Journal of Physics: Conference Series

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To cite this article: N A A Wahid *et al* 2021 *J. Phys.: Conf. Ser.* **1988** 012102

Effect of climate factors on Hand-Foot-Mouth Disease: A generalized additive model approach

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Abstract. Hand, foot, and mouth disease (HFMD) has become an endemic childhood disease in Asia, including Malaysia, over the last few decades. This infectious disease caused by the Entero and Coxsackie viruses has been a major public health threat in Malaysia since 1997. Climate change has been considered an influential factor in HFMD cases and has been explored in other countries using various statistical analyses. The most popular is the Generalized Linear Model (GLM). However, GLM often fails to capture the non-linearity effect of the variables. The study, therefore, proposes to use the Generalized Additive Model (GAM) to analyse the non-linear effects of temperature, humidity, rainfall, and wind speed at varying time lags of HFMD in Selangor. In summary, the result indicates that the weekly temperature, humidity, and rainfall were significantly associated with HFMD cases in Selangor and clarified with two weeks of lag time. This disease's risk increased in the subsequent two weeks with a temperature range of 27°C to 30°C, 70% to 85% of humidity, and 5mm to 20mm of rainfall. Besides, this study also found that the seasonal distribution of HFMD in Selangor has a large peak during the Southwest monsoon. A small peak was observed at the end of the year during the Northeast monsoon. The findings of this study could be a practical guide for HFMD intervention strategies, especially in Malaysia.

Keywords: Climate change; Generalized additive model; Generalized linear model; HFMD; Infectious disease

1. Introduction

Hand, foot, and mouth disease (HFMD) were first documented in New Zealand [1]. Until now, the disease had spread globally. HFMD is an infectious disease primarily caused by two main viruses: enterovirus 71 (EV71) and coxsackievirus A16 (Cox A16). The virus often affects children under the age of five [2]. This infectious disease is transmitted from person to person by direct contact with an infected person's saliva, urine, vesicular fluid, respiratory droplets, or indirectly by tainted objects [3]. Symptoms such as fever, tender sores in the mouth, and a rash of blisters in the palms, feet, and buttocks are the signs of HFMD [4].

In the past few decades, Asian countries such as Taiwan, Singapore, Vietnam, and China have witnessed frequent and widespread outbreaks of HFMD, with deaths mainly among infants due to severe complications [5-8]. In Malaysia, the outbreak of HFMD began in Sarawak in April 1997 and spread in Peninsular Malaysia in June 1997 [9]. In Sarawak, a clear three-year cyclical trend of HFMD has been documented in 1997, 2000, 2003, and 2006 [10]. Due to climate change, essential mutations, lack of efficient monitoring networks, and scarce health services, it is expected that there will be an increase in the number of cases of the disease [11]. Besides, HFMD will develop a pandemic within a short period due to its highly contagious characteristics, thereby posing a major threat to public health [12].

The seasonality pattern of the HFMD has become evident in several countries. In Japan and Taiwan, epidemics occurred during the summer months [13-14]. On the other hand, Finland reported most HFMD cases in the autumn seasons [15]. In some Asian countries, this disease usually peaks in the late spring or early summer, along with a small peak in the late autumn or early winter [16,17]. In European countries such as Belgium, HFMD cases occurred throughout the year, with a small peak in summer and autumn [18]. Based on these mentioned studies, the climate variables are suspected to influence the HFMD incidence rate.

Many researchers have extensively explored the potential of climate variables as early warning efforts to control climate-sensitive infectious diseases, for example, malaria [19], diarrhea [20], dengue fever [21], and HFMD [22-23]. However, in some studies, the evidence on the relationship between climate variables and HFMD is contradictory. In Japan, the analysis showed no significant association between rainfall and HFMD, which is contrary to Singapore [22-23], while in Hong Kong, the risk of HFMD is expected to increase by high wind speed [16]. However, no other study has confirmed these results. A non-linear association between humidity and HFMD cases has been observed in Rizhao, China [24], while a positive linear association has been identified in Taiwan [25].

