EPIDEMIOLOGICAL ASPECTS OF HAND, FOOT AND MOUTH DISEASE IN SARAWAK, MALAYSIA

NORAISHAH BINTI MOHAMMAD SHAM

FS 2017 83

EPIDEMIOLOGICAL ASPECTS OF HAND, FOOT AND MOUTH DISEASE IN SARAWAK, MALAYSIA

By

NORAISHAH BINTI MOHAMMAD SHAM

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirement for the Degree of Doctor of Philosophy

July 2017

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

EPIDEMIOLOGICAL ASPECTS OF HAND, FOOT AND MOUTH DISEASE IN SARAWAK, MALAYSIA

By

NORAISHAH BINTI MOHAMMAD SHAM

July 2017

Chairman: Isthrinayagy A/P S.Krishnarajah, PhD
Faculty: Science

Hand, Foot and Mouth Disease (HFMD) is a contagious disease in human population especially infants and children. In Sarawak, Malaysia, the disease is endemic. Since the first outbreak in 1997, Sarawak remains as the state with the highest number of HFMD notified cases among other states in Malaysia. In Malaysia, there have been many studies related to HFMD that investigates the clinical aspects of the disease. In this study, we aim to study the epidemiological aspects of HFMD in Sarawak, Malaysia and to provide beneficial information based on the analysis of the data in order to reduce the spread of HFMD in Malaysia. In order to achieve the objective of this study, we observe the effect of non-random mixing patterns of HFMD notified cases in Sarawak, Malaysia; obtain appropriate time series model and forecast future HFMD outbreaks in Sarawak, Malaysia; observe the impact of climatic factors on HFMD in Sarawak, Malaysia; analyze spatial and temporal patterns of HFMD in Sarawak, Malaysia and provide recommendations for future HFMD surveillance and control programme in Sarawak, Malaysia.

In order for us to really understand the insights of HFMD, we characterized the disease by analyzing 71,512 HFMD notifications from week 1, 2006 to week 52, 2013 for Sarawak, Malaysia. The dataset was obtained from Infectious Disease Control Section (IDSC), Sarawak State Health Department (SSHD). Analysis of HFMD during the study period showed that the disease outbreak in 2006 was the highest with 14,875 notified cases. A three-year (2011-2013) daily data of 24,879 notifications were used to study the effects of age factors in a non-random mixing pattern. As a result, 76.95 percentage (18,427) of children below the age of five were predominant to HFMD in Sarawak. It is also shown that the ratio of male to female is slightly higher for this age group.

HFMD can spread through close personal contact, the air (through coughing or sneezing), contact with feces or contaminated objects and surfaces. Few countries claimed that climate played a role to the disease transmission. A time series model is constructed with and without the climate factors such as temperature and rainfall to see the effect of climatic factors on the spread of HFMD. The feasibility and practicality of modelling and forecasting HFMD trends was demonstrated. ARMA (Autoregressive Moving Average) and ARMAX (Auto Regressive Moving Average with exogenous variables) models were generated using HFMD notification data and climate variables from 2006 to 2012. The forecast result was then compared to the actual HFMD notification data in 2013. It is found that ARMA(1,4) model is able to give good prediction and forecast at 94 percent of the notified cases fall within the 90 percent forecast interval based on historical data.

We analyze temporal and spatial patterns of the disease in Sarawak using Geographical Information System (GIS). We evaluated the potential of clustering of HFMD notified cases by divisions in Sarawak using two approaches; choropleth mapping and spatial interpolation. We also analyzed the effects of locality which can demonstrate the high or low risk of HFMD notified cases between the rural and urban divisions. The findings indicate that during the outbreak year (2012), spatial autocorrelation exist between the divisions. However, visually HFMD notified cases can be seen to be clustered covering neighbouring divisions in the center of the state also in year 2009. Moreover, high risk was found in urban divisions of Sarawak during the outbreak year.

This study has provided valuable information to the knowledge of HFMD epidemiology, trends and patterns in Sarawak, Malaysia which would help in containing the disease. In addition, throughout this study, few new areas of research were identified and recommendations have been developed in order to enhance HFMD surveillance, prevention and control in Malaysia.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

ASPEK EPIDEMIOLOGI PENYAKIT TANGAN, KAKI DAN MULUT DI SARAWAK, MALAYSIA

Oleh

NORAISHAH BINTI MOHAMMAD SHAM

Julai 2017

Pengerusi: Isthrinayagy A/P S.Krishnarajah, PhD
Fakulti: Sains

Penyakit tangan, kaki dan mulut (HFMD) adalah penyakit yang mudah dijangkiti terutama sekali dikalangan bayi dan kanak-kanak di dalam sesebuah populasi. Penyakit ini adalah endemik di Sarawak, Malaysia. Sejak tercetusnya wabak HFMD yang pertama pada tahun 1997, Sarawak kekal sebagai negeri yang mempunyai jumlah bilangan kes notifikasi HFMD tertinggi berbanding negeri-negeri lain di Malaysia. Terdapat banyak kajian berkaitan dengan HFMD di Malaysia telah dijalankan sebelum ini yang merujuk kepada bahagian klinikal sahaja. Oleh yang demikian, tujuan kajian ini dijalankan adalah untuk melihat aspek epidemilogi penyaki HFMD di Sarawak, Malaysia dan memberi maklumat yang berguna berdasarkan analisis yang dijalankan ke atas data kajian dalam mengurangkan penyebaran penyakit ini. Objektif ini dapat dicapai dengan melihat kesan corak pertalian bukan rawak kes notifikasi penyakit HFMD di Sarawak, Malaysia, membentuk model siri masa yang sesuai dan ramalan bagi wabak pada masa hadapan, melihat kesan faktor iklim pada penyakit HFMD, menganalisis corak spatial dan temporal penyakit HFMD dan memberikan cadangan untuk pencegahan dan pengendalian penyakit HFMD di masa hadapan serta program kawalan penyakit ini di Sarawak, Malaysia.

Dalam usaha untuk mendapatkan kefahaman penyakit HFMD, kami telah menganalisis sebanyak 71,512 data kes notifikasi HFMD dari minggu 1, 2006 hingga minggu 52, 2013 bagi negeri Sarawak, Malaysia. Data kes notifikasi HFMD ini diperolehi daripada Bahagian Kawalan Penyakit Berjangkit (IDSC), Jabatan Kesihatan Negeri Sarawak (SSHD). Analisis terhadap penyakit HFMD dalam tempoh kajian ini menunjukkan wabak penyakit HFMD adalah tertinggi pada tahun 2006 dengan jumlah sebanyak 14,875 kes notifikasi. Data harian bagi tiga tahun (2011-2013) digunakan untuk mengkaji kesan faktor umur dalam corak bercampur secara tidak rambang. Keputusan kajian ini

menunjukkan 76.95 peratus (18,427) kanak-kanak yang berumur lima tahun kebawah mendominasi penyakit HFMD di Sarawak. Disamping itu juga, nisbah lelaki kepada perempuan adalah tinggi sedikit bagi kumpulan umur ini.

