

MODELLING HAND, FOOT AND MOUTH DISEASE IN MALAYSIA USING  
GENERALIZED LINEAR MODELS

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## **DEDICATION**

This thesis is dedicated to my father, who taught me that the best kind of knowledge to have is that which is learned for its own sake. It is also dedicated to my mother, who taught me that even the largest task can be accomplished if it is done one step at a time.

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## **ABSTRACT**

HFMD is an infection which caused by a group of enteroviruses, both Coxsackievirus A16(CA16) and Enterovirus-71(EV71) are the two major pathogens of this disease. People at all ages exposed to HFMD but children of age 5 years and younger is the riskiest group because they have no immunity to the viruses yet. The disease causes children fever, malaise, poor appetite and ulcers in the mouth. There is no specific treatment for HFMD, the general treatment is to cure fever and treat the ulcers to reduce the pains. HFMD is an endemic in Malaysia but this disease is not extensively studied in Malaysia. Several researches focus on the pathological and diagnostic aspects of HFMD but there is a lack of research in studying the interaction between HFMD and weather in Malaysia. Although HFMD incidences were being notified continuously and HFMD outbreak occurred few years repeatedly in Malaysia, the study regarding HFMD is limited and not much information can be obtained. Hence, this research aims to model the association between HFMD incidences and climate in Selangor using Generalized Linear Models. Descriptive analysis, Mann Kendall trend test, Pearson correlation coefficient, Poisson regression and Negative Binomial regression modelling were applied in this study in order to achieve the research objectives. Then, the best model was selected by comparing the values of AIC and underwent model adequacy test. The finding showed that the number of HFMD incidences was related positively to temperature and cumulative rainfall. Specifically, the modelling demonstrated that increase in mean temperature increase the risk of HFMD infection and the higher weekly cumulative rainfall corresponded to higher weekly HFMD cases. From the finding of this study, authority can set up a proper warning system on the possible HFMD outbreak to community when there is an increase in rainfall and temperature. With this information, HFMD transmission could potentially be monitored and hence the HFMD infection can be prevented and reduced. This study is useful for government to increase the public awareness and give a global warning which possibly to reduce the infection cases.

## ABSTRAK

HFMD ( Penyakit tangan, kaki dan mulut) adalah jangkitan yang diakibatkan oleh kumpulan enterovirus, yang mana kedua-dua Coxsackievirus A16 (CA16) dan Enterovirus-71 (EV71) adalah dua patogen utama penyakit ini. Semua orang terdedah kepada HFMD tetapi kanak-kanak berumur 5 tahun ke bawah adalah kumpulan berisiko tinggi kerana mereka tidak mempunyai imuniti terhadap virus ini. Penyakit ini menyebabkan kanak-kanak demam, kekurangan selera makan dan mengalami ulser di mulut. Setakat ini, tiada rawatan khusus untuk HFMD, rawatan umum adalah menyembuhkan demam dan merawat ulser untuk mengurangkan rasa sakit. HFMD merupakan penyakit berjangkit yang sentiasa berlaku di Malaysia tetapi kurang dikaji secara mendalam di Malaysia. Pada sepuluh tahun kebelakangan ini, terdapat beberapa penyelidikan yang mengkaji dalam aspek patologi dan diagnosis, namun masih kurang kajian tentang interaksi antara HFMD and cuaca di Malaysia. Oleh itu, penyelidikan ini bertujuan untuk memodelkan interaksi antara kes HFMD dan iklim di Selangor, Malaysia. Analisis Deskriptif, Ujian Mann Kendall, koefisien korelasi Pearson, Regresi Poisson dan Regresi Binomial Negatif telah diaplikasikan dalam kajian ini. Model yang terbaik telah dipilih dengan membandingkan nilai-nilai AIC. Hasil kajian ini menunjukkan bahawa bilangan kejadian HFMD ada kaitan dengan suhu dan hujan kumulatif. Secara khusus, model menunjukkan peningkatan suhu menambah risiko jangkitan HFMD dan hujan kumulatif yang lebih tinggi meningkatkan kes HFMD. Dengan hasil ini, pihak berkuasa boleh menubuhkan sistem amaran tentang wabak HFMD yang mungkin berlaku kepada komuniti semasa tempoh peningkatan hujan dan suhu. Dengan maklumat ini, penyakit HFMD boleh dicegah dan dikurangkan. Selain itu, kerajaan dapat meningkatkan kesedaran penduduk dengan hasil kajian ini.