The Generalized Linear Model (GLM) is often used in modeling infectious diseases [26-30]. However, these methods do not allow the identification of more complicated non-linear patterns between the predictors and the outcome [31]. In such cases, a non-parametric regression model such as Generalized Additive Model (GAM) is more suitable to be applied. Some studies have been using the GAM analysis in examining the association between HFMD and climate variables [32-33]. However, there is still limited of studies that documented the link between the climate variables and HFMD in Malaysia using this approach. A Negative Binomial GLM has been applied in our previous work, and we noticed that temperature plays an important role in explaining the HFMD cases in Selangor [34]. Since the GLM has its limitation, the GAM approach is more reliable to be conducted in this study. Therefore, the objectives of the current study are to explore the distribution of HFMD cases in Selangor from 2010 to 2016 and establish a relationship between climate variables and HFMD cases via GAM.

2. Materials and methods

2.1. Study area

The analysis of the HFMD for the Selangor areas was carried out. Selangor is considered the most developed country and has a larger population in Malaysia, with a total population of 6.54 million. It has a tropical climate and is one of Malaysia's warmest areas, with an average temperature of 33°C per day. The map of Selangor is shown in figure 1.

2.2. Data collection

Weekly data on confirmed HFMD cases were obtained from the Public Sector Open Data Portal Malaysia provided by the Ministry of Health Malaysia from 2010 to 2016. Cases reported in Malaysia have been diagnosed with one or more symptoms such as fever, ulcers in the mouth, palm rash, and blisters in the toes [35]. Weekly climate data from Subang Station were obtained from the Malaysian Meteorological Department (MetMalaysia). MetMalaysia is an agency under the Ministry of

Environment and Water (MEWA) responsible for providing efficient and effective meteorological, climatological and geophysical services for well-being, safety, and sustainable development to meet national and international needs. The weekly data consists of mean temperatures (℃), relative humidity (%), rainfall (mm), and wind speed (m/s).

Figure 1. Map of Selangor, Malaysia.

2.3. *Statistical methods*

Multicollinearity is expected to exist between the studied climate variables. Multicollinearity issues may result in estimations of a volatile regression coefficient, which may cause major problems in validating and interpreting the model. Thus, a variety of diagnostic measures, such as the variance inflation factor (VIF), the corrected variance inflation factor (CVIF), and tolerance (TOL), will be used to detect the existence of multicollinearity among the climate variables. Based on some references the value of VIF > 5 [36], TOL ~ 0 [37], and CVIF > 10 [38] indicates the existence of collinearity among the explanatory variables. The formula for each diagnostic measure is given as follows:

$$VIF_j = \frac{1}{1-R_j^2} \tag{1}$$

$$TOL_j = \frac{1}{VIF_j} = 1 - R_j^2 \tag{2}$$

$$CVIF_j = VIF_j \times \frac{1-R^2}{1-R_0^2} \tag{3}$$

where j represents the independent variables in the model, R_j^2 is the unadjusted coefficient of determination for regressing the j^{th} independent variable on the remaining ones $R_0^2 = R_{yx_1}^2 + R_{yx_2}^2 + \ldots + R_{yx_k}^2$.

A Generalized Additive Model (GAM) introduced by Hastie and Tibshirani [39] has been adopted in this study. GAM offered more flexibility by using a smooth non-linear function, often referred to as a non-parametric function in the same model as a parametric function. The modeling technique is useful in identifying the exposure-response relationships for many types of data, particularly in exploring a non-parametric relationship [40]. The model approach is often used in atmospheric modeling [41], ecological modeling [42], health applications [43], and others. In this study, there is an overdispersion issue in the data set due to high variability in HFMD counts throughout the study period. A Negative Binomial regression model can therefore be used to solve the problem [44]. The Negative Binomial distribution is a Poisson distribution with an extra-dispersion term, which acts as a random effect that subjects the Poisson to an additional variation with a gamma distribution.

This study will consider a lag effect of climate variables on HFMD cases. Assuming the incubation duration of the HFMD-causing coxsackie viruses was approximately one week [45]. Therefore, this study will examine the effects of climate variables with varying lag times of up to three weeks. For example, lag 0 refers to the current week of climate variables, while lag 1 refers to the previous week. In determining the most appropriate estimated model, the value of Akaike information criterion (AIC) [46], adjusted R-squared, and the deviance explained will be used. The smallest AIC value, the largest adjusted R-square [47], and deviance explained indicate the best performance of the predicted models. All statistical analysis was performed using R programming statistical software, package '*mgcv*' for GAM analysis. The estimated parameters with a *p*-value below 0.05 were found to be statistically significant.