Penyakit HFMD boleh merebak melalui udara. Beberapa negara mendakwa bahawa faktor iklim memainkan peranan dalam penyebaran penyakit ini. Model siri masa telah dibentuk dengan dan tanpa faktor iklim seperti suhu dan taburan hujan untuk melihat kesan faktor iklim keatas penyebaran penyakit HFMD. Kebolehlaksanaan dan praktikal dalam pemodelan serta meramalkan tren bagi penykit HFMD turut ditunjukkan. Model ARMA (Autoregresi Purata Bergerak) dan ARMAX (Autoregresi Purata Bergerak dengan pembolehubah exogen) dibentuk menggunakan data kes notifikasi penyakit HFMD dan pembolehubah iklim dari tahun 2006 sehingga 2012. Hasil ramalan kemudiannya dibandingkan dengan jumlah kes notifikasi sebenar bagi tahun 2013. Model ARMA(1,4) telah memberikan ramalan jangkauan yang baik dengan 94 peratus kes notifikasi berada dalam 90 peratus selang ramalan dengan hanya menggunakan data sejarah sahaja.

Kami menganalisis corak temporal dan spatial penyakit HFMD di Sarawak menggunakan kaedah Sistem Maklumat Geografi (GIS). Kami menilai potensi pengelompokan dalam kes notifikasi penyakit HFMD dari segi bahagian-bahagian dalam negeri Sarawak menggunakan pendekatan pemetaan 'choropleth' dan interpolasi spatial. Kami juga menganalisis kesan kedudukan kawasan yang boleh menunjukkan risiko yang tinggi atau rendah penyakit HFMD melalui kes notifikasi dan juga bahagian bandar dan luar bandar. Hasil kajian menunjukkan bahawa autokorelasi spatial wujud diantara bahagian ketika tahun yang berlakunya wabak (2012). Walaubagaimanapun, pengelompokan di bahagian pusat bandar negeri dapat dilihat secara visual melalui kes notifikasi penyakit HFMD pada tahun 2009. Disamping itu juga, bahagian-bahagian bandar di Sarawak adalah berisiko tinggi ketika tahun yang berlakunya wabak.

Kajian ini turut memberikan maklumat yang berharga mengenai penyakit HFMD dari segi epidemiologi, trend dan corak di Sarawak yang mana dapat membantu dalam menangani penyakit ini. Tambahan lagi, melalui kajian ini, terdapat banyak bidang-bidang kajian baru telah dikenalpasti dan cadangan yang membangun dalam meningkatkan pengawasan penyakit HFMD, pencegahan dan kawalan penyakit ini di Malaysia.

ACKNOWLEDGEMENTS

Firstly, thanks to Almighty Allah SWT for giving me the strength, guidance and patience to complete this research.

I am grateful to have Dr. Isthrinayagy A/P S.Krishnarajah as my main supervisor that guided, showed me the way and helping me to achieve a clearer structure throughout the seven years journey in completing my study. To my supervisory committee, Prof. Dato' Dr. Lye Munn Sunn and Prof. Dr. Noor Akma Ibrahim who encouraged me to pursue the topic.

I would like to extend my appreciation to my main financial support, Ministry of Science, Technology and Innovation (MOSTI) for offering the scholarship. Many thanks to Mr. Davidson of Crisis Preparedness and Response Centre, Communicable Disease Control Section, Sarawak State Health Department (SSHD) and MetMalaysia for all the invaluable assistance on compiling the eight years dataset.

I would like to acknowledge the support of the management at Environmental Health Research Centre (EHRC), Institute for Medical Research (IMR) and Ministry of Health (MOH) who approved my study leave. To all staff of Institute for Mathematical Research (INSPEM) of Universiti Putra Malaysia, thank you for helping me especially the administrative work.

I am also very thankful to have good friends, Ms. Siti Annazirin, Ms. Syarifah Nasrisya, Mr. Lukman and friends for all the support, encouragement, sad and happy moments that they shared with me along this journey.

Last but no least, special thanks to my husband and my parents who took care of my babies. I am so thankful for their valuable time that they sacrificed which I cannot pay. To my daughters (Nuha Wafiyya, Hani Syarafina, Aimy Rumaisya) and future baby that I am carrying, sisters, brothers and other family members, thank you for the prayers of my success, being so understanding and support me without fail, words cannot describe how wonderful and important to have all of you in my life.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

HFMD	Hand, Food and Mouth Disease
CDC	Centers for Disease Control and Prevention
SSHD	Sarawak State Health Department
EV71	Enterovirus 71
Cox A16	Coxsackievirus A16
WHO	World Health Organization
WPRO	WHO Western Pacific Region
PCID	Prevention and Control Infectious Diseases
MOH	Ministry of Health
IDSC	Infectious Disease Surveillance Center
CPRC	Crisis Preparedness and Response Centre
CNS	Central Nervous System
UNEP	United Nations Environment Programme
AR	Auto Regressive
MA	Moving Average
ARMA	Auto Regressive Moving Average
ARMAX	Auto Regressive Moving Average with exogenous variables
ACF	Auto Correlation Function
PACF	Partial Auto Correlation Function
AIC	Akaike's Information Criterion
AICC	Akaike's Information Corrected Criterion
ADF	Augmented Dickey-Fuller
GIS	Geographic Information System
IDW	Inverse Distance Weighted
WMO	World Meteorological Organization
EWS	Early Warning System
GWR	Geographically Weighted Regression
ANS	Automatic Nervous System
PCR	Polymerase Chain Reaction
HFRS	Haemorrhagic Fever with Renal Syndrome
SARIMA	Seasonal Autoregressive Integrated Moving Average
NARNN	Nonlinear Autoregressive Neural Network
CDCIS	Communicable Disease Control Information System
CFDA	China Food and Drug Administration
DF	Dengue Fever
DHF	Dengue Haemorrhagic Fever
MMD	Malaysian Meteorological Department
DOS	Department of Statistics
CSF	Cerebrospinal Fluid
FDS	Flying Doctor Service
GDP	Gross Domestic Product
PCID	Prevention and Control of Infectious Diseases

CHAPTER 1

GENERAL INTRODUCTION

1.1 Preface

This chapter gives an introduction to the Hand, Foot and Mouth Disease (HFMD), risk and the epidemiological aspects of HFMD. This chapter also includes the problem statement, objectives and the significance of the study. The outline of the overall thesis is given in the last section of this chapter.

1.2 Epidemiology of HFMD

1.2.1 Global situation

The definition of Hand, Foot and Mouth Disease (HFMD) according to the National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC) Atlanta is '*a common viral illness that usually affects infants and children younger than 5 years old*' (CDC, 2015). According to World Health Organization (WHO), HFMD is prevalent in many Asian countries and everyone is susceptible including the adults (WHO, 2012). Recently, HFMD outbreaks occurred more in Asian countries such as China, Hong Kong (China), Japan, Thailand, Republic of Korea, Singapore, Taiwan, Vietnam and Malaysia with a large number of reported cases (WHO, 2012). Figure 1.1 shows the major outbreaks of HFMD that occurred in Southeast Asian countries according to year and the number of reported cases. It is seen that Thailand experienced major outbreak with more than 13,000 reported cases for the first six months in year 2012.

Most of the Western Pacific Region countries update and report the number of HFMD cases of their respective countries to WHO. These information will then be compiled and translated to the surveillance summary biweekly report where the graphical display of the case counts and the trend of HFMD by each country in the region is given. The reported number of HFMD cases and death in the region for 2016 is summarized in Table 1.1 (WPRO, 2016).

