HAND FOOT AND MOUTH DISEASE AND ITS SPATIAL RELATIONSHIP WITH VACCINE REFUSAL CASES IN TERENGGANU

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HAND FOOT AND MOUTH DISEASE AND ITS SPATIAL RELATIONSHIP WITH VACCINE REFUSAL CASES IN TERENGGANU

By

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CONTENT

ACKNOWLEDGEMENT ii

CONTENT iii

LIST OF FIGURES viii

LIST OF TABLES x

LIST OF ABBREVIATIONS xi

LIST OF SYMBOLS xiii

LIST OF APPENDICES xiv

ABSTRAK xv

ABSTRACT xvii

Chapter 1 1

INTRODUCTION 1

1.1 Study Background 1

1.2 Problem Statements 13

1.3 Study Rationale 14

1.4 Research Questions 15

1.5 Objectives 15

1.6 Hypothesis 16

Chapter 2 17

LITERATURE REVIEW 17

2.1 Nature of HFMD 17

2.2 Rising of Vaccine Refusal Cases in Malaysia 20

2.3 Spatial Epidemiological Analysis 23

2.4 Conceptual Framework 25

Chapter 3 26

METHODOLOGY 26

3.1 Study Design 26

3.2 Study Area 26

3.3 Study Duration and Timeline 28

3.4 Reference Population 28

3.5 Source Population 28

3.6 Study Criteria 29

3.7 Sample Size Estimation 29

3.8 Source of Data 30

3.9 Tools and Materials of Study 32

3.10 Definition of Operational Terms 32

3.11 Data and Statistical Analysis 33

3.12 Ethical Consideration 38

3.13 Study Flowchart 39

Chapter 4 40

RESULT 40

4.1 Socio-demographic Characteristics of HFMD in Terengganu 2016. 40

4.2 Overall Prevalence of HFMD and Specified to Age, Gender and Districts in Terengganu 2016. 44

4.3 Geographical Distribution of HFMD Cases in Terengganu 2016. 50

4.4 Geographical Distribution of Vaccine Refusal Cases in Terengganu 2016. 51

4.5 Density of HFMD and Vaccine Refusal Cases in Terengganu based on Heatmap 54

4.6 Clusters of HFMD and Vaccine Refusal Cases in Terengganu 2016 56

4.7 Spatial Relationship between of HFMD Cases and Vaccine Refusal Cases...... 57

Chapter 5 59

DISCUSSION 59

5.1 Socio-demographic Characteristics of HFMD in Terengganu 2016................. 59

5.2 Overall Prevalence of HFMD and Specified to Age, Gender and Districts in Terengganu 2016. 63

5.3 Geographical Distribution of HFMD and Vaccine Refusal Cases in Terengganu 2016 64

5.4 Clusters of HFMD and Vaccine Refusal Cases in Terengganu 2016 67

5.5 Spatial Relationship between of HFMD and Vaccine Refusal Cases 68

5.6 Limitation 70

Chapter 6 72
CONCLUSION & RECOMMENDATION 72
6.1 Conclusion 72
6.2 Recommendation 73
REFERENCES 74
APPENDICES 85

LIST OF FIGURES

Figure 1.1 Incidence Rate of HFMD in Malaysia and Terengganu 2009 – 2014…………2

Figure 1.2 Vaccine Refusal Cases in Malaysia 2013 – 2016 ……………………………8

Figure 1.3 Numbers of Vaccine Refusal Cases in Malaysia 2013 – 2016 (by states)…….10

Figure 2.1 Conceptual Framework……………………………………………….…...25

Figure 3.1 Terengganu Population (based on Age Distribution)………………………..27

Figure 3.2 Study Flowchart ……………….…………………….……………………....39

Figure 4.1 HFMD Cases in Terengganu 2016 (by Age)……………………………..…...42

Figure 4.2 Epidemiological Trend of HFMD in Terengganu 2016 (based on Epidemiological Week. …………………………………………………………….....43

Figure 4.3 Geographical Distribution of HFMD Cases in Terengganu 2016 50

Figure 4.4 Geographical Distribution of Vaccine Refusal Cases in Terengganu 2016....51

Figure 4.5 Combined Geographical Distribution of HFMD and Vaccine Refusal Cases in Terengganu ……………………………………………………………………………..53

Figure 4.6 Geographical Density of HFMD Cases in Terengganu 2016…………………54

Figure 4.7 Geographical Density of Vaccine Refusal Cases in Terengganu 2016……….55

