B) % changes in HFMD for a 1 °C increase above the regional monthly average humidity. (C) % changes in HFMD for a 1 mm increase in monthly cumulative rainfall.

and HFMD was observed in all regions except the up-North regions (North-East and North-West regions) which had none significant association between humidity and HFMD, and the magnitudes of increase in HFMD in relation to 1% increase in humidity above the regional mean ranged from 1.9% to 14.1%. Fig. 4 showed the inconsistent results in the relationship between HFMD and rainfall. The negative association was observed in almost all the northern regions (Red River Delta, North-East, and North-West); whereas, the positive HFMD-rainfall relationship was found in South Central Coast and Highland regions. The nonsignificant association between HFMD and rainfall was presented in the rest of regions (Mekong Delta, North-East of the South, North Central Coast).

4. Discussion

This is the first study in the association between socio-ecological factors and the variation of hand-foot-and-mouth disease (HFMD) in multiple provinces across the country of Vietnam. The study reveals that the increases in newborn breastfed within 1 h of birth, households with permanent houses and accessed to safe water significantly associated with a reduction in the incidence of HFMD. At the country level, high temperatures and humidity were significantly associated with an increase in HFMD; whereas, rainfall was reversely associated with HFMD. At the regional level, the temperatures had positive effects on HFMD from the South-East to up North regions, and humidity had positive effects on HFMD from the South to North Central Coast. However, rainfall had inconsistent effects on HFMD. At the provincial level, a non-uniform association between climatic factors and HFMD was observed among the provinces across the country.

In this study, we examined the direct effects of socio-demographic factors on the transmission of HFMD while adjusting for the spatial autocorrelation. There were very few studies (Zhao and Li, 2016; Gou et al., 2017) in this relationship since most of the previous studies looked at the modification effects of socio-economic factors on the climate-HFMD relationship but not the direct effects of these factors. Similar to the study conducted by Zhao and Li (2016) and Gou et al. (2017), the socio-demographic factors such as population density, income per capita, the number of kindergarten schools were found none significant associated with variation in HFMD incidence after controlling for spatial autocorrelation. This may be explained by the interaction between socio-demographic factors and health performance system (HPS) factors including indicators in curative, preventive intervention, behavioural intervention, and inter-sector public health interventions. For example, the provinces with high population density are likely more developed and have better HPS that can compensate for the decrease in the HFMD as a result of the population density, especially the effect of HPS is even higher at a higher than the effect of population density (Zhao et al., 2017). Unfortunately, in this study, we could not obtain data to formulate HPS indexes. However, our study identified two HPS related factors comprising newborn breastfed within 1 h of birth and access to safe water to significantly contribute to reducing the risk of HFMD. One factor provides improvement of immunity among newborn babies, and the other factor may prevent communities from HFMD transmission using properly treated water supply resources. The percentage of households with permanent houses was found to be inversely associated with HFMD in this study. The possible explanations are that the permanent house reflected higher socioeconomic standard of the households, and a permanent house which is built by concrete

