EFFECT OF CLIMATE FACTORS EVALUATION ON HAND-FOOT-AND-MOUTH DISEASE IN MALAYSIA USING GENERALIZED MODELS

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DEDICATION

This thesis is dedicated to my beloved mother, who has always loved me unconditionally, who has been a constant source of encouragement and support throughout each obstacle, and whose good examples have inspired me to work hard for the things I aspire to achieve. I also dedicate this work to all of my family and friends for their unwavering support throughout the process. Each of you has been one of my greatest cheerleaders. I am eternally grateful for their presence in my life.

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ABSTRACT

Hand, foot, and mouth disease, also known as HFMD, affects millions of people worldwide and has been a significant public health issue as well as a substantial burden since 1969. According to a conclusive evidence, the combined impact of rapid population growth, climate change, socioeconomic, and other changes in living ways are the critical determinants of this disease. In Asian countries, this disease has marked an increasing trend of outbreaks leading to fatal complications since the late 1990s. This disease exhibits a cyclic seasonal pattern that can be clarified by climate. Numerous experts from various countries revealed that climate factors play a critical role in predicting HFMD cases. However, the findings vary across countries, implying that the climate of each country has a notable influence on HFMD incidence. In Malaysia, there is indeed a paucity of research and empirical evidence related to these issues. Hence, this study aims to examine the behaviour of the HFMD series in Malaysia and its association with climate factors. Various statistical modelling approaches have been extensively used in previous studies, for example, the Generalized Linear Model (GLM) and the Generalized Additive Model (GAM). However, GLM often fails to account for the non-linearity effect of the variables. In the meantime, GAM demands that each observation be independently distributed. This assumption can be violated when dealing with time-series data comprising clustered variables, such as HFMD data with clustered states. A flexible statistical approach is needed to better understand and interpret the incidence of HFMD and climate change phenomena. Following that, this research proposed a new framework by incorporating a mixed effect into GAM and autoregressive terms, named a generalized additive mixed model (GAMM) with autoregressive terms. Apart from that, the issue of overdispersion was taken into consideration as the type of count data, such as HFMD cases, often displays an overdispersion problem. This is due to the high variability in the data sets. Therefore, to solve this issue, a GAMM Negative Binomial with autoregressive terms is proposed in this study. Besides, a rolling basis cross-validation approach was used to validate the best model between the GLM, GAM, and GAMM, with and without autoregressive terms, in describing the association between HFMD incidence and climate factors in Malaysia. This study found that the HFMD incidence in Malaysia increased during the inter-monsoon and southwest monsoon seasons but decreased during the northeast monsoon. The cross-validation findings imply that the proposed model, GAMM Negative Binomial with autoregressive terms, is the best model to describe the impact of climate factors on HFMD incidence in Malaysia. The model demonstrated that the risk of HFMD increased in the following two weeks with a rainfall of less than 60 mm and decreased with more than 60 mm. The risk of HFMD is decreased when wind speed at a two-week lag is less than 3.5 m/s, and increases when wind speed exceeds 3.5 m/s. The findings can be used as an early risk indicator, assisting local health authorities in developing a simple climate-based disease early warning system to help minimize outbreaks of HFMD.