Figure 4.8 Cross K Function of HFMD and Vaccine Refusal Cases……………………..57

Figure 4.9 Envelope Cross K Function of HFMD and Vaccine Refusal Cases (using Monte Carlo simulation)..58

Figure 5.1 Terengganu Population Density 2016 (people/km^2).......................................64

LIST OF TABLES

Table 3.1 Terengganu Population 2010 26

Table 4.1 Socio-demographic Characteristics of HFMD in Terengganu 2016................40

Table 4.2 Overall Prevalence, Age-Specific and Gender-Specific Prevalence of HFMD..44

Table 4.3 District Prevalence of HFMD in Terengganu 2016 45

Table 4.4 Sub-district Prevalence of HFMD in Terengganu 2016 46

Table 4.4 (Continued) Sub-district Prevalence of HFMD in Terengganu 2016…………47

Table 4.4 (Continued) Sub-district Prevalence of HFMD in Terengganu 2016………….48

Table 4.4 (Continued) Sub-district Prevalence of HFMD in Terengganu 2016………….49

Table 4.5 Nearest Neighboring Index (NNI) for HFMD and Vaccine Refusal Cases in Terengganu 2016………………………………………………………………………..56

LIST OF ABBREVIATIONS

CA-16	Coxsakie A - 16
CDCIS	Communicable Disease Control Information System
DOSM	Department of Statistic Malaysia
EPI	Expanded Program for Immunization
EV-71	Enterovirus - 71
GIS	Geographical Information System
HFMD	Hand Foot Mouth Disease
HLA-A33	Human Leucocytes Antigen-A33
HLA-A2	Human Leucocytes Antigen-A2
IQR	Interquartile Range
JEPeM	‘Jawatankuasa Etika Penyelidikan (Manusia)’
JKNT	Jabatan Kesihatan Negeri Terengganu
MCH	Maternal Child Health

MOH	Ministry of Health, Malaysia
MREC	Medical Research Ethics Committee
NIP	National Immunization Program
NNI	Nearest Neighboring Index
QGIS	Quantum Geograhical Information System
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
USA	United States of America
USD	United States Dollar
USM	Universiti Sains Malaysia
WHO	World Health Organization

LIST OF SYMBOLS

>	More than
<	Less than
=	Equal to
≥	More than and equal to
≤	Less than and equal to
α	Alpha
β	Beta
Θ	Theta
%	Percentage

LIST OF APPENDICES

Appendix A Proforma Form (Hand Foot Mouth Disease case)

Appendix B Proforma Form (Vaccine Refusal case)

Appendix C Ministry of Health (MOH) Ethical Approval Letter

Appendix D Universiti Sains Malaysia (USM) Ethical Approval Letter

Appendix E Terengganu State Health Department Data Collection Approval Letter

ABSTRAK

PENYAKIT TANGAN, KAKI DAN MULUT DAN KAITAN SPATIAL DENGAN KES PENOLAKAN VAKSIN DI TERENGGANU

Latar Belakang: Penyakit tangan, kaki dan mulut (HFMD) adalah penyakit yang disebabkan oleh jangkitan virus yang merupakan masalah kesihatan awam seluruh dunia kerana penyakit ini boleh menyebabkan jangkitan yang luas. Peningkatan kes HFMD di Malaysia pada masa ini memerlukan penyelidikan dan siasatan terutamanya dalam mengesan cara penyakit ini merebak dan ciri-ciri penempatan kes yang mungkin dipengaruhi faktor lain seperti kes penolakan vaksin.

Objektif: Kajian ini bertujuan untuk menganggarkan kadar kejadian kes HFMD di Terengganu, membuat peta taburan kes HFMD dan kes penolakan vaksin serta mencari hubungkait taburan kes di antara HFMD dan kes penolakan vaksin.

Metodologi: Kajian ini menggunakan kaedah hirisan lintang dan sepenuhnya menggunakan data sekunder yang diperoleh daripada sistem notifikasi dalam talian dan rekod pendaftaran kes daripada Unit CDC dan Unit MCH, Jabatan Kesihatan Negeri Terengganu. Data kes HFMD dan penolakan vaksin menggunakan format MS Excel dan data demografi penduduk pula menggunakan format shapefile. Data tersebut dianalisa menggunakan perisian QGIS 2.16.3.