Table 1.1: Reported number of HFMD cases and death

Region	Reported cases	Reported deaths
China	1,620,670	151
Japan	21,512	NA
Macau	2,577	NA
Singapore	29,009	NA
Vietnam	20,438	0

*NA=Not available

The information on the descriptive epidemiology of HFMD outside Western Pacific Region countries are lacking and limited. However, countries such as Bulgaria, Hungary and Australia had reported on HFMD cases that occurred in their country. Bulgaria experienced EV71 outbreaks in 1975 and Hungary in 1978 with few fatal cases. During the summer season of 2000 to 2001, HFMD outbreak has occurred in Sydney where 200 children were suspected to have been infected by EV71 virus (WPRO, 2012).

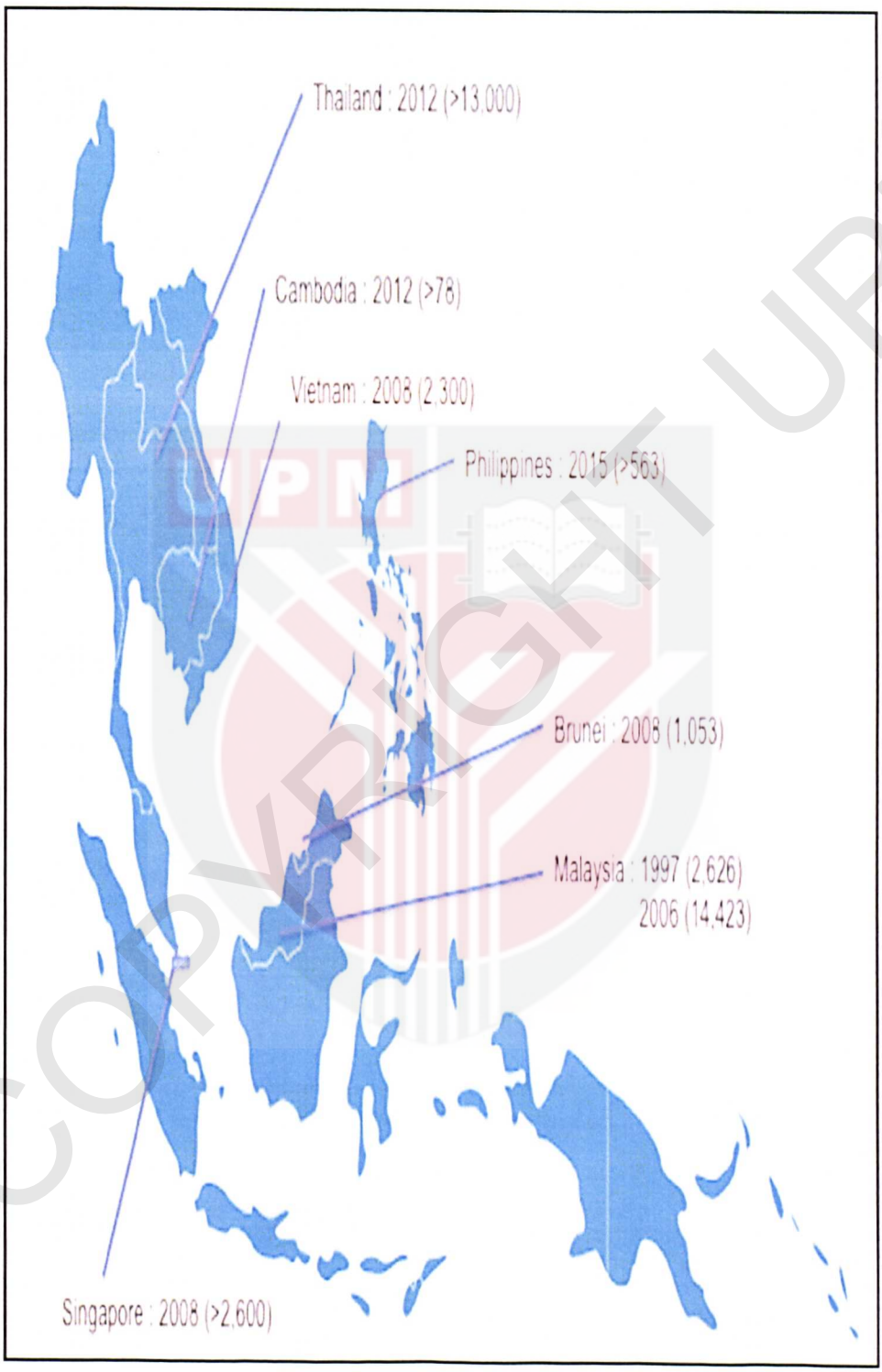

Figure 1.1: Major outbreaks of HFMD in Southeast Asia

1.2.2 Situation in Malaysia

HFMD is a non-zoonotic disease which is managed by the Zoonosis Sector, Disease Control Division in Ministry of Health Malaysia. HFMD in Malaysia is notifiable under the PCID Act 1988. Malaysia experienced the first HFMD outbreak in 1997 in Sarawak with 889 children were hospitalized. During the outbreak, 31 children aged between 5 months to 6 years old died of rapidly progressive cardiorespiratory failure (WPRO, 2012). The ratio of male to female is 1.9:1. According to Health Facts Malaysia from year 2002 to 2015, the national incidence rate of HFMD shows a huge increment from 10.58 cases per 100,000 population in 2002 to 74.09 cases in 2015. Similarly, the mortality rate also shows a cyclical trend from 2002 to 2008 and remain with no death cases per 100,000 population since 2009. In 2012, HFMD cases had the highest incidence rate which reached to 117.66 cases per 100,000 population. This values were clearly seen in Figure 1.2.

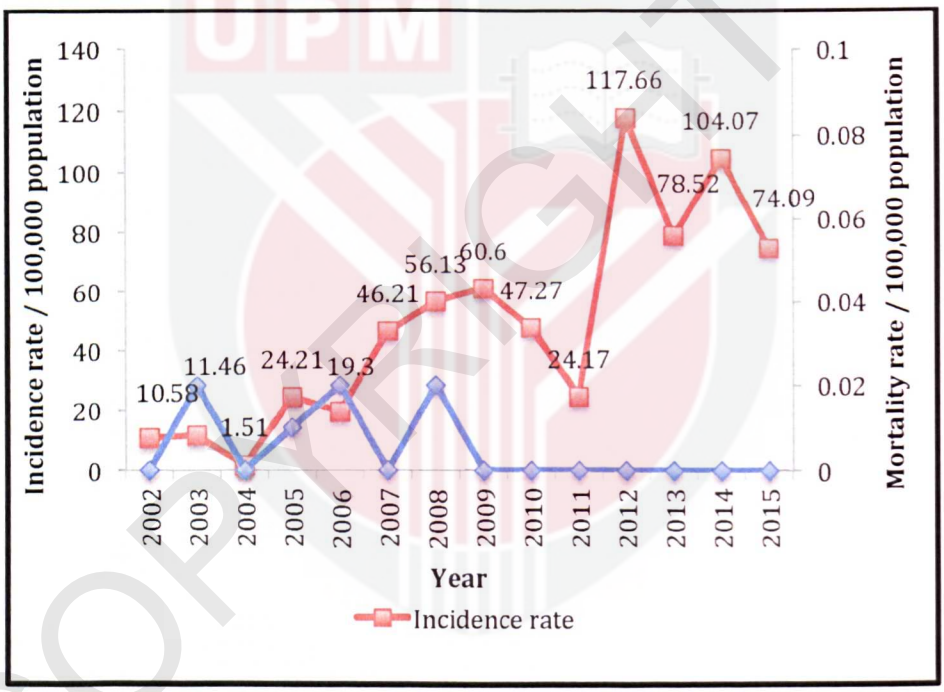

Figure 1.2: HFMD incidence rate and mortality rate for year 2002 to 2015 in Malaysia

