



Research Paper

Effect of climate factors on the incidence of hand, foot, and mouth disease in Malaysia: A generalized additive mixed model



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ABSTRACT

Climate change is one of the critical determinants affecting life cycles and transmission of most infectious agents, including malaria, cholera, dengue fever, hand, foot, and mouth disease (HFMD), and the recent Corona-virus pandemic. HFMD has been associated with a growing number of outbreaks resulting in fatal complications since the late 1990s. The outbreaks may result from a combination of rapid population growth, climate change, socioeconomic changes, and other lifestyle changes. However, the modeling of climate variability and HFMD remains unclear, particularly in statistical theory development. The statistical relationship between HFMD and climate factors has been widely studied using generalized linear and additive modeling. When dealing with time-series data with clustered variables such as HFMD with clustered states, the independence principle of both modeling approaches may be violated. Thus, a Generalized Additive Mixed Model (GAMM) is used to investigate the relationship between HFMD and climate factors in Malaysia. The model is improved by using a first-order autoregressive term and treating all Malaysian states as a random effect. This method is preferred as it allows states to be modeled as random effects and accounts for time series data autocorrelation. The findings indicate that climate variables such as rainfall and wind speed affect HFMD cases in Malaysia. The risk of HFMD increased in the subsequent two weeks with rainfall below 60 mm and decreased with rainfall exceeding 60 mm. Besides, a two-week lag in wind speeds between 2 and 5 m/s reduced HFMD's chances. The results also show that HFMD cases rose in Malaysia during the inter-monsoon and southwest monsoon seasons but fell during the northeast monsoon. The study's outcomes can be used by public health officials and the general public to raise awareness, and thus, implement effective preventive measures.

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1. Introduction

Hand, foot, and mouth disease (HFMD) affects millions of people, especially children in many countries. Coxsackievirus A16 and enterovirus A71 are the most significant serotypes implicated as HFMD causative agents (Cardosa et al., 2003). The virus spreads to others through secretions, blisters or scab fluid, and feces of infected people. Within the first week, those diagnosed with this infectious disease become contagious, and the viruses will spread for days or weeks (Centers for Disease Control and Prevention, 2021). Besides, HFMD is also characterized by a low-grade fever, lack of appetite, and malaise. In addition, the enanthem causes mouth or throat pain, which is the most severe clinical symptom of this disease (Guerra et al., 2020).

HFMD was first initiated clinically by Seddon in early 1957 in New Zealand and he reported the cases to the New Zealand College of General Practitioners in April 1957 (Flewett et al., 1963). From late June to July 1957, Robinson et al. (1958) confirmed that 60 cases of HFMD with an etiological agent of Coxsackievirus (A16) had been purified in Toronto, Canada. The other type of HFMD virus, called Enteroviruses 71 (EV71), was first isolated in 1969 from a 9-month-old child with encephalitis in California (Schmidt et al., 1974). According to a report by the World Health Organization (2011), many outbreaks of HFMD has been reported in Western Pacific regions, including Singapore (Chan et al., 2003), Japan (Taniguchi et al., 2007), Vietnam (Van Tu et al., 2007), the Republic of Korea (Jee et al., 2003), Brunei Darussalam (AbuBakar et al., 2009), Malaysia (Chan et al., 2000), and throughout China (Lin et al., 2003; Zhang et al., 2009). HFMD caused by EV71 infection appears to rise across the region and has been a common cause of severe disease and sometimes fatal HFMD.

Since the late 1990s, Asian countries have experienced an increasing trend of HFMD outbreaks leading to fatal complications. In Malaysia, a significant outbreak of HFMD triggered a series of outbreaks across the Asia Pacific. The first major confirmed outbreak of HFMD, mainly caused by EV71 infection, began in Sarawak in early April 1997 (WHO, 2011), with over 2600 children affected and 48 fatalities (Chua et al., 2007). Later in June 1997, the disease had rapidly spread across Peninsular Malaysia, affecting 4625 people and 11 deaths (Shekhar et al., 2005). Sarawak experienced two major outbreaks between the years 2000 and 2003 (Podin et al., 2006). Several Malaysian researchers discovered that this infectious disease pattern follows a three-year cycle, and they speculated that climate change is a major contributor (NikNadia et al., 2016; Wahid et al., 2020).