Manakala, bilangan kes setiap kawasan dianggarkan dengan menggunakan fungsi *points-in-polygons* dan hubung-kait spatial di antara HFMD and kes penolakan vaksin pula diuji menggunakan ujian fungsi *cross-K*.

Keputusan: Terdapat 811 kes telah dinotifikasi sebagai kes HFMD pada tahun 2016 dan mencatatkan keseluruhan kadar kejadian kes 79.9 per 100,000 populasi. Kejadian kes HFMD banyak tertumpu di daerah Kuala Terengganu, Marang dan Dungun. Kadar kejadian kes HFMD adalah di antara 20.4 sehingga 218.1 per 100,000 populasi. Terdapat kejadian kluster bagi kes HFMD berdasarkan nilai *Nearest Neighbor Index*, ($r = 0.27$, $p < 0.01$). Manakala, lokasi kes HFMD menunjukkan hubung-kait secara statistik dan hampir dengan kes penolakan vaksin (ujian *cross-K*, $p < 0.01$).

Kesimpulan: Kes HFMD dan penolakkan vaksin berlaku secara kluster di Terengganu terutamanya melibatkan kawasan yang mempunyai kadar kepadatan penduduk yang tinggi seperti di daerah Kuala Terengganu, Marang dan Dungun. Selain itu, kedua-dua kes mempunyai hubungkait antara satu dengan yang lain secara statistik dan terletak hampir antara satu dengan lain. Keputusan ini secara tidak langsung akan membantu petugas kesihatan awam untuk memperkasakan kaedah pengurusan kes terutamanya yang melibatkan kes penyakit berjangkit dan juga penyakit yang berkait dengan vaksin.

KATA KUNCI: HFMD, penolakan vaksin, kluster.

ABSTRACT

HAND FOOT AND MOUTH DISEASE AND ITS SPATIAL RELATIONSHIP WITH VACCINE REFUSAL CASES IN TERENGGANU

Background: Hand, foot, and mouth disease (HFMD) is a common viral illness that is considered as a global public health problem with pandemic potential. The progressive increment of HFMD cases in Malaysia needs further investigation especially in the tracking of the disease spread and its spatial pattern to other factor such in vaccine refusal event.

Objective: This study aimed to estimate the prevalence of HFMD in Terengganu, map the geographical distribution of HFMD and vaccine refusal cases; and estimate the spatial relationship between HFMD and vaccine refusal cases.

Methodology: This study applied cross-sectional design and used secondary data from the online notification system and registry maintained by the CDC and MCH Unit Terengganu State Health Department. HFMD cases and vaccine refusal cases were provided in MS Excel format and population demographic data in the ESRI shapefile format. Data were analyzed using QGIS 2.16.3 software. The number of cases per area was estimated using points-in-polygons function while the spatial relationship between HFMD and vaccine refusal cases was tested using cross-K function test.

Result: There was a total of 811 notified HFMD cases in 2016 with the overall prevalence at 79.9 cases per 100,000 population. The HFMD was highly concentrated over the Kuala Terengganu, Marang and Dungun. The prevalence of HFMD ranged from 20.4 to 218.1 cases per 100,000 population. There was evidence of spatial cluster of HFMD based on the Nearest Neighbor Index, ($r = 0.27$, $p < 0.01$). Meanwhile, the locations of HFMD was statistically and closely related to the vaccine refusal cases (cross-K test, $p < 0.01$).

Conclusion: HFMD and vaccine refusal cases formed clusters in Terengganu especially involving the high density population such as Kuala Terengganu, Marang and Dungun. Moreover both HFMD and vaccine refusal cases were closely located.