Podin et. Al (2006) did a study from March 1998 to June 2005 where 2,950 children with EV71 in Sarawak participated in the study. From this number, male to female ratio is 1.3:1. A clinical research done by Hooi et.al (2002) initiated 467 patients of HFMD from May 1997 to June 2001. Majority (87.8%) of the patients are children with age of 4 years and below. Among this age group, children aged 1 to 2 years old is 52%. Hence, it can be concluded that the age group of children between 1 to 2 years old are the most affected group

for HFMD in Peninsular Malaysia during the outbreak. Furthermore, the ratio of male to female is 1.81:1. This study also observed the ethnic groups of the HFMD patients where Malays rise at 61.9% followed by Chinese (31.9%), Indian (3.6%) and other races (2.6%). However, this study remarked that both gender and ethnic shows no significant difference in the isolation rate at *p*-value of 0.8247 and 0.9189 respectively.

Table 1.2 compiled the cumulative number of HFMD notified cases in Malaysia according to the state (MOH, 2013; DGMOH, 2016). Sarawak stood up with the highest number of HFMD cases in 2012 while Perlis had the lowest with 137 cases. However, in 2016 HFMD in Selangor was recorded as the highest with 7,471 notified cases followed by Sarawak which recorded the second highest with 3,007 cases. The table also shows that there were few states with less than 500 cases such as Kelantan, Pahang, Perlis, Terengganu and Wilayah Persekutuan Labuan.

Table 1.2: Total number of HFMD notified cases in Malaysia by state at respective week and year

No.	State	Epid Week 1 to 23, 2012	Epid Week 1 to 31, 2016
1	Johor	1,624	2,294
2	Kedah	606	641
3	Kelantan	1,215	NA*
4	Melaka	584	1,198
5	Negeri Sembilan	552	889
6	Pahang	258	NA*
7	Perak	862	1,361
8	Perlis	137	NA*
9	Penang	818	1,357
10	Sabah	1,031	1,535
11	**Sarawak**	**7,354**	3,007
12	Selangor	4,559	**7,471**
13	Terengganu	233	NA*
14	Wilayah Persekutuan Kuala Lumpur	1,774	2,084
15	Wilayah Persekutuan Labuan	343	NA*

NA = State with HFMD cases less than 500

The sentinel surveillance programme has been conducted by Zoonosis Sector, Disease Control Division in Ministry of Health Malaysia to record epidemiological HFMD data. As for Sarawak, the informations were reported on weekly basis at divisions level in the Sarawak Weekly Epid News since the first

outbreak in 1997. Sarawak State Health Department (SSHD) carried out few activities with specific purpose to reduce the HFMD transmission in the state where every department was involved in advising the operators of child care centers and kindergartens and parents to carry out cleaning, disinfection of their premises, furniture, equipment, toys and take the children to the doctor immediately. The SSHD also helps to educate members of the society by distributing HFMD pamphlets and carry out radio talks in various languages such as Bahasa Melayu, English, Mandarin, Iban and Bidayuh for state-wide broadcast on HFMD. Beside, the enforcement of legislation to the state-wide closure of all child care centers or kindergartens was announced by the Minister of Health Malaysia on March 2006. From Table 1.2, it shows that all states recorded an increase in the number of notified cases from year 2012 to 2016 except for Sarawak. It is assumed that those activities taken by SSHD helps in order to reduce and control HFMD cases while the department regularly monitor and take precautions to contain the disease.

Figure 1.3 shows that a total of 101,070 HFMD notifications have been identified in Sarawak, Malaysia from the first outbreak, 1997 to July 2013. Sarawak experienced more outbreaks that peaked in 2006 with 14,875 cases whereas in 2008 and 2009 with 10,435 and 9,655 cases respectively whilst in 2012 with 13,495 notified HFMD cases.

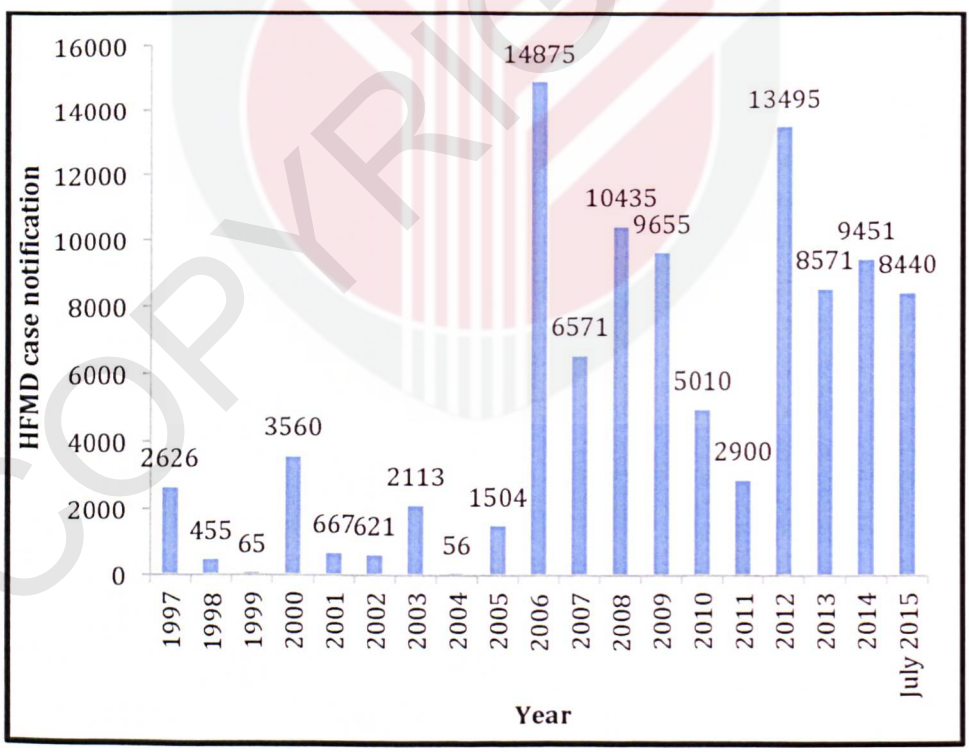

Figure 1.3: HFMD case notification from 1997 to 2013 in Sarawak, Malaysia

1.3 Problem Statement

Population data of China for year 2011 showed that the annual cost related to HFMD is more than US$7.66 million for a population of 1.42 million children aged below 9 years with an average cost of US$208.2 per case (Wang et al., 2016). In overall, 97% of all of the HFMD-related expenses were paid for by the families creating a considerable economic burden. Even though the burden of HFMD in Malaysia is unknown (MOH, 2007), HFMD has been ranked among the top five contributors to the burden of communicable and non-communicable diseases in Malaysia (WHO, 2013). Hence, a study on HFMD in Malaysia is crucial.

Although various measures have been taken to contain the disease and reduce the spread of this infection, there seems to be an increase in the number of reported cases every year not forgetting the outbreak that occurred few times especially in Sarawak. This is an issue which could cause social and economic problem if not addressed. Therefore, we carry out this study to address this problem. Besides, at the very best of our knowledge, there have been many studies of HFMD in Malaysia which focussed on the clinical aspects of the disease but limited number on application of methods to analyse the data and provide effective measures to curb the disease. It is hoped that this study will provide information in suggesting effective measures to reduce HFMD transmission generally in Malaysia.