Equation (4) below are the model specifications used for GAM with the log link function. A smoothing spline for the time at 4 degrees of freedom (DF) per year was applied to adjust the long-term trend and seasonal pattern in weekly cases. Since we noticed that HFMD in Malaysia exhibits a seasonal pattern [48], the cyclic cubic regressions spline has been utilized in the model with a smoothing parameter estimated by restricted maximum likelihood (REML) maximization. The cyclic cubic regressions spline is known as extensions of cubic regressions splines which perform well with cyclic or seasonal data [49-50]. The REML has been chosen as a smoothing parameter selection as they are less prone to local minima than the other criteria and tend to avoid occasional severe under smoothing [51].

$$\begin{aligned}\ln[E(Y)] = {} & \alpha + s(\text{Temperature})_{t-i} + s(\text{Humidity})_{\text{t}-\text{i}} + s(\text{Rainfall})_{t-i} + s(\text{Wind speed})_{t-i} \\ & + s(\text{Time}, \text{DF} = 4/\text{year})\end{aligned} \tag{4}$$

where $E(Y)$ is the expected number of HFMD cases, α is the intercept, *s* represents a smooth function using a smoothing spline, and *i* is a finite distributed lag operator, *i* = 0,1,2, and 3, for example, *i* =1 means distributed at lag 1 week.

3. Results

3.1. Summary of HFMD cases from 2010 to 2016 in Peninsular Malaysia

Figure 2 provides the general description of HFMD cases from 2010 to 2016 in Peninsular Malaysia. A total of 115189 confirmed cases of HFMD has been reported in Peninsular Malaysia from 2010 to 2016. The largest percentage of HFMD incidence was in 2016, while the lowest in 2011. The percentage of this disease for each state in Peninsular Malaysia illustrates in figure 3. Selangor shows the highest total percentage of HFMD cases for seven years, with 38.1%, followed by Johor and Wilayah Persekutuan Kuala Lumpur, with 12.1% and 11.1%, respectively. Perak reported the lowest percentage of this disease, with only 1.3% compared to the other states.

3.2. The pattern of HFMD and related climate factors

Figure 4 shows the monthly variation of HFMD cases in Selangor over seven years of study. Based on this figure, HFMD occurred in January 2011 throughout the year with a minimum of 28 cases. The maximum number of cases was recorded in August 2016 with almost 2,650 cases. A large peak of HFMD cases in Selangor was observed in May during the Southwest Monsoon Season (May to August) and a second smaller peak around October 2010, 2012, 2013, and 2016. On the other hand, for 2011, 2014, and 2015, cases of HFMD have increased during the Northeast Monsoon Season

(November to February). The weekly variation of HFMD with each of the climate variables can be seen in figure 5. The number of HFMD cases fluctuated weekly and peaked at week 20 during the Southwest Monsoon. It shows that the mean humidity and rainfall peaked earlier while the mean temperature peaked later than the peak of HFMD cases. Besides, all climate variables present a similar pattern with HFMD cases in Selangor, except for the wind speed. A link between climate variables and HFMD is therefore expected to exist.