ABSTRAK

Penyakit tangan, kaki dan mulut, juga dikenali sebagai HFMD memberi kesan kepada jutaan orang di seluruh dunia dan ia telah menyebabkan masalah kesihatan awam serta beban yang besar sejak tahun 1969. Menurut keterangan muktamad, gabungan antara kesan pertumbuhan penduduk yang pesat, perubahan iklim, sosioekonomi, dan perubahan cara hidup merupakan faktor penting mempengaruhi penyakit tersebut. Di negara-negara Asia, penyakit ini menunjukkan peningkatan trend wabak yang membawa kepada komplikasi maut sejak akhir 1990-an. Penyakit ini menunjukkan corak kitaran bermusim yang dapat diperjelaskan oleh faktor iklim. Ramai pakar penyelidik dari pelbagai negara lain mendapati bahawa faktor iklim memainkan peranan penting dalam meramalkan kes HFMD. Namun begitu, dapatan kajian di setiap negara adalah berbeza dan ini menunjukkan bahawa iklim di setiap negara mempengaruhi penyakit HFMD. Di Malaysia, terdapat kekurangan dalam penyelidikan dan bukti empirik berkaitan dengan isu ini. Oleh yang demikian, kajian ini adalah bertujuan untuk mengkaji tingkah laku penyakit HFMD dan hubungannya dengan faktor iklim. Pelbagai pendekatan pemodelan statistik telah digunakan secara meluas dalam mengkaji isu ini, sebagi contoh, Model Linear Teritlak (GLM) dan Model Berdaya Tambah Teritlak (GAM). Walau bagaimanapun, kaedah GLM sering gagal untuk menjelaskan kesan tidak linear dari pembolehubah. Sementara itu, kaedah GAM memerlukan andaian bahawa cerapan adalah tidak bersandar. Andaian ini tidak akan dipenuhi jika menggunakan data siri masa yang terdiri dari pembolehubah bersandar seperti data HFMD mengikut negeri. Oleh yang demikian, pendekatan statistik yang fleksibel diperlukan agar dapat memahami dan mentafsirkan kejadian penyakit HFMD dan fenomena perubahan iklim dengan lebih baik. Berikutan itu, kajian ini mencadangkan rangka baru dengan menambah kesan campuran dan auto regresi ke dalam model GAM yang dinamakan sebagai Model Campuran Berdaya Tambah Teritlak (GAMM) dengan auto regresi. Selain itu, masalah serakan data terlebih juga diambil kira kerana data jenis bilangan seperti data kes HFMD sering menunjukkan masalah tersebut. Hal ini disebabkan oleh variasi yang tinggi dalam set data. Oleh itu, kajian ini mencadangkan kaedah baharu bagi menyelesaikan isu tersebut dengan menggunakan model GAMM Negatif Binomial dengan pekali auto regresi. Selain itu, keesahan silang asas bergulir digunakan bagi menentusahkan model yang terbaik antara GLM, GAM, dan GAMM, dengan dan tanpa terma auto regresi, dalam mentafsirkan hubungan antara HFMD dan faktor iklim di Malaysia. Kajian ini mendapati kes HFMD di Malaysia meningkat pada musim antara monsun dan monsun barat daya, tetapi kes menurun semasa monsun timur laut. Analisis keesahan silang asas bergulir menunjukkan bahawa model yang dicadangkan dalam kajian ini iaitu GAMM Negatif Binomial dengan auto regresi adalah model yang terbaik untuk menggambarkan kesan faktor iklim terhadap kejadian HFMD di Malaysia. Model ini menunjukkan bahawa risiko HFMD meningkat dua minggu berikutnya dengan curahan hujan kurang dari 60 mm dan menurun apabila melebihi 60 mm. Risiko HFMD menurun apabila kelajuan angin kurang dari 3.5 m/s dan meningkat apabila melebihi 3.5 m/s. Hasil daripada kajian ini dapat digunakan sebagai petanda awal bagi membantu pihak berkuasa kesihatan tempatan untuk merangka sistem peringatan awal HFMD berpandukan faktor iklim dan seterusnya dapat meminimumkan wabak penyakit ini.

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LIST OF ABBREVIATIONS

AFP	-	Acute flaccid paralysis
AIC	-	Akaike Information Criterion
ARMA	-	Autoregressive Moving Average
BDI	-	Baidu index
CV	-	Coefficient of Variation
CVIF	-	Corrected variance inflation factor
df	-	Degrees of freedom
DLNM	-	Distributed lag non-linear models
edf	-	Effective degrees of freedom
EV71	-	Enterovirus 71
GAM	-	Generalized Additive Model
GAMM	-	Generalized Additive Mixed Model
GCV	-	Generalized Cross-Validation
GLM	-	Generalized Linear Model
HFMD	-	Hand, foot, and mouth disease
MAE	-	Mean absolute error
OCV	-	Ordinary cross-validation
OLS	-	Ordinary Least-Squares
PACF	-	Partial autocorrelation function
P-IRLS	-	Penalized Iteratively Re-weighted Least Square
REML	-	Restricted Maximum Likelihood
RMSE	-	Root mean square errors
TOL	-	Tolerance
VIF	-	Variance inflation factor