1.4 Objectives

1.4.1 General objective

The general objective of this study is to study the epidemiological aspects of HFMD in Sarawak, Malaysia and to provide beneficial information based on the analysis of the data in order to reduce the spread of HFMD in Malaysia. The more specific objectives are as given below.

1.4.2 Specific objectives

More specifically, in this study we

1. characterize the HFMD epidemic and its epidemiological features in Sarawak, Malaysia;
2. observe the effect of non-random mixing patterns of HFMD notified cases in Sarawak, Malaysia;
3. obtain appropriate time series model and forecast future HFMD outbreaks in Sarawak, Malaysia;
4. observe the impact of climate factors on HFMD in Sarawak, Malaysia;
5. analyze spatial and temporal patterns of HFMD in Sarawak, Malaysia;
6. provide recommendations for future HFMD surveillance and control programme in Sarawak, Malaysia.

1.5 Significance of The Study

To the best of our knowledge, this is the first study on epidemiological aspects of HFMD carried out using a rather different approach based mainly on statistical and GIS tools focusing on the state of Sarawak, Malaysia. We hope that this study will benefit the health policy makers especially the state health department surveillance team in order to take relevant action to manage and contain the spread of HFMD in Sarawak, Malaysia.

1.6 Thesis Outline

We summarize the chapters of this thesis as follows.

In chapter 2, the literature review regarding HFMD is presented. It provides a historical background of the re-emergence of HFMD, the signs and symptoms, causes and disease transmission, prevention and treatment, HFMD viruses, the infection, risk factor, surveillance and control, vaccination and lastly the monitoring of HFMD. Chapter 3 discusses in detail the materials and methods used to analyze HFMD dataset throughout the study which includes research area, data sources, data preparation, contact patterns, the correlation matrix, time series and spatial data analysis.

While in chapter 4, we present the results on the effect of mixing pattern of specific age group of individuals on HFMD in Sarawak by specifically considering non-random mixing in the population, time series model and the effects of weather factors of HFMD in Sarawak and later we perform the spatial patterns of the disease. It is hoped that with all the results that we obtain, it will help the health authorities to prioritize the vulnerable group and specific area timely for any future outbreak of the disease.

The discussion and summary of the study are presented in chapter 5. Lastly, we suggest for future works and recommendations in chapter 6.

1.7 Conclusion

Each individual in Malaysia especially in Sarawak are susceptible to HFMD regardless the age. However, infants and children are the most susceptible age group which will get infected by the virus. HFMD guidelines has been initiated by Ministry of Health (MOH) Malaysia to help health personnels and authorities in order to get them prepared when the disease outbreak occur in the future.

REFERENCES

Allard, R. (1998). Use of time-series analysis in infectious disease surveillance. *Bulletin World Health Organization*, *76* (4): 327-333.

Amrita, T. (2013). Aiming at bivalent VLP vaccine for HFMD. *BioSpectrum*. Retrieved from http://www.biospectrumasia.com/biospectrum/influencers/198430/aiming-bivalent-vlp-vaccine-hfmd#.Uy-sdv2gGT8

Anderson R. M., & Mary, R. M. (1992). *Infectious Diseases of Humans. Dynamics and Control.* Oxford: Oxford University Press.

Ang, L. W., Koh, B. K., Chan, K. P., Chua, L. T., James, L., & Goh, K. T. (2009). Epidemiology and control of hand, foot and mouth disease in Singapore, 2001-2007. *Annals Academy of Medicine, Singapore*, 38(2): 106-112.

Apolloni, A., Chiara, P.& Vittoria, C. (2013). Age-specific contacts and travel patterns in the spatial spread of 2009 H1N1 influenza pandemic. *BMC Infectious Diseases*, 13:176.

Azmi, S. Z., Latif, T., Ismail, A. S., Juneng, L., & Jemain, A. A. (2010). Trend and status of air quality at three different monitoring stations in the Klang Valley, Malaysia. *Air Quality Atmosphere and Health*, 3: 53-64.

Bhunia, G. S., Kesari, S., Chatterjee, N., Kumar, V., & Das, P. (2013). Spatial and temporal variation and hotspot detection of kala-azar disease in Vaishali district (Bihar), India. *BMC Infectious Diseases*, 13(64).

Bie, Q., Qiu, D., Hu, H., & Ju, B. (2010). Spatial and Temporal Distribution Characteristics of Hand-Foot-Mouth Disease in China. *Journal of Geo-information Science*. 12(3), doi: 10.3724/SP.J.1047.2010.00380

Boon, P. (2015, March 13). Director: HFMD outbreak declared in Sarawak. *The Borneo Post*. Retrieved from http://www.theborneopost.com/2015/03/13/director-hfmd-outbreak-declared-in-sarawak

Box, G. E., Jenkins, G. M., & Reinsel, G. C. (2008). *Time Series Analysis: Forecasting and Control.* (4 ed.). New Jersey: John Wiley S& Sons.

Box, G. E., & Pierce, D. (1970). Distribution of residual autocorrelations in autoregressive-integrated moving average time series models. *Journal of the American Statistical Association*, 65: 1509-1526.

Brockwell, P. J., & Davis, R. A. (1996). *Introduction to Time Series and Forecasting*. New York: Springer.

CDC, China. (2008). *Report on the hand, foot, and mouth disease in Fuyang City, Anhui Province and the prevention and control in China*. Beijing, Chinese Center for Disease Control and Prevention.

CDC, A. (2011). Hand, Foot, and Mouth Disease (HFMD). *CDC Atlanta*. Retrieved from http://www.cdc.gov/hand-foot-mouth/about/index.html

CDC, A. (2015). Hand, Foot, and Mouth Disease (HFMD). *CDC Atlanta* Retrieved from http://www.cdc.gov/features/handfootmouthdisease/

Chaikaew, N., Tripathi, N. K., & Souris, M. (2009). Exploring spatial patterns and hotspots of diarrhea in Chiang Mai, Thailand. *International Journal of Health Geographics*, 8(36). Doi:10.1186/1476-072X-8-36

Chan, K. P., Goh, K. T., Chong, C. Y., Teo, E. S., Lau, G., & Ling, A. E. (2003). Epidemic hand, foot and mouth disease caused by human enterovirus 71, Singapore. *Emerging Infectious Diseases*, 9(1): 78–85.

Chan, L. G., Parashar, U. D,, Lye, M. S., Ong, F. G., Zaki, S. R., Alexander, J. P., Ho, K. K., Han, L. L., Pallansch, M. A., Suleiman, A. B., Jegathesan, M., & Anderson, L. J. (2000). Deaths of children during an outbreak of hand, foot and mouth disease in Sarawak, Malaysia: clinical and pathological characteristics of the disease. Outbreak study group, *Clinical Infectious Disease*, 31(3): 678-683.

Chin, M. Y. (2012, February 27). Access to healthcare a challenge for Sarawak's interior folk. *The Star (Malaysia)*. Retrieved from http://www.thestar.com.my/lifestyle/features/2012/02/27/access-to-healthcare-a-challenge-for-sarawaks-interior-folk/.

Deng, T., Huang, Y., Yu, S., Gu, J., Huang, C., Xiao, G., & Hao, Y. (2013). Spatial-temporal clusters and risk factors of hand, foot, and mouth disease at the district level in Guangdong province, China. *PloS ONE*, 8(2); e56943.