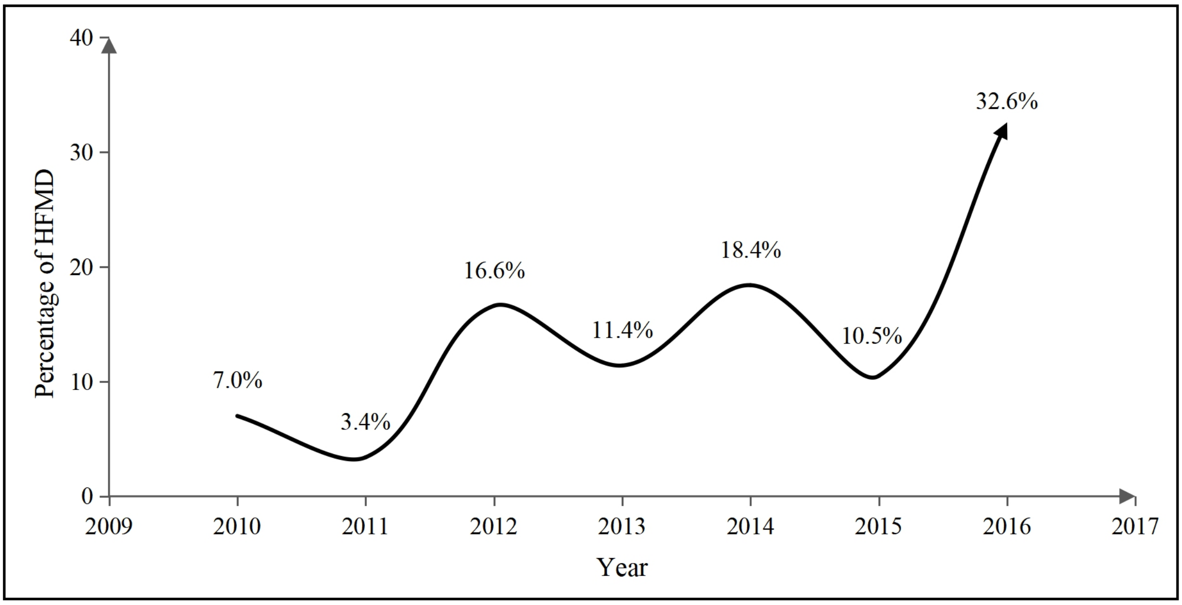

Figure 2. Percentage of HFMD cases in Peninsular Malaysia, 2010-2016.

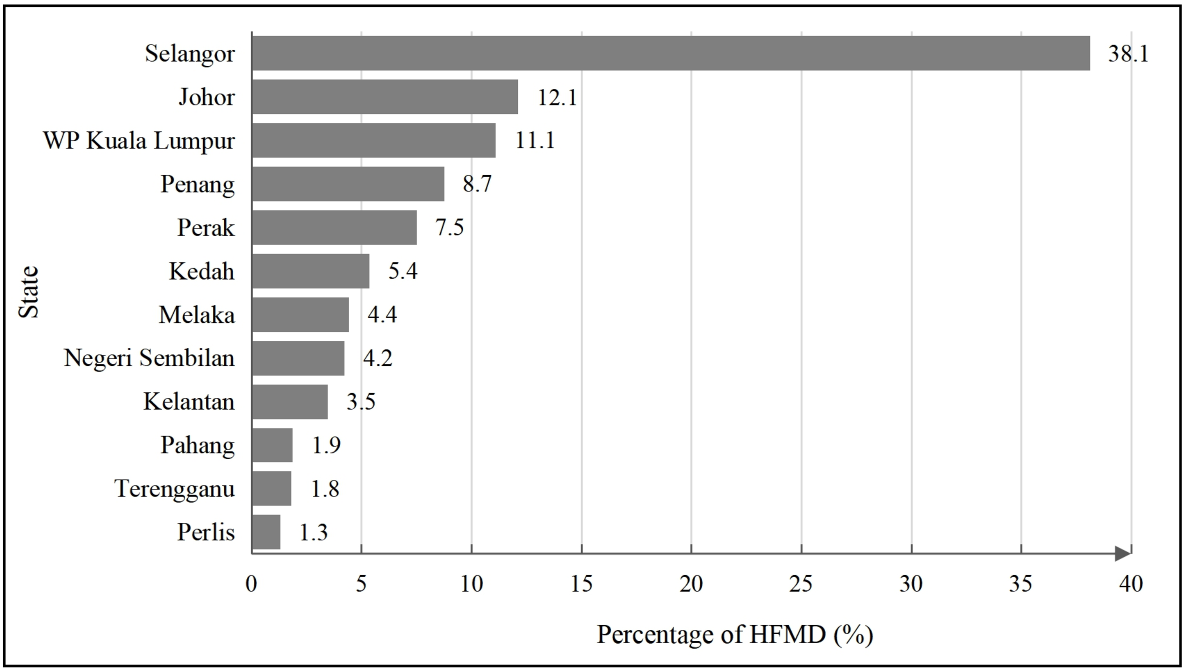

Figure 3. Percentage of HFMD cases by state, 2010-2016.