LIST OF SYMBOLS

ω_i	-	Any prior weights on particular data points
k	-	Basis dimension
b	-	Basis function
θ	-	Canonical parameter
℃	-	Celsius
D_{resid}	-	Deviance residuals
$\boldsymbol{W^k}$	-	Diagonal matrix with element of weights
$\boldsymbol{D}$	-	Full rank matrix
$\boldsymbol{A}$	-	Hat matrix for the model
$l(\widehat{\beta}_{max})$	-	Maximized likelihood of the saturated model
$l(\widehat{\beta})$	-	Maximum value of the likelihood function of model
$\bar{x}$	-	Mean
m/s	-	Metre per second
mm	-	Millimetre
$\boldsymbol{K}_j$	-	Non-negative definite smoothing matrix
n	-	Number of observations
p	-	Number of predictors in the model
$\boldsymbol{S}$	-	Penalty matrix of the known coefficient
%	-	Percent
$\boldsymbol{b}$	-	Random effects
β	-	Regression coefficients
Y	-	Response variable
ϕ	-	Scale parameter
s	-	Smooth function
λ	-	Smoothing parameter
σ	-	Standard deviation
$\widehat{\boldsymbol{M}}$	-	$n \times n$ diagonal matrix

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CHAPTER 1

INTRODUCTION

This chapter provides an overview of the entire study, beginning with the background information about the key concepts underpinning this study, followed by the problem statement, research questions, objectives of the study, and the study's scope. The contribution of the study will be discussed in the final section.

1.1 Background of the Study

Hand, foot, and mouth disease (HFMD) is a common viral illness infection that spreads rapidly throughout the world. HFMD was first clinically diagnosed by Seddon in New Zealand in early 1957 (Flewett et al., 1963). Thomas Henry Flewett coined the name of this disease after a similar outbreak of HFMD in the year 1960 (Alsop et al., 1960). HFMD is caused by enterovirus, with most cases caused by Coxsackie Virus A16 and Enterovirus 71. From late June to July 1957, Robinson et al. (1958) reported that 60 cases of HFMD with an etiological of Coxsackievirus A16 had been detected in Toronto, Canada. The other type of HFMD virus, called Enterovirus 71 or known as EV71, was isolated for the first time in California in 1969 (Schmidt et al., 1974). EV71 had caused sporadic outbreaks of HFMD and severe neurological diseases such as meningitis, encephalitis, and acute flaccid paralysis (AFP) (Chen et al., 2007).

This disease is most frequently associated with children under the age of five, but it occasionally infects adolescents (Melnick et al., 1996). The virus spreads in contact with saliva, blister fluid, and patient stool. The infection has mild characteristics, beginning with a fever and blisters on the hands, feet, mouth, and tongue (Ministry of Health Malaysia, 2012). These symptoms will emerge after three to seven days of infection. In the beginning, a person will experience a mild fever,

poor appetite, sore throat, and malaise, or in other words, feels vaguely unwell (Centers for Disease Control and Prevention, 2011). Patients with HFMD caused by EV71 have higher risk of developing severe symptoms, including central nervous system disorders and fatalities resulting from pulmonary oedema in a small proportion of children, particularly children aged under five years old. On the other hand, HFMD patients who have been infected by the Coxsackie A16 virus typically recover within 7 to 10 days (Cohen, 1998).

HFMD has become a crucial problem for global public health since the outbreak of this disease occurred in many areas, such as in China, Japan, Hong Kong, the Republic of Korea, Singapore, Thailand, Taiwan, Vietnam, the United States of America, Europe, Brazil, and Malaysia. However, over the last decade, Asian countries have experienced an increasing trend of HFMD outbreaks, which primarily affected children (Chan et al., 2000), resulting in thousands of deaths due to severe complications (Xing et al., 2014). A significant outbreak of HFMD in Malaysia triggered a series of outbreaks across the Asia Pacific. In Malaysia, the HFMD outbreak, primarily caused by EV71 infection, began in Sarawak in early April 1997. It subsequently spread to Peninsular Malaysia by June 1997 (World Health Organization, 2011). This disease has become endemic in Malaysia, even though Malaysia has already provided the best health care systems and advanced technologies.