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## LIST OF ABBREVIATIONS

AIC	-	Akaike's Information Criterion
AQI	-	Air quality index
CA16	-	Coxsackievirus A16
EDF	-	Empirical Distribution Function
ELISA	-	EV71 IgM-capture enzyme-linked immunosorbent
EV71	-	Enterovirus-71
GDP	-	Gross domestic product
GICA	-	EV71 IgM-colloidal gold immunochromatographic assay
GLM	-	Generalized linear models
HFMD	-	Hand, foot and mouth disease
MK	-	Mann Kendall
MMD	-	Malaysian Meteorological Department
PCC	-	Pearson correlation coefficient
REDI	-	Regional Emergency Diseases Intervention
URTI	-	Upper respiratory tract infection
WHO	-	World Health Organization

## LIST OF SYMBOLS

$\exp()$	-	Exponential function
$\ln()$	-	Natural Logarithm
$R_i$	-	Rank of observation $x_i$
$Z_s$	-	Standardized test statistic
$d_i$	-	Deviance residuals
$t_j$	-	Tied observations
$\beta_i$	-	Regression coefficient
$\mu_i$ @ $\bar{x}$ @ $\bar{y}$ @ $E(x)$	-	Mean of the sample
$\Sigma$	-	Summation
$H_0$	-	Null hypothesis
$H_a$	-	Alternative hypothesis
$K$	-	Number of estimated parameters
$m$	-	Number of tied ranks group
$n$	-	Sample size
$r$	-	Pearson correlation coefficient
$S$	-	Test statistic of Mann Kendall trend test
$se()$	-	Standard error
$X$	-	Independent variable
$Y$	-	Dependent variable
$\alpha$	-	Desired significance level
$\Gamma()$	-	Gamma function
$V(x)$	-	Variance
$b'$	-	First derivative
$b''$	-	Second derivative
$y!$	-	Factorial of a positive integer $y$
$\eta(\mu_i)$	-	Link function which relating the $\mu_i$ to the linear predictor
$\theta$	-	Canonical parameter
$\sigma$	-	Standard deviation
$\epsilon$	-	Random error
$\phi$	-	Dispersion parameter