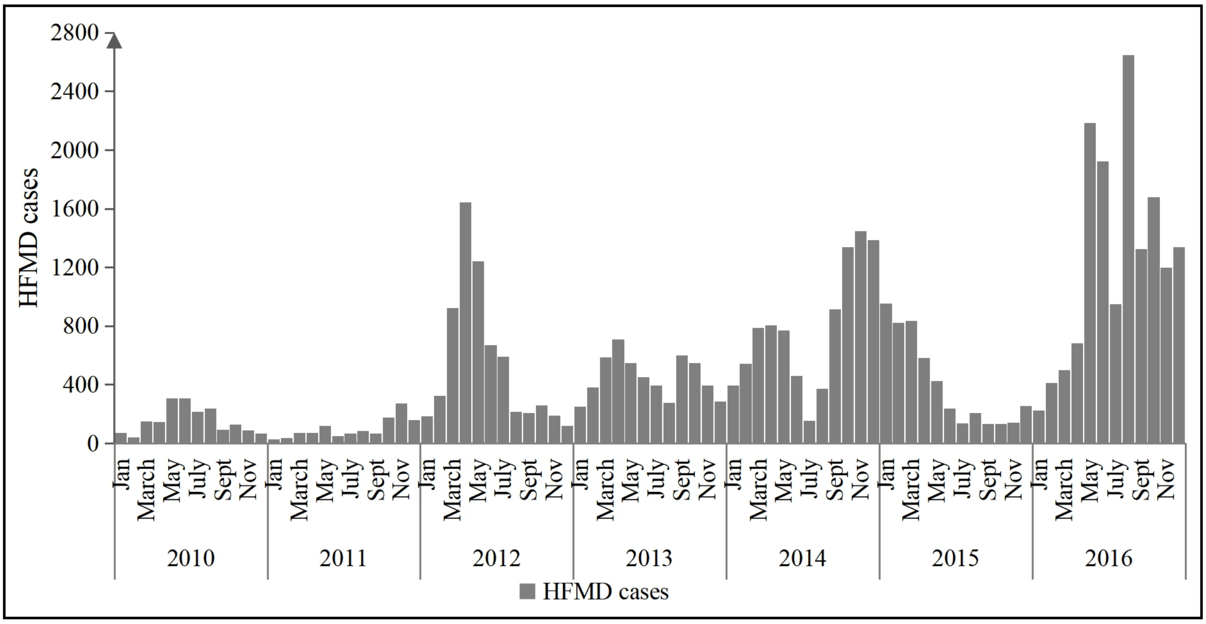

Figure 4. Monthly pattern of HFMD cases in Selangor, a period of 2010 - 2016.