The pattern and behaviour of HFMD have become the main concern among researchers with varying expertise from various countries (Hussain et al., 2021; Baek et al., 2020; Wang et al., 2019; Dai et al., 2019; Truong et al., 2019; Nguyen et al., 2017; Bo et al., 2014; Wang et al., 2011). It is known that the pattern of HFMD is associated with geographical location and monsoon period of the study areas. A seasonal pattern of daily HFMD cases with a single peak and bimodal peaks is observed per year in China. A significant peak occurred during the late spring and summer (May-July), while a minor peak occurred in the autumn or winter season (November-February) (Qi et al., 2018). Compared to China, a seasonal HFMD pattern with an increasing number of cases from May and a peak between July and September was observed in Korea (Baek et al., 2020). Additionally, in Vietnam, a

major peak of HFMD was observed in April, followed by a small peak between August and December during the preschooling period (Truong et al., 2019). Apart from that, Taiwan has also documented two HFMD peaks (Ho et al., 1999). The first peak was observed between April and July, whereas the second peak occurred from September to December. The observed seasonality of HFMD incidence in these countries suggests that climate factors may influence it.

Recently, there is evidence showing that climate change has a significant effect on a variety of health diseases, including hemorrhagic fever, ischemic heart disease, dengue disease, acute respiratory infection, and HFMD (Santos et al., 2017; Joshi et al., 2017; Cheong et al., 2013; Bayentin et al., 2010). Several studies have attempted to establish a link between climate conditions and the occurrence of HFMD. The results shows that the occurences differ by country. In Rizhao, China (Wu et al., 2014) and South Korea (Kim et al., 2016), researchers observed a significant non-linear association between humidity and HFMD cases. In comparison, studies in Taiwan established a positive linear correlation of the two variables (Chang et al., 2012). In addition, research in Hong Kong (Ma et al., 2010) and Shandong Province, China (Liao et al., 2015) have found that high wind speed increased the risk of HFMD; however, just a few studies have backed up these claims. Despite the fact that a significant correlation between rainfall and HFMD cases has been established in Singapore (Hii et al., 2011), this finding contradicts a study from Japan (Onozuka and Hashizume, 2011) which found no evidence for a link between rainfall and HFMD cases. Studies in the various nations mentioned above had varying outcomes; thus, it is also worth looking into these potential influencing factors in the Malaysian situation.

Several types of statistical approaches have been used in a study related to HFMD and climate factors. This includes correlation analysis, Geographically Weighted Regression (GWR), time-series models, Classification and Regression Tree Model (CART), and generalized modelling techniques. A Pearson correlation analysis was performed to assess the relationship between the incidence of HFMD and climate factors in Singapore (Leong et al., 2011). The study indicate that HFMD in Singapore was significantly correlated with air temperature, air pressure, and wind

speed. Other than that, Geographically Weighted Regression (GWR) has been applied in various studies to examine the associations between climate factors and HFMD incidence. In addition, GWR has been used in exploring the spatial relationships of HFMD occurrences with different conditions that require climatic variables and the density of the child population in China (Hu et al., 2012). The study stated that temperature, humidity, wind speed, and child population density were positively related to HFMD cases in China. They conclude that the GWR approach could be used to geographically discern the relationship between HFMD and climate variables.

Time-series forecasting models are one of the most common statistical approaches among researchers to examine the performance of meteorological factors on the occurrences of HFMD. The Seasonal Autoregressive Integrated Moving Average (SARIMA) method was used to determine the association of climate variables with HFMD epidemics among children in Zhengzhou, China (Feng et al., 2014). The study mentioned that SARIMA models (Box and Jenkins models) have the flexibility to monitor the autocorrelation of the time series data. They found that the predictive power for SARIMA models of HFMD and EV-71 increased after the addition of the mean atmospheric temperature a at lag two weeks. Besides, an autoregressive integrated moving average model with external variables (ARIMAX) was applied to explore whether the addition of external predictors such as the Baidu index (BDI) and temperature could boost the risk prediction of HFMD in Guangdong, China (Du et al., 2017). The researchers used the time series analysis to allow the establishment of robust and effective ARIMAX models with the correct validity level, which matches the provincial-wide HFMD incidence. Consequently, they conclude that using the ARIMAX model and introducing the BDI helps to greatly enhance the estimation of HFMD incidence. Finally, they proposed that using an ARIMAX multivariate model would offer better prediction than the univariate model.