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# CHAPTER 1

## INTRODUCTION

### 1.1 Background of the study

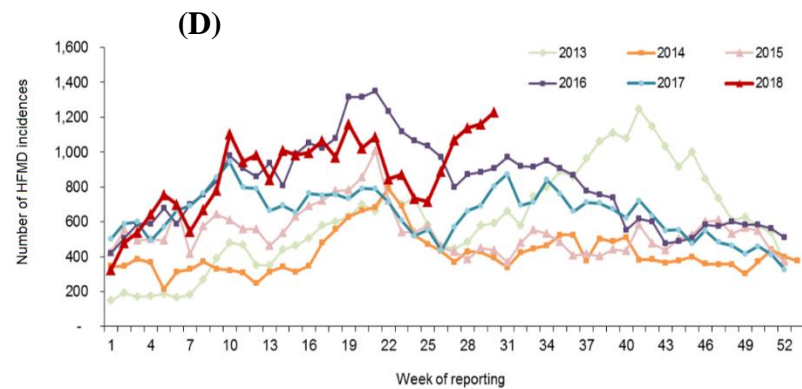
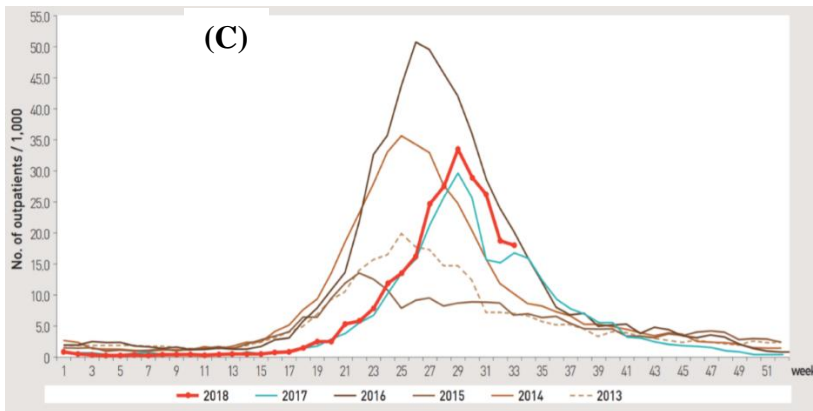
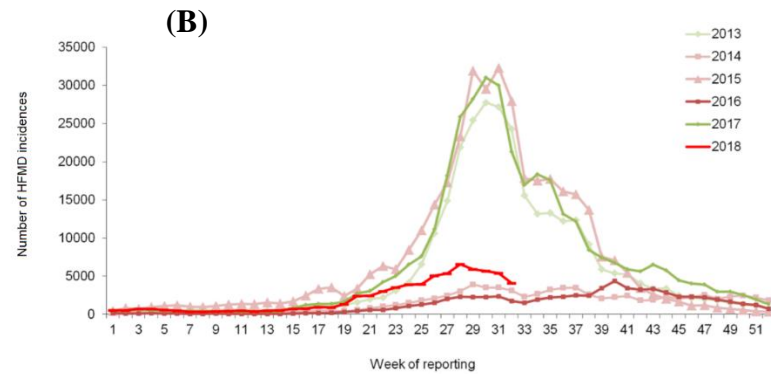
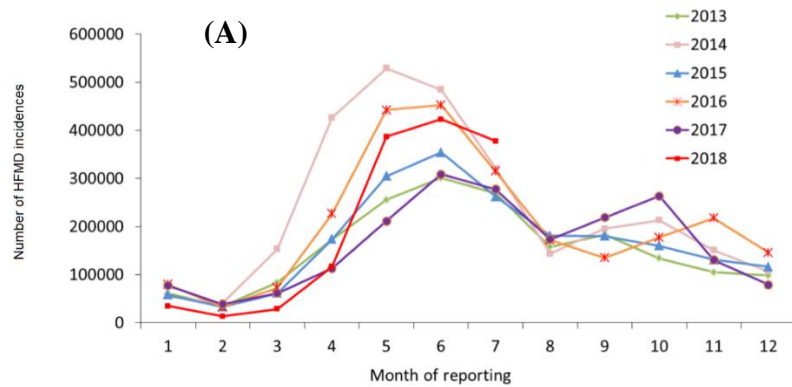
Hand, foot and mouth disease (HFMD) is an infection which is caused by a group of enteroviruses. The two major pathogens of HFMD are Coxsackievirus A16 (CA16) and Enterovirus-71 (EV71) (Malaysia Ministry of Health, 2018a). EV71 infection is characterized by flu-like symptoms, rash on hands, feet and buttocks, ulcers in mouth, poor appetite, diarrhea and vomit (Qiu, 2008). EV71 can cause severe disease and sometimes lead to death (WHO & REDI Centre, 2011). While CA16 infection generally cause ulcers or blisters on the hands, feet and in the mouth as well as pharyngitis, a small amount of patients also develop encephalitis, aseptic meningitis and even fatal myocarditis and pneumonia (Mao et al., 2014).

People at all ages are exposed to HFMD but children of age 5 years and younger is the riskiest group because they have no immunity to the viruses yet. HFMD transmits through direct contact with faeces, respiratory secretions and blister fluid of infected patients or the contact with contaminated objects or contaminated environments. The disease causes children fever, malaise, poor appetite and ulcers in the mouth in 1-2 days' period. The symptoms followed by red rash without itching on palm, feet and buttocks. Severe health effects or death may occur when disease further develops into complications such as encephalitis, aseptic meningitis and acute flaccid paralysis. HFMD can be symptomless and the recovered person is possible to get infected with the disease again by different types of enteroviruses. There is no specific treatment for HFMD, the general treatment is to cure fever and treat the ulcers to reduce the pains. Patients should drink enough fluids to avoid body dehydration. Therefore, prevention should be practised to minimize the risk of disease transmission such as avoid to stay in crowded place, avoid direct contact with infected patient,



maintain personal hygiene and always disinfection of common use items (Hii, Rocklov & Ng, 2011; Malaysia Ministry of Health, 2018a).