KEY WORDS: HFMD, vaccine refusal, cluster

CHAPTER 1

INTRODUCTION

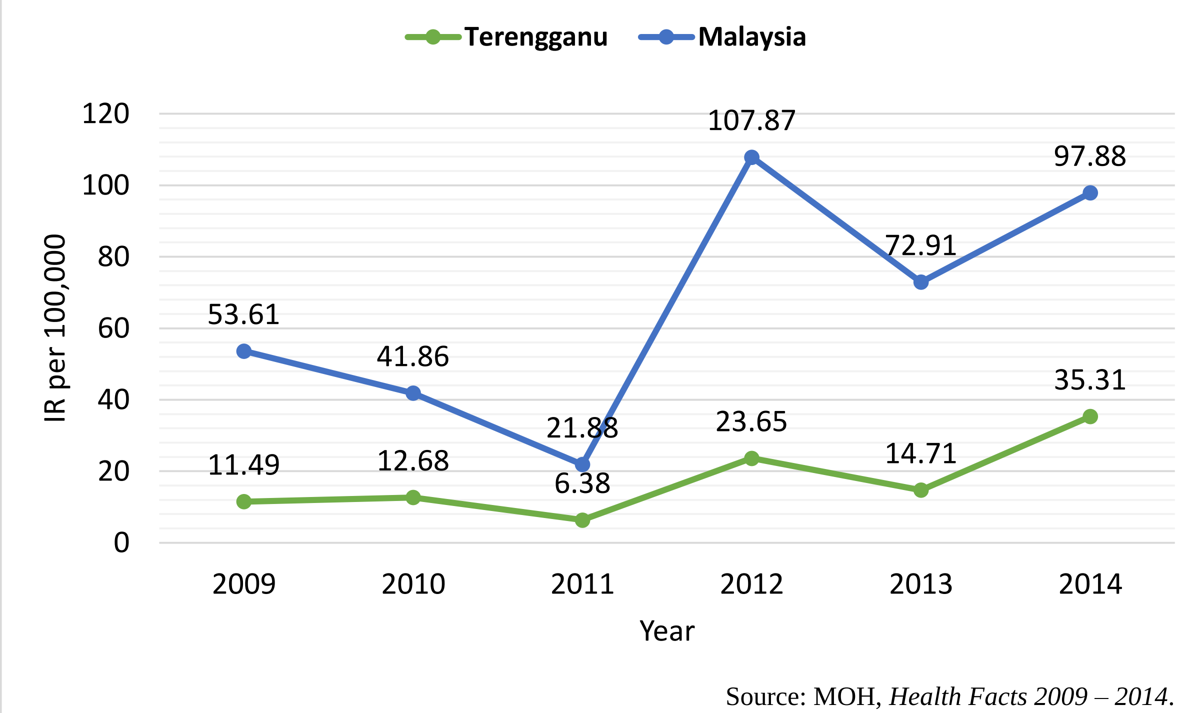
1.1 Study Background

Hand, foot, and mouth disease (HFMD) is a common viral illness that usually affects infants and children. Typically, it is presented with fever, mouth ulcer, and a skin rash. HFMD is considered as global public health problem with pandemic potential. Many outbreaks of HFMD have been reported in countries of the Western Pacific Region, including Japan, most region in China, India, Vietnam, Cambodia, Singapore and also Malaysia (Aswathyraj *et al.*, 2016).

1.1.1 Epidemiology of HFMD

In China during 2010 – 2012, there were 1.2 HFMD cases per 1000 person-years and 500 – 900 deaths were reported for each year (Reed and Cardosa, 2016). While in Singapore, the annual incidence rate of HFMD increasing from 125.5 in 2001 to 435.9 in 2007 per 100,000 population while the mortality rate was very low at 0.06% (3/5210 cases) in 2001 (Ang *et al.*, 2009). The average incidence rate per 100,000 population in Malaysia for year 2000 to 2008 was 25.0 with ranged from 1.5 to 60.6 (Chan *et al.*, 2011).

While data from Ministry of Health (MOH) for 2007 and 2008 showed that the incidence rate of HFMD was 56.1 and 60.6 per 100,000 population respectively (MOH, 2016). The rate was suddenly increasing may be because of the HFMD was declared as part of notifiable disease in 2006. Based on the latest data from MOH, the numbers of HFMD cases since 2011 to 2014 showed 347.33% of increment from 7002 cases to 31322 cases and almost all states in Malaysia had recorded rapid increment for that period. HFMD cases in Terengganu increased from 75 cases in 2011 to 415 cases in 2014 with 453% of increment. The trend of incidence rate of HFMD in Malaysia and Terengganu since 2009 – 2014 has illustrated in the following Figure 1.1.



Source: MOH, *Health Facts 2009 – 2014*.