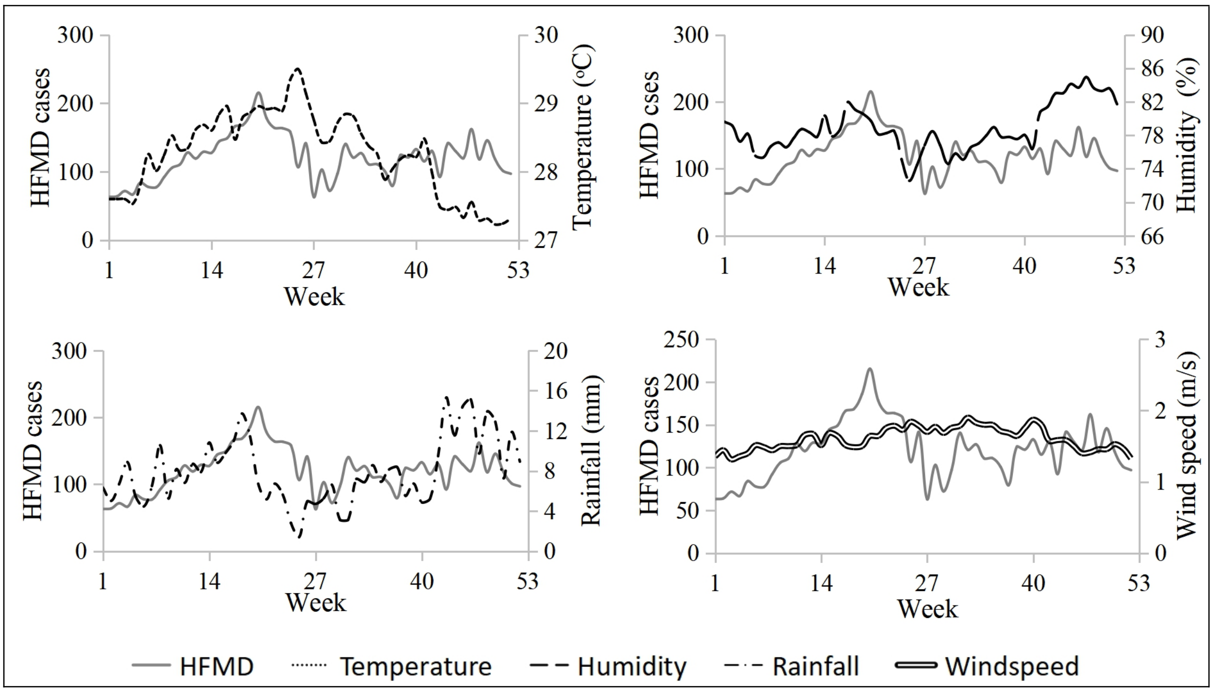

Figure 5. Weekly variation of HFMD cases with all climate variables in Selangor.

3.3. *Modeling via Generalized Additive Model (GAM)*

The multicollinearity issues in the dataset were considered before continuing with the modeling analysis. Multicollinearity can be identified using various methods. However, in this study, the multicollinearity for each climate variable was determined using TOL, VIF, and CVIF. As shown in table 1, we found that the TOL, VIF, and CVIF values' for all climate variables are more than 0 and do not exceed 5 and 10, respectively, which implies that our dataset is free of multicollinearity issues. Thus, we may include all the variables in the model.

Table 1. Multicollinearity diagnostic test for each climate variable.

Variables	Multicollinearity Diagnostic Test		
	VIF	CVIF	TOL
Temperature	1.9051	1.8798	0.5249
Humidity	2.1183	2.0902	0.4721
Rainfall	1.6466	1.6247	0.6073
Wind speed	1.3164	1.2989	0.7596

After verifying the multicollinearity issues, the four different models were estimated using the GAM Negative Binomial regression model. The models were estimated using different lagged effects of climate variables, for example, no lag time, one week, two weeks, and three weeks lag time. Each of the models is assigned as follows:

Model 0: No lag time of climate variables
Model 1: 1 week lag time of climate variables
Model 2: 2 weeks lag time of climate variables
Model 3: 3 weeks lag time of climate variables

The findings for each model are represented in table 2 to table 5. The results show that the GAM Negative Binomial for Model 2 gives the smallest AIC, larger values of *R*-squared, and percentage of deviance explained compared to the other models. We noticed that all climate variables are statistically significant at a 5% significance level except for wind speed in Model 2. After comparing the models, it can be perfectly described that the suggested model of HFMD in Selangor is best explained by two weeks lagged effect of climate variables using the GAM Negative Binomial regression model.

The smoothed associations between the weekly HFMD and climate variables with several patterns obtained from the GAM Negative Binomial model are shown in figure 6. Relative risk values greater than one imply that the exposure variable is a positive risk factor, while values less than one indicate a negative risk factor, and values equal to one indicate an uncorrelated factor. As shown in figure 6(a), the visual inspection of HFMD with the temperature curve at lag two weeks revealed that the relative risk increased with a temperature between 27°C to 30°C. Besides, the risk of HFMD increased sharply with lag two weeks of humidity between 70% to 80%. For rainfall, the risk of HFMD rise between 5 to 20 mm at a lag time of two weeks. These factors might be linked to human behaviour or activity. For example, individuals are more comfortable and tend to spend their time out of the house in more crowded areas whenever the temperature is between 27°C and 30°C, and therefore may increase outdoor activities. Thus, this scenario may also lead to an increase in the risk of HFMD transmission in those circumstances.

Table 2. GAM Negative Binomial, Model 0

Linear Terms	Estimate	Standard Error	*p*-value
Constant	4.3365	0.0216	0.0000***
Smooth Terms	Edf	Ref.df	*p*-value
Temperature	1.4282	8	0.0924
Humidity	2.4737	8	0.0014***
Rainfall	0.0010	8	0.9050
Wind speed	1.5989	8	0.0786
Time	23.8338	26.08	0.0000***
R-squared		0.790	
Deviance Explained		85.2%	
AIC		3567.67	

Significant codes: 0.05 '***'

Table 3. GAM Negative Binomial, Model 1

Linear Terms	Estimate	Standard Error	*p*-value
Constant	4.3467	0.0220	0.0000***
Smooth Terms	Edf	Ref.df	*p*-value
Temperature	0.9994	8	0.1594
Humidity	1.1503	8	0.0976
Rainfall	0.5294	8	0.2192
Wind speed	0.2411	8	0.3086
Time	23.8096	26.07	0.0000***
R-squared		0.779	
Deviance Explained		84.5%	
AIC		3581.74	