DGMOH, (2016, August 11). Situasi Semasa Penyakit Tangan Kaki dan Mulut (HFMD) di Malaysia. Retrieved from https://kpkesihatan.com/2016/08/11/kenyataan-akhbar-kpk-11-ogos-2016-situasi-semasa-penyakit-tangan-kaki-dan-mulut-hfmd-di-malaysia/

Dom, N. C., Ahmad, A. H., Nasir, R. A., & Ismail, R. (2010). Proceedings from CSSR 2010: *Spatial Mapping of Temporal Risk Characteristic of Dengue Cases in Subang Jaya*, Kuala Lumpur, Malaysia.

DOS, Malaysia. *Population and housing census Malaysia 2010 report, (2010)*.

Eagle, R. F., & Granger, C. W. J. (1987). Co-integration and error correction: representation, estimation and testing. *Econometrica*, 55: 251-276.

Evans, A. D., & Waddington, E. (1967). Hand, foot and mouth disease in South Wales. *British Journal of Dermatology*. 79(27): 309-317.

Farrington, C. P., & Whitaker, H. J. (2005). Contact surface models for infectious diseases: estimation from serologic survey data. *Journal of the American Statistical Association*, 100(470): 370-379.

Faulkner, C. F., Godbolt, A. M., DeAmbrosis, B., & Triscott, J. (2003). Hand, foot and mouth disease in an immunocompromised adult treated with aciclovir. *Australasian Journal of Dermatology*. 44(3): 203–206.

Feng, H., Duan, G., Zhang, R., & Zhang, W. (2014). Time series analysis of hand-foot-mouth disease hospital establishment of forecasting models using climate variable. *PloS One*, 9(1): e87916.

Fisher, N. I., Lewis, T., & Embleton, B. J. J. (1987). *Statistical Analysis of Spherical Data*. Cambridge: Cambridge University Press.

Haburi, H., Rosli, Z., Norlisam, L., Azlai, T., & SitiFauziah, M. A. (2010). *Extreme Weather of Sarawak 2009*. Sarawak, Malaysia.

Hafiz, H., Shohaimi, S., & Hashim, N. R. (2012). Risk mapping of dengue in Selangor and Kuala Lumpur, Malaysia. *Geospatial Health*, 7(1): 21-25.

Hamed, B., & Salim, N. *Prediction of Dengue Outbreak in Malaysia Using The Combination of Clinical, GIS and Meteorological Data and Machine Learning Techniques.* Paper presented at the Postgraduate Annual Research Seminar, Universiti Teknologi Malaysia, Johor Bharu. 2015.

Hand, Foot and Mouth Disease, 2000-2003, Japan, (2004). Infectious Agents Surveillance Report. 25(9):224–225.

Hii, Y. L., Rocklöv, J., & Ng, N. (2011). Short term effects of weather on hand, foot and mouth disease. *PLoS One*, 6(2): e16796. doi:10.1371/journal.pone.0016796

Ho, M. (2000). Enterovirus 71: The virus, its infections and outbreaks. *Journal of Microbiology, Immunology and Infection*, 33(4): 205-216.

Ho, M., Chen, E. R., Hsu, K. H., Twu, S. J., Chen, K. T., Tsai, S. F., Wang, J. R., & Shih, S. R.,(1999*). An Epidemic of Enterovirus 71 Infection in Taiwan*. Taiwan Enterovirus Epidemic Working Group, 341(13), 929-935.

Hooi, P. S., Chua, B. H., Lee, C. S. M., Lam, S. K., & Chua, K. B. (2002). Hand, foot and mouth disease: University Malaya Medical Centre Experience. *Medical Journal of Malaysia*, 57(1): 88-91.

Huang, C. C., Liu, C. C., Chang, C. C., Chen, C. C., Wang, S. T., & Yeh, T. F. (1999). Neurologic complications in children with enterovirus 71. *The New England Journal of Medicine*, 341(13): 936-942.

Huang, Y., Deng, T., Yu, S., Gu, J., Huang, C., Xiao, G., & Hao, Y. (2013). Effect of meteorological variables on the incidence of hand, foot, and mouth disease in children: a time-series analysis in Guangzhou, China. *BMC Infectious Diseases*,13(134), doi:10.1186/1471-2334-13-134

Hurvish, C. M., & Tsai, C. L. (1989). Regression and time series model selection in small samples. *Biometrica*. 76: 297-307.

Hussin, Z. A. M., AbdulMajid, N. A., Said, M. A. M., Baharudin, S. H., & Mahmood, N. N. *The Application of Geographic Information System (GIS) and Remote Sensing Techniques in Mapping of Children with Malnutrition – An Introduction.* Paper presented at MapAsia 2003, Kuala Lumpur. Retrived from http://www.medic.usm.my/~helic/gis_files/Malnutrition%20Mapping.pdf

Jee, Y. M., Cheon, D. S., Kim, K., Cho, J. H., Chung, Y. S., Lee, J., Lee, S. H., Park, K. S., Lee, J. H., Kim, E. C., Chung, H. J., Kim, D. S., Yoon, J. D., & Cho, H. W. (2003). Genetic analysis of the VP1 region of human enterovirus 71 strains isolated in Korea during 2000. *Archives of Virology*, 148(9): 1735–1746.

Komatsu, H., Shimizu, Y., Takeuchi, Y., Ishiko, H., & Takada, H. (1999). Outbreak of severe neurologic involvement associated with Enterovirus 71 infection. *Pediatric Neurology*, 20(1):17–23.

Kheirandish, S., Liaghat, M., Azahar, T. M., & Gohari, A. (2012). Comparison of interpolation methods in prediction the pattern of basal stem rot diesease in palm oil plantation. *Geoinformatica - An International Journal (GIIJ)*, 2(1):12-16.

Kumar, K. B., Kiran, A. G., & Kumar, B. U. (2016). Hand, foot and mouth disease in children: A clinico epidemiological study. *Indian Journal of Paediatric Dermatology*, 17:7-12

Kumar, V. S., Budur, S. V., Odappa, G. H., Bankolli, S. Y., & Rao, A. P. (2015). Clinical profile of hand, foot, and mouth disease and its associated complications among children in Shimoga City, Southern Karnataka: A hospital-based study. *Indian Journal of Public Health*, 59:141-144

Lai, P. C., So, F. M., & Chan, K. W. (2009). *Spatial Epidemiological Approaches In Disease Mapping Analysis.* Kuala Lumpur: CRC Press.

Lazim, M. A. (2012). *Introductory Business Forecasting-A Practical Approach.* (3 ed.). Kuala Lumpur: Univision Press Sdn Bhd.

Leong, P. F., Labadin, J., Rahman, S. B. A., & Juan, S. F. S. (2011). *Quantifying The Relationship Between The Climate And Hand-Foot-Mouth Disease (HFMD) Incidences*. Paper presented at ICMSAO 2011 4th International Conference on Modeling, Simulation and Applied Optimization, Kuala Lumpur.

Li, Q., Guo, N. N., Han, Z. Y., Zhang, Y. B., Qi, S. X., Xu, Y. G., Wei, Y. M., Han, X., & Liu, Y. Y. (2012). Application of an autoregressive integrated moving average model for predicting the incidence of hemorrhagic fever with renal syndrome. *American Journal of Tropical Medicine Hygiene*, 87(2): 364-370.