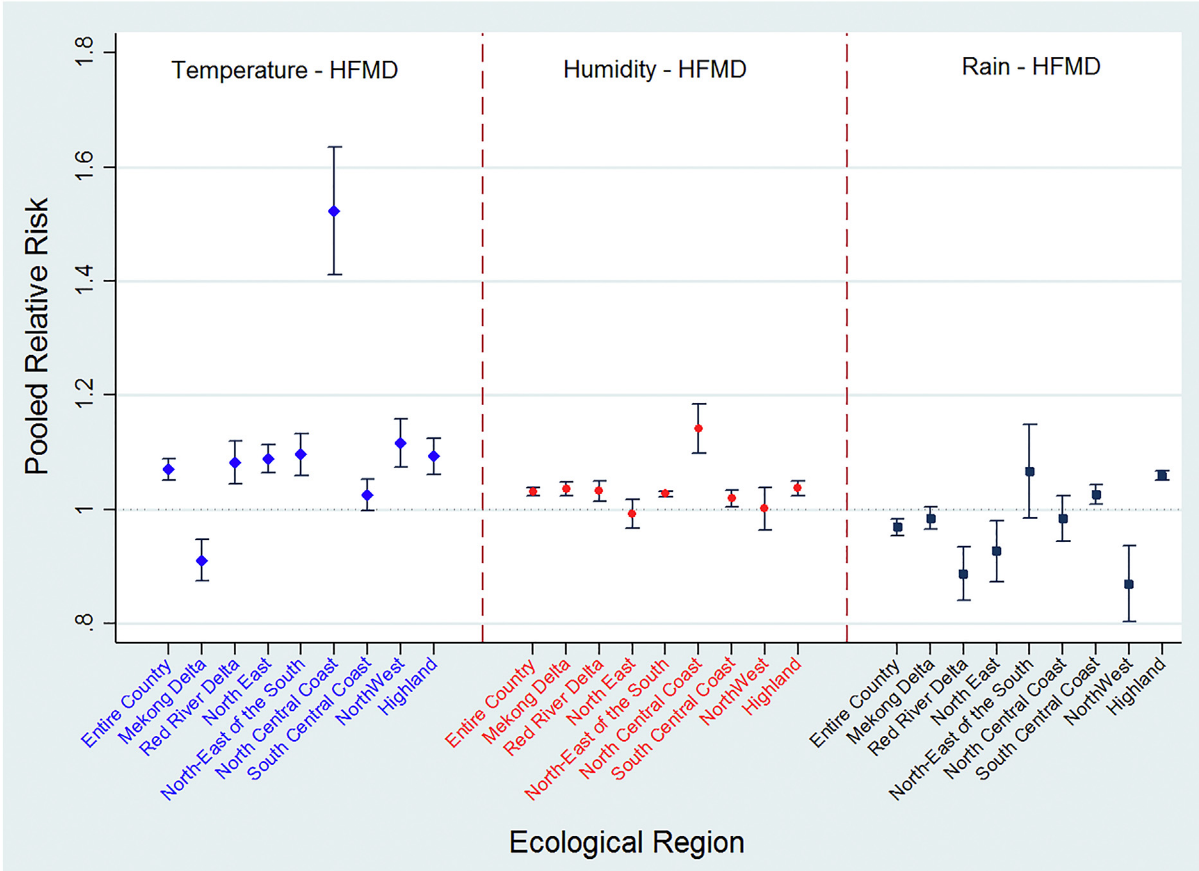

Fig. 4. Pooled estimates of effect sizes of the association between climatic factors and HFMD.

and well-designed may help in reducing transmission of microbiological agents from environment (e.g. during flooding or extreme weather events).

The positive association between temperature and HFMD incidence found in this study is in-line with the findings reported from a series of previous studies (Onozuka and Hashizume, 2011; Xu et al., 2015; Liu et al., 2015a; Wei et al., 2015; Zhao et al., 2017; Xiao et al., 2017; Gou et al., 2017). These studies indicated that 1 °C increase in daily or weekly temperature associated with an increase of HFMD from 11% to nearly 100%. However, none of them examined the effects of monthly temperatures on HFMD variation. The non-uniform spatial variation of temperature-HFMD was also observed from the study in multiple geographical areas, in which the spatial heterogeneity varied from 70% (Xiao et al., 2017) to 98% (Zhu et al., 2016). This finding is similar to our result which indicated a 96% of the variability in the temperature-HFMD relationship due to heterogeneity (*Cochran Q test*, I^2) and this convinces the non-uniform effects of temperatures within a large region that were reported from previous studies (Hondula et al., 2012; Hondula and Barnett, 2014). Therefore, it is important to study and adopt mitigation strategies to cope with heat-related health risk in terms of location-specific heat thresholds, plans, and heat-related warning system (Sheridan and Lin, 2014). In terms of temporal pattern, nonlinear relationships between temperature and HFMD were observed and discussed in the previous studies (Xiao et al., 2017; Zhu et al., 2016; Wang et al., 2016), in which it is noteworthy that dropping down of risk was seen at very hot temperatures. This may be explained by the shortening survival time of enterovirus in the environment due to extremely hot temperatures (Xiao et al., 2017). However, the study also mentioned that previous theories in the temperature-HFMD relationship failed to fully explain the nonlinear behaviour of temperature-HFMD association, especially why they differ across studies.