In a few studies, the Classification and Regression Tree Model (CART) was used to classify the relationship between the incidence of HFMD and climatic factors. This method was performed to determine the threshold effects of climate factors on HFMD cases in China (Du et al., 2016). The researchers have developed a suite of

two spatiotemporal CART models, including fitting a tree to a high HFMD risk and the incidence. From the analysis, they found that HFMD cases in China were associated with temperature and humidity. A temperature greater than 24.85°C and humidity between 80.59% and 82.55% would lead to a higher risk of HFMD. In addition, a study in three separate areas in Gansu, China, used the CART approach to explore the interactive non-linear impact between climate factors and HFMD cases (Gou et al., 2018). They used CART to discover the threshold value that had the best potential to split nodes in the optimal trees. The CART analysis revealed that the average temperature and humidity were the first two important determinants of climate factors on HFMD. The average temperature and humidity in the three areas are more sensitive in the southeast Tianshui compared to the northwest Jiuquan.

The generalized modelling techniques are the most popular approach used by previous studies to explore the association between HFMD cases and climate factors. This includes the Generalized Linear Model (GLM), Generalized Additive Model (GAM), and Generalized Additive Mixed Model (GAMM). The GLM is the most commonly used modelling approach, which can integrate various statistical models, including linear regression, logistic regression, and Poisson regression (Nelder and Wedderburn, 1972). Additionally, GLM enables the extension of linear modelling concepts to a wider class of response types, such as count data and binary responses. Li et al. (2014) and Onozuka and Hashizume (2011) used GLM with a negative binomial distribution approach to examine the association between HFMD and climate change. Both studies applied a negative binomial regression, which accounts for overdispersion problems in the datasets. Nevertheless, the GLM modelling technique has its own restrictions. It is incapable of fitting complex non-linear and non-monotonic relationships that commonly appear in the data structure.

The GAM has been proposed to model the non-linear effect with a non-Gaussian response. Previously, researchers have been using the GAM approach to examine the non-linear association between the incidence of HFMD and climate factors (Chen et al., 2019; Huang and Wang, 2018; Kim et al., 2016; Chen et al., 2014). According to Hastie and Tibshirani (1995), the GAM approach requires only two fundamental assumptions: the function is additive, and the component is

smoothed. This modelling technique is a semi-parametric extension of GLM that enables the handling of non-linear covariate effects in a flexible manner. For instance, Chen et al. (2014) performed a GAM modelling technique in conjunction with Poisson auto-regression to determine the non-linear relationship between climate variables and the occurrence of HFMD in China. They stated that the robustness of the key findings was ascertained using varying degrees of freedom in the smooth function of time used to adjust for seasonal and long-term trends.

Another study by Chen et al. (2019) used a GAM with a negative binomial family to identify the non-linear associations between weekly HFMD cases and average temperature, relative humidity, and Baidu index (BDI) in two different cities in China. They firmly believe that the GAM approach is beneficial in identifying the exposure-response relationship for various types of data, particularly in exploring non-parametric relationships. However, the GLM and GAM approaches are limited by the fact that the response variables must be independent. Since the previous studies typically used time-series data of HFMD, for example, daily, weekly, or monthly, a serial correlation among the repeated series might occur. Therefore, the independence assumption of the GLM and GAM models is violated.

In Malaysia, only limited studies were reported focusing on these issues using the above mentioned statistical methods. Prior research has focused exclusively on time series analysis. A study by NikNadia et al. (2016) used a cross-sectional time series analysis to model the association between EV71 epidemic periods and EV71 seroprevalence, adjusting for age and climate variables including temperature, rainfall, rainy days, and ultraviolet radiance. Their research reveals that the seroprevalence rate in children could be used to predict the occurrence of EV71 epidemics and is influenced by temperature and rainfall. Apart from that, Sham et al. (2014) modelled and forecasted HFMD cases in Sarawak utilizing a time-series analysis, specifically an Autoregressive Moving Average (ARMA). They conclude that the ARMA (1,4) model fits the data well and has good prediction ability of over 90% accuracy. These previous studies demonstrate that the concept of using statistical modelling to assess the effect of climate change on HFMD incidence is relatively new in Malaysia.

Due to the GLM and GAM constraints regarding the independence assumption of response variables, a Generalized Additive Mixed Model (GAMM) with autoregressive terms is therefore proposed in this study to account for these issues by incorporating the additive parametric function of climate factors and autoregressive terms into a random effect. A new framework for the statistical modelling approach will be developed to examine the impact of climate factors on HFMD in Malaysia. This study can contribute to health policymakers in forecasting future outbreaks, raising public awareness, and implementing an effective HFMD prevention strategy. As a result, Malaysians can take extra precautions against the spread of this disease.