Lin, T. Y., Twu, S. J., Ho, M. S., Chang, L. Y., & Lee, C. Y. (2003). Enterovirus 71 outbreaks, Taiwan: occurrence and recognition. *Emerging Infectious Diseases*, 9(3):291–293.

Liu, M. Y., Liu, W., Luo, J., Liu, Y., Zhu, Y., Berman, H., & Wu, J. (2011). Characterization of an outbreak of hand, foot, and mouth disease in Nanchang, China in 2010. *PLoS One*, 6(9):e25287.

Liu, M. Y., Liu, J., Lai, W., Luo, J., Liu, Y., Vu, G. P., Yang, Z., Trang, P., Li, H., & Wu, J. (2016). Characterization of enterovirus 71 infection and associated outbreak of hand, foot, and mouth disease in shawo of china in 2012. *Scientific Reports*, 6:38451

Liu, Y., Wang, X., Liu, Y., Sun, D., Ding, S., Zhang, B., Du, Z., & Xue, F. (2013). Detecting Spatial-temporal clusters of HFMD from 2007 to 2011 in Shandong province, China. *PLoS ONE*, 8(5):e63447.

Liu, J. (2011). Threshold dynamics for a HFMD epidemic model with periodic transmission rate. *Nonlinear Dynamics*, 64(1-2), 89-95. doi:10.1007/s11071-010-9848-6

Luz, P. M., Mendes, B. V. M., Codeço, C. T., Struchiner, C. J., & Galvani, A. P. (2008). Time series analysis of dengue incidence in Rio de Janeiro, Brazil. *American Journal of Tropical Medicine Hygiene*, 79(6): 933-939.

Ma, E., Lam, T., Chan, K. C., Wong, C., & Chuang, S. K. (2010). Changing epidemiology of hand, foot, and mouth disease in Hong Kong, 2001–2009. *Japan Journal Infectious Disease*, 63(6): 422–426.

Mao, Q., Wang, Y., Bian, L., Xu, M., & Liang, Z. (2016). EV71 vaccine, a new tool to control outbreaks of hand, foot and mouth disease (HFMD). *Expert Review of Vaccine*s, 15(5): 599-606.

McLeod, A., & Li, W. (1983). Diagnostic checking ARMA time series models using squared-residual autocorrelations. *Journal of Time Series Analysis*, 4: 269-273.

Michael, C. S., & James, C. F. (2011). Time series model to predict burden of viral respiratory illness on a pediatric intensive care unit. *Medical Decision Making*, 31, 494-499.

MOH, Malaysia. *Hand, Foot and Mouth Disease (HFMD) Guidelines (2007).*

MOH, Malaysia. *Health Facts 2012.*

MOH, Malaysia. *Press Conference of HFMD Current Situation in Malaysia (2013).*

MOH, Malaysia Penyakit Tangan, Kaki Dan Mulut (2013). Retrieved from http://www.moh.gov.my/index.php/pages/view/193

Moran, P. A. P. (1950). Notes on Continuous Stochastic Phenomena. *Biometrika*, 37(1): 17-23.

Mossong, J., Hens, N., Jit, M., Beutels, P., Auranen, K., Mikolajczyk, R., Massari, M., Salmaso, S., Tomba, G. S., Wallinga, J., Heijne, J., Sadkowska-Todys, M., Rosinska, M., & Edmunds, W. J. (2008). Social contacts and mixing patterns relevant to the spread of infectious disease. *PloS Med*, 5(3): e74. doi:10.1371/journal.pmed.0050074

Nakhapakorn, K., & Jirakajohnkool, S. (2006). Temporal and spatial Autocorrelation statistics of dengue Fever. *Dengue Bulletin*, 30, 177.

Nicholas, M., Denis, L. A., & Labadin, J. (2010). *Preliminary Investigation of the Relationship between Weather Data and Hand-Foot-Mouth Disease Cases in Sarawak.* Paper presented at the Second International Conference on Computational Intelligence, Modelling and Simulation (CIMSiM) 2010, Bali, Indonesia.

Ooi, E. E., Phoon, M. C., Ishak, B., & Chan, S. H. (2002). Seroepidemiology of human enterovirus 71, Singapore. *Emerging infectious diseases*, 1;8(9):995-997.

Onozuka, D., & Hashizume, M. (2011). The influence of temperature and humidity on the incidence of hand, foot, and mouth disease in Japan. *Science of the Total Environment*, 410-411:119-125. doi:10.1016/j.scitotenv.2011.09.055

Paul, T. (2014, March 17). Sinovac's EV71 vaccine effective against HFMD. Vaccine News daily. Retrieved from http://vaccinenewsdaily.com/vaccine_development/330036-sinovacs-ev71-vaccine-effective-against-hfmd/

Podin, Y., Gias, E. L., Ong, F., Leong, Y. W., Yee, S. F., Yusof, M. A., Perera, D., Teo, B., Wee, T. Y., Yao, S. C., & Yao, S. K. (2006). Sentinel surveillance for human enterovirus 71 in Sarawak, Malaysia: lessons from the first 7 years. *BMC Public Health*, 6(1):180.

Ramirez-Fort, M. K., Downing, C., Doan, H. Q., Benoist, F., Oberste, M. S., Khan, F., & Tyring, S. K. (2014). Coxsackievirus A6 associated hand, foot and mouth disease in adults: Clinical presentation and review of the literature. *Journal of Clinical Virology*, 60(4): 381-386

Ryu, W. S., Kang, B., Hong, J., Hwang, S., Kim, J., & Cheon, D. S. (2010). Clinical and etiological characteristics of enterovirus 71-related diseases during a recent 2-year period in Korea. *Journal of Clinical Microbiology*, 48(7): 2490–2494.

Said, S. E., & Dickey, D. A. (1984). Testing for Unit Roots in Autoregressive-Moving Average Models of Unknown Order. *Biometrika*, 71(3): 599-607.

Samphutthanon, R., Tripathi, N. K., Ninsawat, S., & Duboz, R. (2014). Spatio-Temporal Distribution and Hotspots of Hand, Foot and Mouth Disease (HFMD) in Northern Thailand. *International Journal of Environmental Research Public Health*, 11(1): 312–336.

Sarawak State Health Department (2012). *Sarawak Weekly Epid News*. Retrieved from http://jknsarawak.moh.gov.my

Sarawak State Planning Unit (SSPU), 2015. *Sarawak Facts and Figures 2015*. Chief Minister's Department.

Sarawak Government (2013). *The Geography of Sarawak*. Retrieved from http://www.sarawak.gov.my/en/about-sarawak/geography

Schmidt, N. J., Lennette, E. H., & Ho, H. H. (1974). An apparently new enterovirus isolated from patients with disease of the central nervous system. *Journal of Infectious Diseases*, 129(3): 304-309.

Shah, V. A., Chong, C. Y., Chan, K. P., Ng, W., & Ling, A. E. (2003). Clinical characteristics of an outbreak of hand, foot and mouth disease in Singapore. *Annals of the Academy of Medicine, Singapore*, 32(3):381-387.

Shafie, A., (2011). Evaluation of the Spatial Risk Factors for High Incidence of Dengue Fever and Dengue Hemorrhagic Fever Using GIS Application. *Sains Malaysiana*, 40(8): 937-943.

Singh, S., Poh, C. L., & Chow, V. T. (2002). Complete sequence analyses of enterovirus 71 strains from fatal and non-fatal cases of the hand, foot and mouth disease outbreak in Singapore (2000), *Microbiology and Immunology*, 46: 801–808.