In 1973, the properties of EV71 were first recognised when the epidemics of HFMD occurred in Japan. In the 1970s, two large EV71 outbreaks occurred in Europe. The first in Bulgaria and the second outbreak, with 1,550 cases and 47 deaths were reported 3 years later in Hungary. In 1997, severe outbreak was reported in Malaysia with 2,618 HFMD cases and 34 deaths. In 1998, the larger EV71 epidemic occurred in Taiwan; estimated 1.5 million people were infected and 405 children were admitted to hospital for serious complication. In 2008, around 490,000 infections and 126 fatal cases in children were recorded in China. The widespread epidemics have been reported in other countries including Australia, Mongolia, Japan, Singapore, Brunei Darussalam and Vietnam. The disease can occur anytime but in countries with varying climates, it occurs more frequent in the spring to fall (Solomon et al., 2010; WHO & REDI Centre, 2011). Subsequently, World Health Organization(WHO) started to review HFMD issues. WHO cooperated with Regional Emergency Diseases Intervention (REDI) Centre, monitored HFMD across Western Pacific Region to detect the outbreaks and other significant event through the Regional Event Based Surveillance System. However, the summary dated 28-August-2018 is the last update and WHO has ceased to produce the bi-weekly surveillance summary. Figure 1.1 illustrate the number of HFMD incidences reported in China, Japan, Korea and Singapore from year 2013 to 2018. All the data are obtained from WHO Western Pacific Region. Based on the data, the HFMD incidences in China and Korea consistent with seasonal trends from year 2014 to 2017. In Japan, the reported HFMD cases in year 2014, 2016 and 2018 are fewer compared to other year (WHO, 2018).



**Figure 1.1** (A) HFMD incidences reported monthly in China, (B) HFMD incidences reported weekly in Japan, (C) HFMD incidences reported weekly in Korea, (D) HFMD incidences reported weekly in Singapore from year 2013 to 2018 (from WHO, 2018)

In Malaysia, severe HFMD outbreak associated with a number of fatal cases due to infection of brain stem was reported in Sarawak in year 1997. There was a total of 4,253 HFMD cases with 2,113 incidences from Sarawak and 2,140 occurrences from Peninsular Malaysia were reported in June 1997. In the same period, 41 fatal cases were recorded and the infected children mean age was 1.6 years with about 80% of the reported cases were children aged of 4 years and younger and more than 50% were children of aged below 2 years old. Then, a recurrence of HFMD outbreak due to EV71 occurred in late 2000 in Peninsular Malaysia. In 2003, a small outbreak started in Sarawak and spread to Peninsular Malaysia with unknown number of cases. In late 2005, 2 fatal HFMD cases were reported in Peninsular Malaysia and 6 deaths cases were reported in Sarawak, Malaysia in the early 2006 (Chua & Kasri, 2011). Further epidemic occurred in year 2012, September 2014 to April 2015 and year 2016. Similar to other outbreaks, both EV71 and CA61 are the main pathogens.

Considering the continuous occurrence of HFMD incidences and outbreak, this study intended to model the association between HFMD incidences and climate using Generalized Linear Models (GLM). Studies from Singapore, China and Korea have investigated the association between HFMD incidences and meteorological factors in recent decade. Hii et al (2011) revealed weekly temperature and rainfall had statistically significant association with HFMD cases in Singapore. Li et al (2013) studied the relationship between HFMD and meteorological variables using Negative Binomial multivariate regression in Guangzhou, China. Kim et al (2016) showed HFMD occurred more frequent from Spring to early Summer and the disease cases hit the peak in late June every year. The analysis expressed that the number of HFMD incidences was positively correlated with average temperature, relative humidity and rainfall. Nguyen et al (2017) studied a spatial and temporal pattern of HFMD in Vietnam by using GLM with Poisson family allowing over-dispersion. With Poisson regression modelling technique, Du et al (2018) published the first research to explore the association between air pollution and weather factors on HFMD incidences.

The causal association between pathogens and meteorological parameters relate to the interaction between weather and HFMD incidences even though the

underlying factors are not known yet. Feng et al (2014) discussed the temperature and other meteorological factors that might influence the spread of pathogen in the environment, pathogen survivability and individual susceptibility. The temperature, humidity, PH value, exposure to sunlight and salinity affect the survivability of pathogens outside the patients. Epidemiological experimental studies have shown the enteroviruses could survive on nonporous fomites for at least 45 days which depends on the environmental factor such as temperature and humidity. Studies claimed that the activity of pathogens pattern are not known yet but HFMD incidences are associated with the surrounding temperature and maximum temperature. However, micro environment and enteroviruses have a complicated relationship.

In December 2015, The China Food and Drug Administration approved the world's first EV71 vaccine. The vaccine was considered an effective safe prevention of EV71 infection since no serious side effects were reported among the clinical trial of 12,000 children; the common response after the dose are mild which is temporary fever (WHO China Representative Office, 2015). However, the vaccine might be ineffective in preventing HFMD infection since the disease is caused by a group of enteroviruses.