Significant codes: 0.05 ‘***’

Table 4. GAM Negative Binomial, Model 2

Linear Terms	Estimate	Standard Error	*p*-value
Constant	4.3484	0.0212	0.0000***
Smooth Terms	Edf	Ref.df	*p*-value
Temperature	1.892	8	0.0105***
Humidity	2.450	8	0.0062***
Rainfall	1.742	8	0.0125***
Wind speed	1.306	8	0.0828
Time	23.872	26.12	0.0000***
R-squared		0.792	
Deviance Explained		85.7%	
AIC		3566.94	

Significant codes: 0.05 ‘***’

Table 5. GAM Negative Binomial, Model 3

Linear Terms	Estimate	Standard Error	*p*-value
Constant	4.3365	0.0215	0.0000***
Smooth Terms	Edf	Ref.df	*p*-value
Temperature	2.0773	8	0.0023***
Humidity	1.0789	8	0.1335
Rainfall	1.4660	8	0.0239***
Wind speed	0.0105	8	0.4393
Time	23.9336	26.14	0.0000***
R-squared		0.690	
Deviance Explained		85.3%	
AIC		3574.30	

Significant codes: 0.05 ‘***’

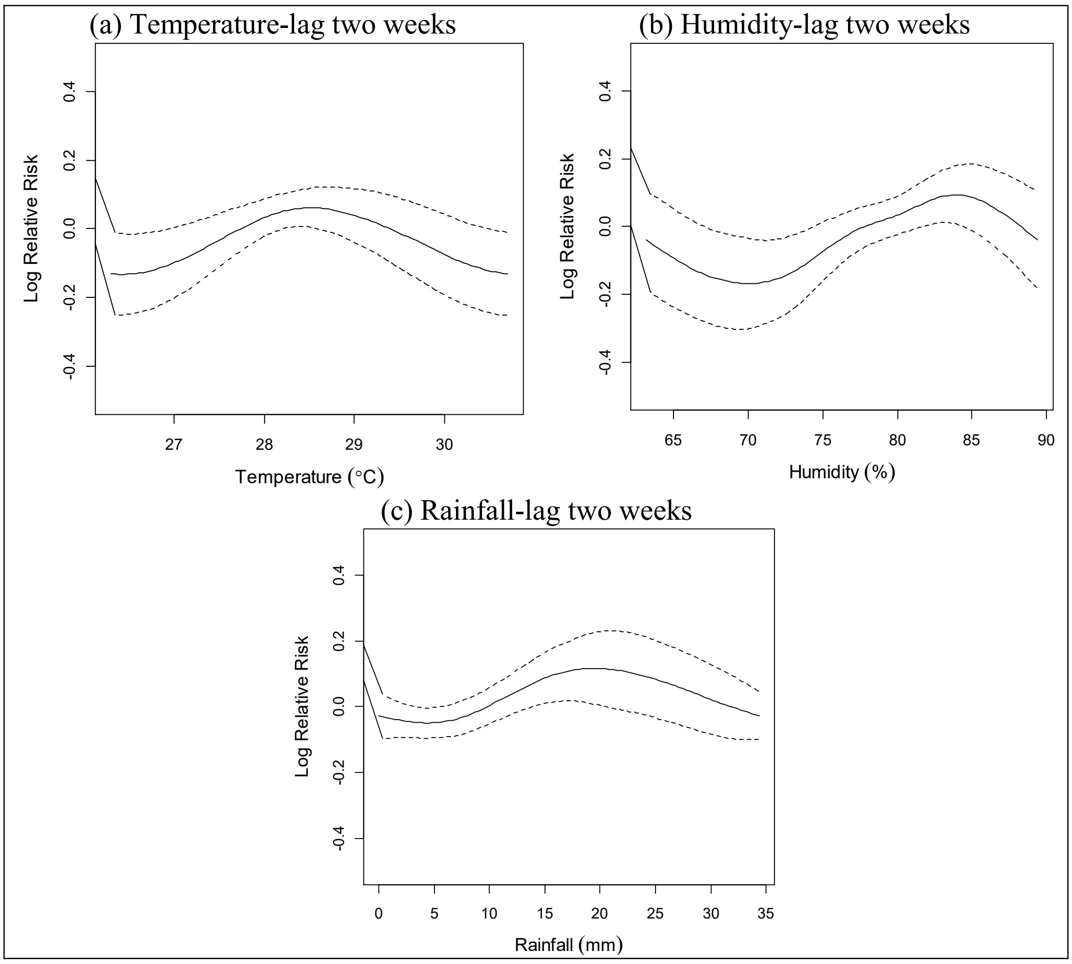

Figure 6. The smoothed association between HFMD and climate variables in Selangor, 2010-2016.