Researchers from various countries have studied the impact of climate change on HFMD, including temperature, relative humidity, rainfall, and wind speed. The findings, however, have been consistent. For instance, studies in Rizhao, China (Wu et al., 2014) and South Korea (Kim et al., 2016) found a significant non-linear relationship between humidity and HFMD cases, whereas other studies found a positive correlation (Chang et al., 2012; Deng et al., 2013; Du et al., 2016; Qi et al., 2018a). Additionally, some studies indicate that high wind speeds raise the risk of HFMD (Li et al., 2018; Ma et al., 2010; Qi et al., 2018a; Zhang et al., 2019). Other studies, however, discovered a negative association between wind speed and HFMD (Wang et al., 2015, 2016). In contrast, a study by Huang et al. (2013) and Wang et al. (2017) revealed an insignificant relationship.

Even though a significant relationship between rainfall and HFMD has been established in Singapore (Hii et al., 2011), this finding contradicts a study from Japan (Onozuka & Hashizume, 2011) which found no evidence for a link between rainfall and HFMD cases. Apart from that, several studies have shown that the incidence of HFMD significantly increases as the temperature increases (Thanh, 2016; Kim et al., 2016; Wahid et al., 2020). Nevertheless, it is contrary to Chen et al. (2019) and Song et al. (2018) studies, in which they found the incidence of HFMD was not significantly affected by temperatures. Since previous studies in various countries produced disparate results, it is also necessary to investigate these related issues for the Malaysian case.

The Generalized Linear Model (GLM) is commonly used in exploring the relationship between the incidence of infectious diseases and climate variables since it allows response variables that may have non-Gaussian distributions. Nonetheless, GLMs were found to be limited in their ability to fit the complex non-linear and non-monotonic relationships, which often occur in data structure. Thus, a model known as Generalized Additive Models (GAMs) is used to model the non-linear effect with a non-Gaussian response. However, both models are limited to the fact that the response variables must be independent. Since HFMD cases are observed on a weekly basis; hence, the auto-correlation among the repeated series might exist. Therefore, a Generalized Additive Mixed Model (GAMM) is adopted in this study by incorporating the additive parametric function of climate variables and auto-regressive terms in random effect.

The model is expected to overcome the auto-correlation in observations that can allow more flexible functional dependence on the covariates' response variable by adding fixed and random effects to linear predictors. In addition, the model helps establish the relationship between climate factors and HFMD to develop future HFMD prediction models.

2. Materials and methods

2.1. Study area

Malaysia consists of East Malaysia and Peninsular Malaysia. In this study, fourteen regions were chosen as the study area. Fig. 1 shows the map of the studied regions in Malaysia. The Malaysian climate is influenced by the southwest and northeast monsoons. The northeast monsoon is usually associated with heavy rainfall. It flows from November to February, while the southwest monsoon, which is known as the dry period, flows from May to August. The inter-monsoon season, March–April and September–October, is the period between these two monsoons.



Fig. 1. Map of the selected state in Malaysia.

2.2. Data collection

The daily HFMD cases for fourteen states in Malaysia from 2010 to 2016 were accessed from the Public Sector Open Data Portal Malaysia. The data was released by the Ministry of Health Malaysia. In Malaysia, HFMD cases have been diagnosed with one or more symptoms, including fever, mouth ulcers, rash, or blisters on the hands and toes (Ministry of Health Malaysia, 2012). The data are then converted to weekly resolutions to be compatible with existing climate data. The climate variables data, which include the weekly temperatures (°C), percentage of relative humidity (%), rainfall (mm), and wind speed (m/s), are obtained from the Malaysian Meteorological Department (MetMalaysia). The data used in this study is from 2010 to 2016.

2.3. Statistical methods

The analysis in this study is divided into several sections. A preliminary analysis focuses on the descriptive statistics used to examine the HFMD cases in Malaysia from 2010 to 2016. The optimal lag number of climate variables between weekly HFMD cases and climate factors is determined using a Spearman rank correlation analysis. Since changes in climate conditions can influence HFMD characteristics, this study considers the delayed effect of climate factors and incubation periods. According to several reports, HFMD events are better clarified when climate variables are used within a two-week lag period (Feng et al., 2014; Hii et al., 2011; Kim et al., 2016; Ma et al., 2010). It is related to the incubation period for enteroviruses and the potential for parental knowledge and reaction to children’s signs and symptoms.

The first step of the analysis includes multicollinearity testing and an overdispersion test. Based on the multicollinearity test, the identified collinear predictors will be eliminated from the study. The analysis then continued with the covariate selection for GAMM with and without autocorrelated errors to identify the optimal model. Both optimal models are then compared and validated to establish the best model in describing the relationship between climate factors and HFMD. The flow of the analysis is given in Fig. 2. All statistical analyses were performed using the ‘mgcv’ package in R programming software.