SSHD, 2006. *HFMD in Sarawak*. Retrieved from http://jknsarawak.moh.gov.my/en/modules/mastop_publish/?tac=122

Stroud, P. D., Sydoriak, S. J., Riese, J. M., Smith, J. P., Mniszewski, S. M., & Romero, P. R. (2006). Semi-empirical power-law scaling of new Infection rate to model epidemic dynamics with inhomogeneos mixing. *Mathematical Biosciences*, 203:301–318.

Tai, W. C., Hsieh, H. J., & Wu, M. T. (2009). Hand, foot and mouth disease in a healthy adult caused by intrafamilial transmission of enterovirus 71. *British Journal of Dermatology*, 160: 881-898.

The State of Sarawak. Economic Research, Country Reports, Vol.: ER/008/2015. Malaysia Rating Corporation Berhad (MARC).

Tiing, F. C. S., & Labadin, J. (2008). *A Simple Deterministic Model for the Spread of Hand, Foot and Mouth Disease (HFMD) in Sarawak*. Paper presented at the Second Asia International Conference on Modelling & Simulation (AMS) , Kuala Lumpur.

Tu, P. V., Thao, N. T., Perera, D., Huu, T. K., Tien, N. T., Thuong, T. C., How, O. M., Cardosa, M. J., & McMinn, P. C. (2007). Epidemiologic and virologic investigation of hand, foot, and mouth disease, Southern Vietnam, 2005. *Emerging Infectious Diseases*, 13(11): 1733–1741.

Vazifedan, T., & Shitan, M. (2012). Modeling polio data using the first order non-negative integer-valued autoregressive, INAR(1) model. *International Journal of Modern Physics:Conference Series*, 9:232-239.

Vynnycky, E., & White, R. G. (2010). *How do models deal with contact patterns? An Introduction to Infectious Disease Modelling* (pp. 177-219). United States: Oxford University Press.

Vynnycky, E., & White, R. G. (2010). *An Introduction to Infectious Disease Modelling*. (1 ed.). United States: Oxford University Press.

Wang, J. F., Guo, Y. S., Christakos, G., Yang, W. Z., Liao, Y. L., Li, Z. J., Li, X. Z., Lai, S. J., & Chen, H. Y. (2011). *Hand, foot and mouth disease: spatiotemporal transmission and climate*. International Journal of Health Geography, 10(25). doi:10.1186/1476-072X-10-25

Wang, X., Xing, M., Zhang, C., Yang, Y., Chi, Y., Tang, X., Zhang, H., Xiong, S., Yu, L., & Zhou, D. (2014). Neutralizing antibody responses to enterovirus and adenovirus in healthy adults in China. Emerging Microbes & Infections, 3: e30

WHO, 2012. *Hand, Foot and Mouth Disease*. Retrieved from http://www.wpro.who.int/mediacentre/factsheets/fs_10072012_HFMD/en/

WHO China, 2008. *Hand, foot and mouth disease in Fuyang City, Anhui Province and the prevention and control in China.*

WHO, 2013. *Country cooperation strategy at a glance*. Retrieved from http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_mys_en.pdf

WHO, 2017. *Emerging Diseases*. Retrived from http://www.who.int/topics/emerging_diseases/en/

Witso, E., Palacios, G., Ronningen, K. S., Cinek, O., Janowitz, D., Rewers, M., Grinde, B., Lipkin, W. I. (2007). Asymptomatic circulation of HEV71 in Norway. *Virus research*, 123(1):19-29.

WPRO, (2016, November 21). *Hand, Foot and Mouth Disease Situation Update Number 495.* Retrieved from http://www.wpro.who.int/emerging_diseases/hfmd_biweekly_20160823.pdf?ua=1

WPRO, 2012. *A guide to clinical management and public health response for hand, foot and mouth disease (HFMD).* Manila, Philippines.

WPRO, 2010. *Vaccine Preventable Diseases Reference Laboratory Networks in the Western Pacific Region.* Manila, Philippines.

WPRO, 2017. *Emerging Disease Surveillance and Response*. Retrived from http://www.wpro.who.int/emerging_diseases/about/ESRUnit/en/

Wu, Y., Yeo, A., Phoon, M. C., Tan, E. L., Poh, C. L., Quak, S. H., & Chow, V. T. (2010). The largest outbreak of hand; foot and mouth disease in Singapore in 2008: the role of enterovirus 71 and coxsackievirus A strains. *International Journal of Infectious Diseases*, 14(12):e1076-81.

Xing, W., Liao, Q., Viboud, C., Zhang, J., Sun, J., Wu, J. T., Chang, Z., Liu, F., Fang, V. J., Zheng, Y., & Cowling, B. J. (2014). Hand, foot, and mouth disease in China, 2008–12: an epidemiological study. *The Lancet Infectious Diseases*, 14: 308–318. pmid:24485991

Yang, H., (2016, January 4). Sinovac obtains new drug certificate and production license for EV71 vaccine. *PR Newswire*. Retrived from http://www.sinovac.com/?optionid=754&auto_id=803

Yin, X., Yi, H., Shu, J., Wang, X., Wu, X., & Yu, L. (2014). Clinical and epidemiological characteristics of adult hand, foot and mouth disease in northern Zhejiang, China, May 2008-November 2013. *BMC Infectious Diseases*, 14:251.

Yu, L., Zhou, L., Tan, L., Jiang, H., Wang, Y., Wei, S., & Nie, S. (2014). Application of a new hybrid model with seasonal autoregressive integrated moving average (SARIMA) and nonlinear autoregressive neural network (NARNN) in forecasting incidence cases of HFMD in Shanzhen, China. *PLoS One*, 9(6): e98241.

Zhang, Y., Tan, X. J., Wang, H. Y., Yan, D. M., Zhu, S. L., Wang, D. Y., Ji, F., Wang, X. J., Gao, Y. J., Chen, L., & An, H. Q. (2009). An outbreak of hand, foot, and mouth disease associated with subgenotype C4 of human enterovirus 71 in Shandong, China. *Journal of Clinical Virology*, 44(4):262-267

Zhao, J., Jiang, F., Zhong, L., Sun, J., & Ding, J. (2016). Age patterns and transmission characteristics of Hand, Foot and Mouth disease in China. *BMC Infectious Diseases*, 16(1):691

Zhu Q., Hao Y., Ma J., Yu S., & Wang, Y. (2011). Surveillance of hand, foot, and mouth disease in mainland China (2008–2009). *Biomedical Environmental Science*, 24:349–356.

Zhu, F. C., Meng, F. Y., Li, J. X., Li, X. L., Mao, Q. Y., Tao, H., Zhang, Y. T., Yao, X., Chu, K., Chen, Q. H., Hu, Y. M., Wu, X., Liu, P., Zhu, L. Y., Cao, F., Jin, H., Chen, Y. J., Dong, Y. Y., Liang, Y. C., Shi, N. M., Ge, H. M., Liu, L., Chen, S. G., Ai, X., Zhang, Z. Y., Ji, Y. G., Luo, F. J., Chen, X. Q., Zhang, Y., Zhu, L. W., Liang, Z. L., & Chen, X. L. (2013). Efficacy, safety, and immunology of an inactivated alum-adjuvant enterovirus 71 vaccine in children in China: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*. 381(9882): 2024-2032.