4. Discussions

In the current study, the GAM Negative Binomial was used to determine the effect of climate factors on HFMD cases in Selangor. To date, very few studies have documented the link between HFMD and climate variables in Malaysia using this modeling technique. The current study examined the cases of HFMD in Selangor and found that the cases varied every year over the seven-year study period. In particular, there was an apparent increase in the number of cases in 2012, 2014, and 2016. Generally, the result shows that a large peak of HFMD cases in Selangor and a smaller peak around October were observed during the Southwest Monsoon in May. This is close to the situation in Singapore, Taiwan, and Japan [6,13,14].

Climate factors such as temperature, relative humidity, and rainfall have been shown to have a significant impact on the occurrence and transmission of certain infectious diseases. For example, Leishmaniasis disease, which is transmitted by the mosquito Phlebotomus papatasis. A study in Southwestern Asia found that Phlebotomus papatasi’s distribution depends on temperature and humidity [52]. On the other hand, a study about malaria disease reported that both temperature and rainfall rate affect malaria transmission. The higher temperatures increase mosquito development, female feeding, and maturation of malaria parasites inside their bodies [53]. Our study related to the effects of climate variables on the HFMD in Selangor has yielded several noteworthy findings. We have noticed a significant association between temperature and HFMD and humidity and rainfall, consistent with other countries' findings, for example, in China [28] and Vietnam [55]. Also, we found no statistically significant association between wind speed and HFMD in Selangor, which was similar to the previous outcome in China [33] and South Korea [56]. However, these findings contradict a study in Hong Kong [16]. All these results revealed that each country and region has a unique relationship with its climate variables. The relationship between the climate factors and any disease must be established before proceeding with further analysis.

For the effect of the lag period, we have noted that HFMD activities are better explained when climate variables are used for two weeks, and this is similar to previous findings in Hong Kong [16]. The potential delay in parental awareness of the response to clinical symptoms, especially children [33] and the time-consuming phase of patients receiving medical treatment, affects time-lagging diseases [57]. In summary, our findings in this research indicate that the temperature, humidity, and rainfall with the lagged effect of two weeks has been established as a key indicator of the HFMD cases in Selangor.

5. Conclusion

In the past decade, Asian countries have seen frequent and widespread HFMD outbreaks, including Malaysia. To the best of our knowledge, this is the first study in Malaysia using the Generalized Additive Model with a Negative Binomial regression analysis in determining the effects of climate variables on HFMD cases at different time lags. Generally, there are two peaks of HFMD cases in Selangor. The largest peak is during the Southwest monsoon, while the smallest peak is observed at the end of the year during the Northeast monsoon. This study also provides quantitative evidence that the HFMD cases in Selangor Malaysia were associated with temperature, humidity, and rainfall at two weeks lag period. The risk of HFMD cases in Selangor increased in the subsequent two weeks with a temperature range between 27°C to 30°C, 70% to 85% humidity, and 5 to 20 mm rainfall. This information could help predict the scale of future outbreaks and intervention strategies. In addition, this could help the entire population be better prepared before the outbreak spreads, such as good hygiene practices.

The present study has some limitations: we used the weekly cases of HFMD data rather than daily data because weekly measures were the minimum unit of measurement provided by the Ministry of Health Malaysia. In order to have a comprehensive understanding and strengthen the evidence on the impact of climate influences on HFMD, similar studies must be undertaken over a longer period of time in other states in Malaysia.

Acknowledgments

The authors would like to express their greatest appreciation to the Ministry of Health Malaysia for providing the HFMD data and the Malaysian Meteorological Department for providing the climate data. This work was supported by the Ministry of Higher Education under the Fundamental Research Grant Scheme FRGS/1/2020/STG06/UTM/02/3 and Research University Grant with vote no: QJ130000.3854.19J58 and Zamalah UTM Scholarship under Universiti Teknologi Malaysia.

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