2.4. Multicollinearity test

In a regression model, multicollinearity is characterized as the existence of high correlations between two or more independent variables. Multicollinearity issues are addressed in this study to avoid inaccurate regression coefficient estimates, which can cause major problems in validating and interpreting the model. Various diagnostic methods were used, including the variance inflation factor (VIF), corrected variance inflation factor (CVIF), and tolerance (TOL). The climate variables are collinear if $VIF > 5$ (Kutner et al., 2005), $CVIF > 10$ (Curto & Pinto, 2011), and $TOL \sim 0$ (Marquardt, 1970). As a consequence, in the following study, the collinear climate variables will be omitted. The following is the equation for each diagnostic measure:

$$VIF_k = \frac{1}{1 - R_k^2} \tag{1}$$

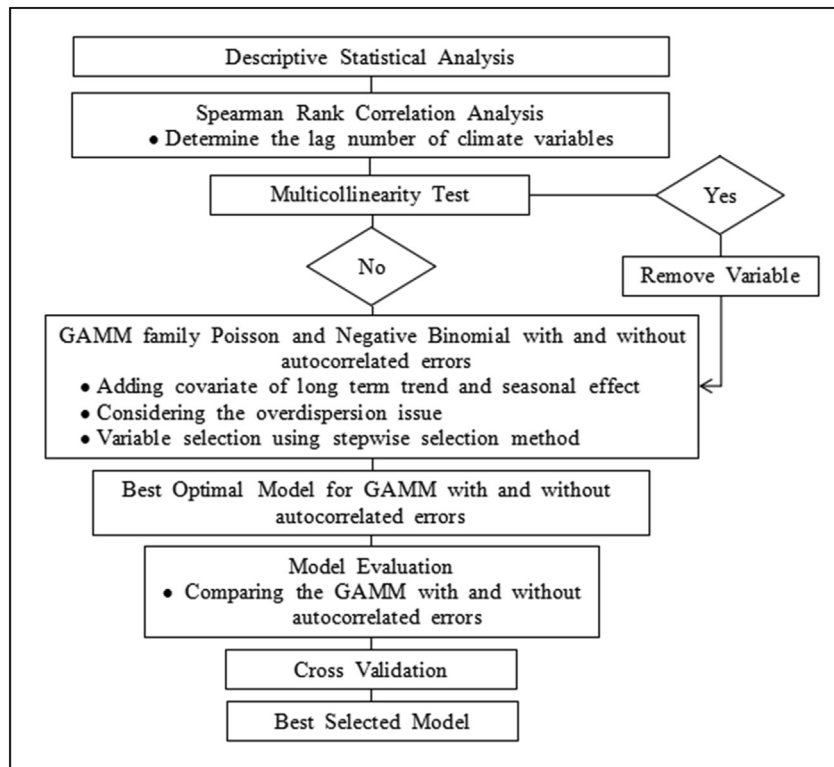


Fig. 2. The flow of analysis.

$$CVIF_k = VIF_k \times \frac{1 - R^2}{1 - R_0^2} \tag{2}$$

$$TOL_k = 1 / VIF_k = 1 - R_k^2 \tag{3}$$

where k represents the independent variables in the model, R_k^2 is the unadjusted coefficient of determination for regressing the k^{th} independent variable on the remaining ones $R_0^2 = R_{y^x_1}^2 + R_{y^x_2}^2 + \dots + R_{y^x_p}^2$.

2.4.1. Generalized modeling approaches

A Generalized Additive Model (GAM) has been used to model the impact of climate change on HFMD. A GAM is a variant of the Generalized Linear Model (GLM) in which at least one or more linear predictors are the sum of smooth functions. The function can be substituted for a parameter estimate in GAM, resulting in a smooth non-parametric function rather than a single scalar number as the estimate. The general equation for GAM is as follows.

$$y_i = \beta_0 + f(x_i) + \varepsilon_i \tag{4}$$

where y_i is the response variable, β_0 is the intercept, x_i represents the predictor variable, f is a smoothing function, and ε_i is an error term that is assumed to be independent and normally distributed, $\varepsilon_i \sim N(0, \sigma_\varepsilon^2)$.

However, in this study, the weekly HFMD counts from 2010 to 2016 were typical time-series data. GAM approach is not suitable when dealing with the time-series data as it assumed that the data are independent yet correlated. The model could be improved by incorporating it within the model rather than assuming it can be accommodated in normally distributed random error. A better model can be achieved using a Generalized Additive Mixed Model (GAMM) with autocorrelated errors. The random effect and the autoregressive term are added to the model. GAMM is a variant of the Generalized Linear Mixed Model (GLMM), which includes a smooth function that handles smooth terms as random effects. This method excellently performs in residual autocorrelation control, yielding robust estimates and standard errors (Guo et al., 2016).