1.2 Problem Statement

HFMD is currently regarded as an emerging infectious disease that affects the population worldwide. Hence, profiling and modelling the behaviour of HFMD has become the main research interest. However, many of the models do not consider the structures and properties of the data set in their analysis. Therefore, this present study will address several issues related to HFMD.

Firstly, the behaviour of HFMD data, which includes their data structure, the pattern of the incidence and the influence factors, may differ according to the regions. This could be due to the differences in climate conditions, monsoon seasons, and geographical locations. The issues of seasonal and cyclical patterns of HFMD play an important role in the modelling process. A seasonal term needs to be added to the model to cater for the variations of the parameters. Besides, the auto-correlation among the repeated series might exist in the data sets since the HFMD series is observed daily or weekly basis, which is typically time-series data. These issues may result in a violation of the independence assumption of models. The independence or correlated data series may affect the modelling outcome, for example, underestimate the standard errors of the estimated regression coefficients. Thus, the autocorrelation terms should be incorporated into the model to avoid these issues. Other than that, count data such as HFMD cases often display an overdispersion problem due to the

high variability in the data sets. The issue of having overdispersion in the data series could also lead to an invalid conclusion about the estimated parameter models since the standard errors may be underestimated. Thus, the behaviour of the HFMD data series needs to be taken care of before any modelling process is carried out.

Secondly, a GLM and GAM approach have been intensively used in modelling HFMD. Both approaches accept more complex data structures of the response variables with non-normal distributions such as Poisson, Binomial, and Gamma. To handle the issues of overdispersion in the data series, the GLM and GAM of the negative binomial distribution are proposed, as they are deemed the most convenient and practical approaches. However, both models are limited to the fact that the response variables must be independent. Since the issue of auto-correlation may exists in the HFMD series, these independence assumptions are violated, and hence, may affect the efficiency of the model. Therefore, this research will propose a new framework by incorporating a mixed effect into GAM, named a generalized additive mixed model (GAMM). The model is expected to overcome the auto-correlation in observations and allow a more flexible functional dependence of the response variable on the covariates by adding autoregressive terms and random effects to the linear predictors. The GAMM approach performs excellently well in terms of residuals autocorrelation control, resulting in robust estimates and standard errors.

To date, there are limited number of studies that document the link between climate and the incidence of HFMD in Malaysia. In fact, no concrete and consistent conclusions can be drawn in relation to climate and HFMD. Previous studies only focused on the technique of time series, specifically the Autoregressive Moving Average (ARMA) and cross-sectional time series analysis in establishing the climate-disease relationship. These two methods, however, have some limitations in terms of establishing a link between HFMD incidence and climate factors. The ARMA model is restricted to linear model that works on stationary time-series and demands that a sample comes from a normal distribution. Meanwhile, the cross-sectional time series analysis are unable to analyse the behaviour over a period to time and does not help to determine cause and effect of variables. Therefore, the

necessity to examine the HFMD incidence in the context of climate change is a novel and intriguing starting point for this research. Moreover, the concept of generalized modelling in assessing the impact of climate change on HFMD is relatively new in Malaysia. The challenge now is to investigate how a generalized model can be applied to determine the effect of climate factors on HFMD in Malaysia.

1.3 Research Questions

The research questions of this study are as follows:

(a) What is the pattern of HFMD series in Malaysia?

(b) How to handle the overdispersion and auto-correlation in the data series?

(c) Which climate factors have a major influence on the HFMD incidence in Malaysia?

(d) Is the proposed model the best model for describing the association between climate factors and HFMD incidence in Malaysia?

1.4 Objectives of the Study

The research objectives of this study are as follows:

(a) To examine the behaviour of the HFMD series in Malaysia by providing a complete profile pattern.

(b) To develop the Generalized Additive Mixed Model framework based on negative binomial distribution by adding autoregressive terms and random

effects to address the autocorrelated series problem in the HFMD series and concurrently overcome the issue of overdispersion.

(c) To determine the most dominant climate variable that has the greatest impact on HFMD based on the estimated parameter.

(d) To identify the best model for describing the association between climate factors and HFMD incidence in Malaysia using a cross-validation approach.