## **1.2 Problem statement**

HFMD is endemic in Malaysia but this disease is not extensively studied in Malaysia, the study regarding HFMD is limited and not much information can be obtained. Several researches focus on the pathological and diagnostic aspects of HFMD but there is a lack of research in studying the interaction between weather and HFMD. In general, public are aware that HFMD occurrence is related to the weather, but the association between HFMD and climate in Malaysia is still required academic documentation to support the assumption. Therefore, it is important to have the study of modelling HFMD with climate factors in Malaysia to explore the relationship between HFMD infection and climate factors statistically. The HFMD modelling could identify the significant association between HFMD and the climates as well as

identify which meteorological parameters associate significantly with HFMD and how is the strength.

### **1.3 Research objective**

The objectives of the research are:

- I. To determine the spatial statistic of HFMD incidences in Malaysia
- II. To determine and assess the trend of HFMD incidences and climate in Selangor
- III. To model the association of HFMD incidences and climate in Selangor using Generalized Linear Models

### **1.4 Scope of the study and limitation**

The HFMD data in this study are secondary data which are retrieved from online open access sources supported by government and the meteorological data are secondary data obtained from Malaysian Meteorological Department (MMD). The duration of both HFMD data and meteorological data is recorded from year 2012 to 2017. HFMD data are recorded in weekly basis of 52 weeks or 53 weeks while meteorological data are recorded in daily basis.

MMD recorded a total of 41 principle meteorological stations for 13 states in Malaysia, with several stations for a particular state. However, in the study, meteorological data from one station was used to represent one state in the modelling. For example, Selangor state has 3 principle meteorological stations which are Subang, Petaling Jaya and KLIA Sepang. The recorded meteorological data from Petaling Jaya station were used to represent the Selangor state.

In the study, the analysis of the HFMD and meteorological data included descriptive statistics, Mann Kendall trend test and Pearson correlation coefficients. Regression technique was applied to model the association between HFMD incidences and climate factors and Akaike's Information Criterion (AIC) was used to select the best model.

### **1.5 Significance of the study**

As the old saying goes, "Prevention is better than cure". With the descriptive statistics of HFMD incidences in Malaysia, the areas which are exposed to HFMD risk can be identified. This information is useful in increasing the awareness among the people and hence will be followed by improving the preventive care to reduce the disease occurrence. For people who stay in the risky area, they should always practise the precautionary measures such as enhancing the personal hygiene and alert about children or own physical health. For the group who wish to travel to HFMD risky area, they should be more careful to avoid getting infected with HFMD.

By knowing the trend of HFMD incidences, the effectiveness of current preventive cares on HFMD can be monitored. If the HFMD cases were occurring increasingly from time to time, government should put in more efforts on promoting the public awareness on HFMD and seek for effective actions to reduce the HFMD incidences happened in the country. If the nationwide HFMD incidences were well controlled, similar preventive cares can be applied on other infectious disease to monitor the disease occurrences. Besides that, global warming is a global issue nowadays, the climate trends assessed in this study could show the severity of climate change in Selangor area.

To date, not much studies have been done to relate the HFMD incidence to the climate in Malaysia. As a tropical country, the humid, warm and rainy weather is conducive for HFMD transmission. With the study of association between HFMD

incidence and climate, HFMD transmission could potentially be monitored and hence the HFMD infection can be prevented and reduced. The study is useful for government to increase the public awareness and give a global warning which possibly to reduce the infection cases. During the high HFMD risk period, public should reduce the social contacts, enhance the hygiene practices, avoid to stay in crowded area and practise other precautionary measure.

The finding of the study is informative to inspire further investigate of similar research in diverse area in order to increase the understanding on the relationship between weather and HFMD. The finding is informative for further study regarding causal association between pathogens and meteorological parameters also. The result is useful as a risk indicator in forecasting the disease outbreak and be a benchmark for other infectious disease research as well.

## **1.6 Organization of the thesis**

This thesis consists of five chapters:

- (a) Chapter 1 introduces the background and the problem statements that motivate the analysis and modelling in the study.
- (b) Chapter 2 covers the literatures of numerous related studies in Malaysia and other countries to offer a comprehensive review.
- (c) Chapter 3 discusses the methodology applied in this thesis.
- (d) Chapter 4 presents the results of the analysis descriptively and statistically and discusses the finding of the study.
- (e) Chapter 5 concludes the study and give recommendation for future research.

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