The general equation for GAMM with autocorrelated errors is as follows.

$$y_{ij} = \beta_0 + f(x_i) + U_j + \xi_{ij} + \rho \epsilon_{j,i-1} \tag{5}$$

where y_{ij} is the response variables, the weekly number of HFMD cases in state $j, j = 1,2,3, \dots, 14$ on a week $i, i = 1,2,3, \dots,365$, and β_0 is the intercept. The symbol U_j denotes the random effect intercept by states while ξ_{ij} is an error term for independent component, which both are assumed to be normally distributed as $U_j \sim N(0, \sigma_U^2)$, and $\xi_{ij} \sim N(0, \sigma_\xi^2)$, respectively. A smooth function f is represented by using a smoothing spline, and $\rho \epsilon_{j,i-1}$ refers to the error of a first-order autoregressive, AR(1) component that is accounting for serially correlated errors in the data sets and $|\rho|$ must be less than one (Ruppert et al., 2003). The strength of the autocorrelation, ρ indicates the nature of the serial correlation.

In this study, the effect of climate factors on HFMD cases in Malaysia is examined using a GMM with a family Poisson. However, due to the high variability in HFMD counts during the study period, overdispersion issues in the datasets may occur. Hence, GMM with a family negative binomial is adopted (Breslow, 1984). The analysis used two different statistical GMM approaches: GMM with autocorrelated errors and GMM without autocorrelated errors. Both models incorporated the additive parametric function of climate variables. The variances between and within fourteen states in Malaysia are observed by including a random effect as an indicator variable in the model. Equation (6) and equation (7) represent the full GMM model without and with autocorrelated errors, respectively.

$$\ln[E(HFMD_{ij})] = \beta_0 + s(\text{Temperature}_{ij})_{t-2} + s(\text{Humidity}_{ij})_{t-2} + s(\text{Rainfall}_{ij})_{t-2} + s(\text{Wind speed}_{ij})_{t-2} + s(\text{Time}_{ij}, \text{DF} = 4 / \text{year}) + U_j + \xi_{ij} \tag{6}$$

$$\ln[E(HFMD_{ij})] = \beta_0 + s(\text{Temperature}_{ij})_{t-2} + s(\text{Humidity}_{ij})_{t-2} + s(\text{Rainfall}_{ij})_{t-2} + s(\text{Wind speed}_{ij})_{t-2} + s(\text{Time}_{ij}, \text{DF} = 4 / \text{year}) + U_j + \xi_{ij} + \rho \epsilon_{j,i-1} \tag{7}$$

In order to adjust the long-term trend and seasonal pattern in weekly cases, a smoothing spline of time with 4 degrees of freedom (DF) per year was added in both models. Besides, the two weeks effect of all climate variables is assigned as $t - 2$ in the models. The cyclic cubic regressions spline was used for all variables, with a smoothing parameter estimated using a penalized quasi-likelihood (PQL). The cyclic cubic regressions spline is a variant of the cubic regressions spline that fits well for cyclic or seasonal data (Underwood, 2009; Sigauke, Kumar, Maswanganyi, & Ranganai, 2019). This spline was preferred because Malaysia’s HFMD and climate data display a seasonal pattern (Wahid et al., 2020). A stepwise forward selection method was used to obtain the best optimal model since it is extensively used, particularly in medical applications (Yamashita et al., 2007), enabling both forward and backward procedures (Chowdhury & Turin, 2020). The Akaike Information Criterion (AIC) (Akaike, 1998) was used as a cut-off value for the selection process since it often provides the most sparse model (Chowdhury & Turin, 2020).

2.5. Model evaluation

In the model evaluation process, the efficiency of both models was measured by using AIC, Bayesian information criterion (BIC), root mean square error (RMSE), and mean absolute error (MAE) values. The estimated models with the lowest AIC, BIC, RMSE, and MAE have the best performance. The formulas are specified as follows:

$$AIC = -2\ln(\hat{L}) + 2p \tag{8}$$

$$BIC = -2\ln(\hat{L}) + p\ln(n) \tag{9}$$

$$RMSE = \sqrt{1 / (n) \sum_{t=1}^n (y_t - \hat{y}_t)^2} \tag{10}$$

$$MAE = 1 / (n) \left| \sum_{t=1}^n y_t - \hat{y}_t \right| \tag{11}$$

where p is the number of estimated parameters in the model, n is the number of observations, \hat{L} is the maximum value of the likelihood function for the model, y_t represents the observed values, while \hat{y}_t represents the predicted values.