1.5 Scope of the Study

This study is related to the HFMD incidence in Malaysia from 2010 to 2016, focusing on fourteen Malaysian states. The fourteen states are Perlis, Kedah, Perak, Kelantan, Pahang, Terengganu, Melaka, Johor, Negeri Sembilan, Penang, Selangor, Sabah, Sarawak, and Wilayah Persekutuan Kuala Lumpur. The states are divided into five regions, which are the Southern, Northern, East Coast, Central, and East Malaysia, based on their geographical coordinates. This study only considered and focused on the four elements of climate factors, which include temperature (℃), humidity (%), rainfall (mm), and wind speed (m/s). The other environmental factors, such as the air pollution index (API), were not included in this study. This is because there are limited references of API during the study was carried out. Besides, the Malaysian Meteorological Department only provides these four elements of climate factors.

A multicollinearity test based on several diagnostic measures, including the variance inflation factor (VIF), corrected variance inflation factor (CVIF), and tolerance (TOL), will be applied to identify the collinear climate factors. The GLM and GAM models will be employed in this study to determine the association between the incidence of HFMD and climate factors in Malaysia. A Poisson model is being considered for both approaches; however, due to the high variability in HFMD counts, overdispersion issues may occur in the data sets. Hence, GLM and GAM with a negative binomial family were adopted to solve this matter. Nevertheless, both

models are inappropriate when dealing with time-series data as they assume that the data is independent yet correlated. Therefore, this research proposed to develop a better model, namely GAMM, by incorporating the random effect and autoregressive terms. In the modelling analysis, the climate factors were assigned as the fixed effects, while the states of Malaysia were assigned as the random effects. All the analysis in this study was performed using the R programming statistical software package.

1.6 Significance of the Study

This study provides evidence on the impact of climate change on HFMD incidence, specifically in Malaysia. The association explored in this study helps to shed light on the link between climate factors and HFMD incidence, which is necessary for the development of future HFMD prediction models. This research, on the other hand, has the potential to enhance awareness of HFMD, particularly among Malaysians. Besides, the improved model from this study can be used as a predictive model to estimate the risk of HFMD under climate change scenarios as well as determine the potential hotspot areas. Moreover, the variability in the relationship could be used to initiate preventive measures against climate determinants of HFMD, such as giving necessary information about the disease to parents or caregivers. This study can be regarded as a contribution to policymakers' regulation of infectious disease prevention in specific areas, depending on the characteristics of the local climate. In addition, the findings can be used as an early risk indicator, assisting local health authorities in developing a simple climate-based disease early warning system to help minimize outbreaks.

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1. **Wahid, N. A. A.**, Suhaila, J. & Abd Rahman, H. (2021). Effect of climate factors on the incidence of hand, foot, and mouth disease in Malaysia: A generalized additive mixed model. *Infectious Disease Modelling*, *6*, 997-1008. https://doi.org/10.1016/j.idm.2021.08.003.

2. **Wahid, N. A. A.**, Suhaila, J. and Sulekan, A. (2020). Temperature Effect on HFMD Transmission in Selangor, Malaysia. *Sains Malaysiana*, *49*(10), 2587-2597. http://dx.doi.org/10.17576/jsm-2020-4910-24.

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1. **Wahid, N. A. A.**, Suhaila, J. and Abd Rahman, H. (2021). The Influence of Climate Factors on Hand-Foot-Mouth Disease: A Five-State Study in Malaysia. *Universal Journal of Public Health, 9*(5), 324-331. http://dx.doi.org/10.13189/ujph.2021.090515. **(Indexed by SCOPUS)**

2. **Wahid, N.A.A.**, Suhaila, J. and Rahman, H.A. (2021). A Systematic Review of the Statistical Methodology Used in Establishing the Link Between Climate Factors and HFMD Incidence. *Malaysian Journal of Fundamental and Applied Sciences*, *17*(5), 514-528. https://doi.org/10.11113/mjfas.v17n5.2129. **(Indexed by SCOPUS)**

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1. **Wahid, N. A. A.**, Suhaila, J. and Rahman, H. A. (2020). Seasonal pattern of Hand, Foot, and Mouth Disease in Malaysia using a generalized linear model. *Technology Reports of Kansai University*, *62*(7), 3603-3615.

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