The positive association between HFMD and relative humidity found in this study is similar to the findings from previous studies. Onozuka and Hashizume (2011) indicated that a 4.7% increase in HFMD was associated with every 1% increase in relative humidity, and the threshold of humidity for significant change in HFMD was observed at above 80% of humidity. Wang et al. (2016) observed a hockey-stick relationship of relative humidity with HFMD with markedly increasing risk over 80%, and Yang et al. (2017) found a threshold of humidity at 84%. The study (Yang et al., 2017) revealed that male urban children at age of 0–4 years appeared to be more vulnerable to the effect of relative humidity on HFMD. In our study, the centred humidity for increasing risk of HFMD was 76% but this value is monthly average humidity which is corresponding to an above 80% of daily or weekly humidity. Up-to-date, the mechanism of the humidity-HFMD relationship remains critically unknown although there are several possible explanations. First, it has been known that humoural or cellular immunity might be influenced by climatic factors (Bull, 1980). Second, the bodies' metabolism is slowdown due to high relative humidity because of decreased sweating (Gerba et al., 1996; Xu et al., 2012), especially among young children who have less self-care ability, results in more invasion of virus or bacteria into the immune system. Third, during the humid days, the virus may be easily attached to the small articles in the air or the toy's surfaces, so sharing toys and other supplies among children might facilitate the spread of disease (Fletcher et al., 2004).

Our study found inconsistent relationships between rainfall and HFMD. The pooled effect estimate indicated that positive rainfall-HFMD was observed only in South Central regions, comprising South Central Coast and Highland provinces where monthly cumulative rainfalls are more influenced by LaNiña and El Niño episodes in comparison with other regions across Vietnam (Gobin et al., 2016). Further studies should be conducted to better understand the influence of these climatic phenomena to the relationship between infectious diseases such as HFMD and weather factors. The inconsistent findings in rainfall-HFMD were also reported from the previous studies. For example, Wang et al. (2016) indicated that moderate rainfall (50th–90th percentile, 0 mm < rainfall < 17.7 mm) was associated with an over two-fold higher risk of HFMD hospitalization relative to no rainfall in Hong Kong, and Hii et al. (2011) revealed that moderate weekly precipitation below 75 mm was positive associated with HFMD relative to no rainfall but the association was reversed when the cumulative rainfall was above 75 mm. Whereas, the study conducted by Onozuka and Hashizume (2011) found no evidence of the association between rainfall and HFMD. This complex relationship between rainfall and HFMD can be explained by the both-side effects of rainfall. Rainfalls could have an adverse impact on water and food sanitation for reasons. Heavy rainfall can mobilize pathogens from human/animal excreta present in soils and on environment surface or sub-surfaces and move them into surface water exposing inhabitants to infectious agents (Levy et al., 2016), and they can also lead to resuspension of pathogens in sediment or in soils (Jofre et al., 2010) and cause contamination of groundwater (Gelting et al., 2005). On the other hand, rainfalls can play a role as a protective factor against infectious diseases such as HFMD. Heavy downpours could break down the transmission from contaminated groundwater into the host bay reshaping reservoirs into water current (Wang et al., 2016). In addition, the study (Belanger et al., 2009) illustrated that physical activity is negatively associated with heavy rainfall, so extreme precipitation could result in interrupting the transmission by reducing social contact (Wang et al., 2016).

This study has some limitations. First, the study has limited sample size. Only 4 years do data of the multiple provinces were available for collection because the disease surveillance system started requiring to the lower-level health centres (province, district) to report HFMD since 2009–2010. Second, there was a lack of socio-demographic data that can be potential factors for variation of HFMD incidence. For example, in this study, we did not have enough data to compute the health performance indexes which were found to be associated with HFMD. However, some related indicators such as standard commune clinic, newborn baby care, access to safe water and hygienic toilet were examined in this study. We recommend that further study at a smaller scale which we can conduct some surveys to obtain more data to compute the health performance indexes for this purpose. Finally, as an ecological study design, this study had not accessed to individual-level data such as individual characteristics (age, sex, etc.) and adaptive capacity of individuals or groups of people to the change in climatic factors such as high temperatures, humidity, and rainfalls. It is, of course, hard to deal with this limitation due to complication monitoring of climatic factors at individual levels however future studies can use a hybrid study design which use individual-level data of a sub-population to improve ecological inference.

5. Conclusion

Our study provides evidence on the relationship between socio-ecological factors and spatiotemporal variation of hand-foot-and-mouth disease (HFMD) based on a large-scale dataset including 63 provinces across Vietnam. We found a significant influence of some health performance related factors (% of newborn breastfed within 1 h of birth, and % of household accessed to safety water) and living condition (% of the permanent house) in reducing HFMD incidence. Temperature and humidity are positively associated with HFMD at the country scale and varied from provinces to provinces. Rainfall is inconsistently associated with HFMD. Our findings can help better understanding of how socio-ecological factors affect the transmission of HFMD in multiple provinces entire Vietnam which has never been done before. In addition, the relationship between climatic factors and HFMD reflects an important implication for the climate change adaptation strategies and public-health decision, of which development of weather-based early warning systems should be considered to strengthen communicable disease prevention system.

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