2.6. Model validation

Cross-validation is a method for evaluating a model's predictive efficiency and determining how well it performs outside of the sample when applied to a new data set known as test data. In this study, to choose the appropriate model that can describe the relationship between climate factors and HFMD cases in Malaysia, the best optimal model from each approach was validated using six-fold rolling basis cross-validation (Hyndman, 2014). This cross-validation approach can be employed when dealing with time-series data and dependent observations. The steps of the cross-validation process are described as follows:

- i. Split the data according to year subsets from 2010 to 2016.
- ii. Start the first-fold rolling basis cross-validation using the data year 2010 for training purposes and test the model using the data year 2011.
- iii. Calculate the accuracy of the test data for the year 2011 using the root mean square error (RMSE).
- iv. Use the data from 2010 to 2011 as training datasets, and then test the model using the following test data, the data year 2012.
- v. Repeat the process until the last fold.
- vi. Compute the accuracy of the model by averaging the RMSE over the six test sets.

3. Results and discussion

3.1. Summary statistics of HFMD cases and climate factors over 2010–2016

Fig. 3 shows the percentage of HFMD cases in each state. Sarawak has the highest number of HFMD cases in Malaysia, with 30.6%, followed by Selangor, Johor, and Wilayah Persekutuan Kuala Lumpur with 24.5%, 7.8%, and 7.1%, respectively. The lowest percentage of HFMD cases was recorded in four states: Pahang, Terengganu, Perlis, and Wilayah Persekutuan Labuan. These findings might be influenced by the factors of urbanization and the population density in each state of Malaysia. As shown in Fig. 4, the highest cases of HFMD were reported in August 2016, with a total of 8520 cases, while the lowest cases were recorded in January 2011. Besides, it is noticeable that the HFMD cases followed a three-year trend from 2010 to 2016.

3.2. Association between HFMD and climate factors

Fig. 5 shows the weekly distribution of HFMD cases for each of the climate factors. HFMD cases in Malaysia increased between week 10 and week 27 during the inter-monsoon and Southwest monsoon seasons and decreased after week 40 during the Northeast monsoon season. Similar findings have been published in Vietnam (Van Tu et al., 2007), Japan (Onozuka & Hashizume, 2011), Singapore (Ang et al., 2009), and Taiwan (Chen et al., 2007). The figure also demonstrates that the temperature and HFMD patterns are almost identical for each week. It also shows that wind speed peaks earlier than HFMD cases, whereas humidity and rainfall peaks later. As a result, there is likely to be a connection between HFMD cases and climate factors in Malaysia.

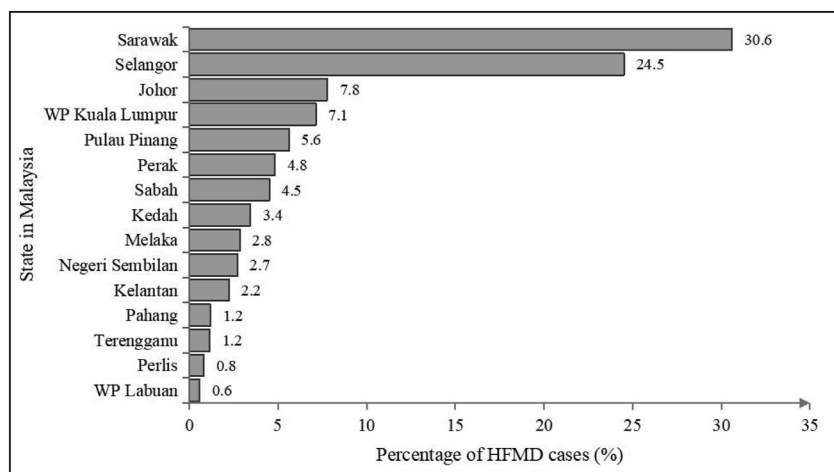


Fig. 3. Percentage of HFMD cases for each state in Malaysia, 2010–2016.

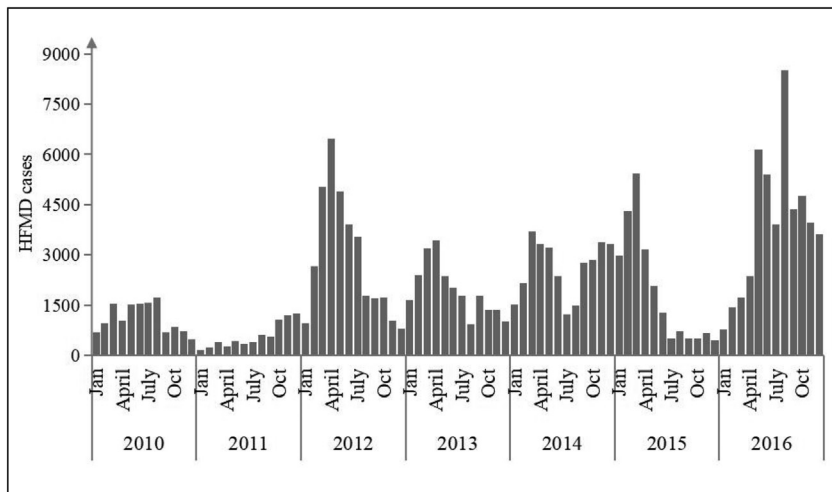


Fig. 4. Monthly distribution of HFMD cases in Malaysia, 2010–2016.

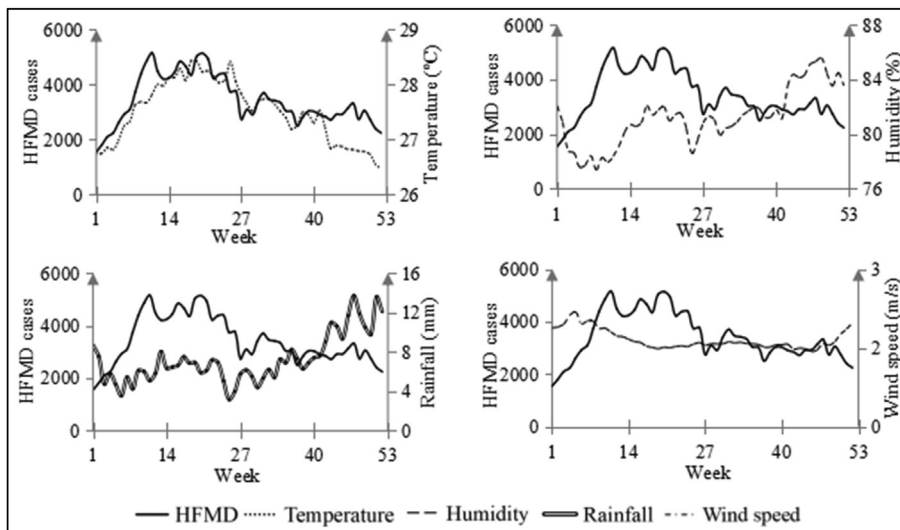


Fig. 5. The weekly pattern of HFMD cases with climate factors in Malaysia.

3.3. Multicollinearity checking

In this study, multicollinearity problems were taken into account. The values of VIF, Tolerance and CVIF were examined in this analysis to detect the presence of multicollinearity in the data sets. As shown in Table 1, the VIF, Tolerance, and CVIF values for all climate variables do not surpass their respective threshold values, indicating no multicollinearity issues. As a result, the present research will include all climate variables in the model.

Table 1
Multicollinearity test for each climate variable.

Variables	Multicollinearity Test		
	VIF	Tolerance	CVIF
Temperature	2.1298	0.4695	1.8052
Humidity	4.0817	0.2450	3.4596
Rainfall	1.5987	0.6255	1.3550
Wind speed	3.6441	0.2744	3.0887

Table 2
Forward stepwise selection method.

Step	Climate factors	AIC
1	Temperature	12810.13
	Humidity	12765.64
	Rainfall	12811.43
	Wind speed	12760.44
2	Wind speed	12743.07
	Temperature	
	Wind speed	12722.74
	Humidity	
3	Wind speed	12740.27
	Humidity	
	Rainfall	
	Wind speed	12719.52
	Humidity	
	Temperature	
	Wind speed	12703.82
	Humidity	
	Rainfall	

Table 2 shows the results using a stepwise forward selection method to find the best model for variable selection. In the first step, the wind speed has the lowest AIC value than the other predictors, so it was considered the best single predictor in the first step. The two-predictor models that include wind speed as the first predictor was fitted in the second stage, and humidity was the second most appropriate predictor with the lowest AIC value. The same procedure was followed until adding the predictor did not result in the smallest AIC. Finally, wind speed, humidity, and rainfall are climate variables that should be included in the optimal model. It represents the AIC value that is the smallest as compared to the other models.

3.4. Application of generalized additive mixed model

The generalized additive mixed model (GAMM) without autocorrelated errors and with autocorrelated errors as given in Eq. (6) and Eq. (7) will be used in this analysis. In the first phase, GAMM with a family Poisson for both models is tested. However, it shows that overdispersion occurs in the data sets. To address these concerns, we use a GAMM with a Negative Binomial to analyze both models.

Table 3 summarizes the results for both models. The findings show that using a GAMM without autocorrelated errors, the time and the two weeks delay of humidity, rainfall, and wind speed significantly affects HFMD cases in Malaysia. However, humidity becomes negligible when the first-order autoregressive term is included in the model as the *p*-value is less than 0.05. By comparing the values of AIC, BIC, MAE, and RMSE of both models, the model with autocorrelated errors produces a lower value. Furthermore, the GAMM model with autocorrelated errors has a lower average RMSE value than the other model from the cross-validation analysis. As a result, the GAMM Negative Binomial with autocorrelated errors is the best model for explaining the relationship between HFMD and Malaysian climate factors. Fig. 6 illustrates the detailed step for obtaining the RMSE of rolling basis cross-validation for GAMM Negative Binomial without autocorrelated errors. The RMSE value for cross-validation is computed by averaging the RMSE values of the tested data across all folds.

Table 3
GAMM Negative Binomial with and without autocorrelated errors.

Parameter	GAMM Negative Binomial							
	Without autocorrelated errors				With autocorrelated errors			
	Estimate	Standard Error	<i>p</i> -value		Estimate	Standard Error	<i>p</i> -value	
Constant	2.6610	0.2825	0.0000***		2.6696	0.2776	0.0000***	
Smooth terms	Edf	Ref.df	F	<i>p</i> -value	Edf	Ref.df	F	<i>p</i> -value
s(Humidity) _{t-2}	3.4440	43	0.4400	0.0000***	1.4150	43	0.0620	0.1123
s(Rainfall) _{t-2}	2.0840	43	0.2450	0.0016***	2.1380	43	0.2740	0.0006***
s(Windspeed) _{t-2}	5.0240	43	1.8150	0.0000***	2.0900	43	0.1590	0.0132***
s(Time)	25.0600	26	184.8390	0.0000***	23.5890	26	67.3470	0.0000***
A variance of the random effect	1.1151				1.0735			
First-order autocorrelation, ρ	–				0.4594			
AIC	12703.82				11553.54			
BIC	12749.59				11605.85			
MAE	27.96				27.90			
RMSE	66.77				66.53			
RMSE _{CV}	72.38				72.36			

Significant codes: 0.05 '***'; RMSE_{CV} is the average RMSE for cross-validation; Edf is the effective degree of freedom; Ref. df is reference degree of freedom.

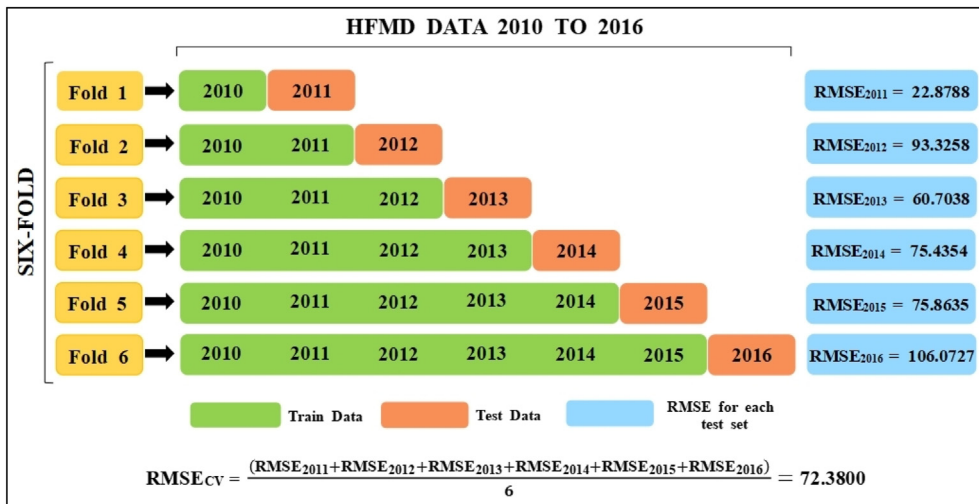


Fig. 6. A six-fold rolling basis cross-validation for GAMM Negative Binomial without autocorrelated errors.

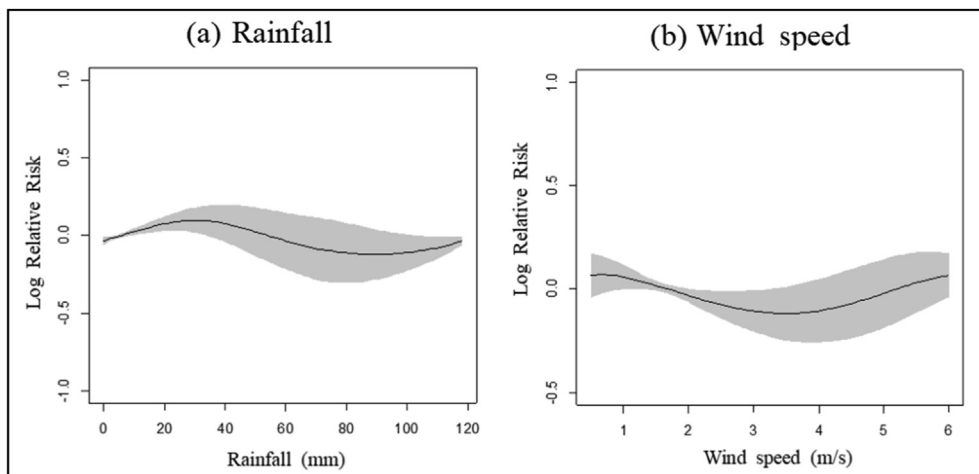


Fig. 7. Smoothing curve between HFMD and climate factors, GAMM Negative Binomial with the first-order autoregressive term.

Fig. 7 depicts the smoothing curve between HFMD and climate factors in Malaysia using GAMM Negative Binomial with autocorrelated errors. When the relative risk values are more than one, the climate factors suggest a positive risk factor. Where the values are less than one, the risk factor is negative, and when the value is one, the risk factor is uncorrelated. Fig. 7(a) shows that the relative risk of HFMD increased when rainfall was less than 60 mm and decreased when rainfall was more than 60 mm. Furthermore, at a two-week lag, the relative risk of HFMD decreased as the wind speed was up to 3.5 m/s and increased when above 3.5 m/s, as shown in Fig. 7(b). It is expected that human behaviors may be linked to this important variable. For example, as the amount of rainfall and wind speed increases, people choose to remain indoors or cancel activities at crowded places, thus minimizing the chance of HFMD incidence. Moreover, the random effect variance indicates that the HFMD between states variability is 1.0735. The first-order autocorrelation from the model confirmed that there is exists a serial correlation in the data sets. The ρ equal to 0.4594 indicates a positive serial correlation of HFMD in which the error terms appear to have the same sign from week to week.

In conclusion, the findings of this study reveal that rainfall and wind speed with a two-week lag effect are major predictors of HFMD cases in Malaysia. Our results are in line with researches in Hong Kong (Wang et al., 2016) and Shanghai, China (Qi et al., 2018a). In addition, the present study found no connection between humidity and HFMD in Malaysia, which is in accordance with previous findings from Singapore (Leong et al., 2011) and China (Feng et al., 2014; Liu et al., 2015; Du et al., 2016). These findings, however, contradict previous research in South Korea (Kim et al., 2016), Japan (Onozuka & Hashizume, 2011), Vietnam (Thanh et al., 2016), and other areas of China (Gou et al., 2018; Liao et al., 2015; Song et al., 2018). This suggests

that the relationship between HFMD and climate variables differs depending on the country or region, as the climates differ significantly between countries.

4. Conclusion

The present study quantifies the non-linear association between the HFMD and climate factors with its delayed effect. A generalized additive mixed model (GAMM) has been employed as the statistical tool because of its flexibility in handling the independence of the data series. The results yield several notable findings as follows:

- HFMD cases in Malaysia were found to be higher during the inter-monsoon and southwest monsoon seasons but lower during the northeast monsoon;
- The GAMM with autocorrelated errors is the best model for describing the link between climate factors and HFMD cases;
- Rainfall and wind speed had a significant impact on HFMD cases;
- Rainfall up to 60 mm with a two-week delay may increase the risk of HFMD, while rainfall above 60 mm reduces the risk;
- Wind speed with a two-week delay below 3.5 m/s may decrease the risk of HFMD, while wind speed above 3.5 m/s increases the risk.

In general, this study provides evidence of the impact of climate change on infectious diseases related to human health. The government needs to strengthen surveillance by enhancing early disease detection, providing accurate planning, and better health care financing mechanisms. The developed model can then be used as a predicting model to estimate the risk of HFMD under climate change scenarios as well as determine the potential hotspot areas. This study can be considered as a contribution to policymakers for regulation in preventing infectious diseases according to the characteristic local climate in a specific region. Other important factors such as socio-demographics and population density should be included in the analysis for future research.

CRedit authorship contribution statement

Nurmarni Athirah Abdul Wahid: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Visualization. **Jamaludin Suhaila:** Conceptualization, Validation, Methodology, Writing – review & editing, Visualization, Supervision. **Haliza Abd. Rahman:** Conceptualization, Validation, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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