Figure 1.1 Incidence Rate of HFMD in Malaysia and Terengganu 2009 - 2014

The average mortality rate of HFMD for 2000 to 2009 was 0.01 per 100,000 population (range 0 – 0.3). Based on MOH data, there were no deaths reported in 2002, 2004, 2007 and 2009 until 2011. However in May 1997, large and severe outbreaks of HFMD have been reported in Sarawak caused 41 mortality from previously healthy infants and young children (Yusof *et al.*, 2014). The outbreaks were associated with Enterovirus-71 (EV-71) that was isolated from the fatal cases with brain stem encephalitis (Hooi *et al.*, 2002; Noraishah *et al.*, 2013). Then, another fatal HFMD outbreaks recurred in 2000, 2003, 2006, 2008 and 2009 and other than EV-71, the Echovirus 7 was also isolated from cases of acute encephalomyelitis (Chan *et al.*, 2011).

1.1.2 Nature of HFMD

HFMD is a common infectious disease caused by systemic infections of human enteroviruses. Human enteroviruses are one of genus in the family *Picornaviridae* together with genera *Rhinovirus*, *Cardiovirus*, *Aphthovirus*, *Hepatovirus* and *Parechovirus*. The members of the enterovirus genus that infect humans include the polioviruses, coxsackie virus groups A and B, echoviruses and enteroviruses 68-71 (Jonathan Cohen, 2003).

Coxsackievirus-A16 (CA-16) is the most common pathogen in cases of HFMD and its clinical course is usually uneventful, with full recovery. However, HFMD cases caused by EV-71 can be more severe and possibly complicated with meningitis, encephalitis and neurogenic pulmonary edema.

A study done based on 1998 epidemic in Taiwan revealed the significant difference in the clinical features of CA-16 infection and EV-71 infection was that in EV-71 the fever was usually higher than 39°C and longer than 3 days (Chen *et al.*, 2010).

EV-71 infection can be classified into 4 stages including the stage 1 which present as common symptoms such as oral ulcers and vesicular rash; stage 2 will identified by symptom and sign of central nervous system involvement including aseptic meningitis with headache, irritability or myoclonic jerk and cerebrospinal fluid pleocytosis (>5 x 106 leucocytes/liter) but without altered level of consciousness and focal signs. Then stage 3 started with cardiopulmonary failure, pulmonary edema or hemorrhage; and stage 4 is convalescence state defines as recovery from cardiopulmonary failure.

HFMD generally is a self-limiting disease and most of the cases occur in the summer and fall and the incubation period is 4 – 6 days. HFMD is moderately contagious and spread from person to person by direct contact with nose and throat discharges, saliva, fluid from blisters, or the stool of infected persons.

A person is most contagious during the first week of the illness and most of the outbreaks are often found in nurseries, playgroups, schools, and households where young children have lots of close contacts with one another (Chang *et al.*, 2011).

1.1.3 Surveillance and Impact

HFMD surveillance in Malaysia started after the Sarawak outbreak in 1997 with sentinel surveillance. Both private and government clinics were included as sentinel sites for each district. HFMD has become an important public health disease due to its tendency to cause large outbreaks and deaths among children and infants. As recorded the HFMD cases are increasing every year; moreover, HFMD outbreaks occurred in many of neighboring countries such as Singapore, Thailand and Vietnam in recent years (Charoenchokpanit and Pumpaibool, 2013).

Besides, HFMD not only affect the health sector but also give an impact to the economy as estimated in study by Pichichero *et al.*, (1998) the median duration of illness for HFMD was 7 days and median number of missed days from school was 1 days. Direct medical costs ranged from USD69 to USD771 per case while the indirect costs ranged from USD63 per case for HFMD to USD422 per case for other severe complications (Pichichero *et al.*, 1998). The direct medical costs are including the outpatient care, inpatient care and self-medication while direct non-medical costs consist of transportation, nutrition, accommodation and nursery, and the indirect costs for lost income associated with caregiving.

Apart from that, recent study done in China had assessed the economic cost and health-related quality of life (HRQoL) of HFMD patients across China, including the underdeveloped provinces with higher incidence of HFMD.

They found that the economic cost per HFMD case ranges from around $200 for a mild outpatient case to over $3,000 for a severe case, with most costs being direct medical costs. While the cases who were diagnosed with EV-A71 infection, had longer duration of illness, and were three years old or younger will associated with higher total cost (Zheng *et al.*, 2017). Furthermore, in outbreaks, it will cost more than that as the institution affected need to be closed for at least 10 days for the investigation, prevention and control purposes.

From the factors mentioned above, the prevention and control of the HFMD should be prioritized since there is no effective HFMD vaccine so far. The HFMD prevention and control in young children rely on how good the caregivers' hygienic habit and the awareness of parents which is universally accepted as the effective method to control the disease.

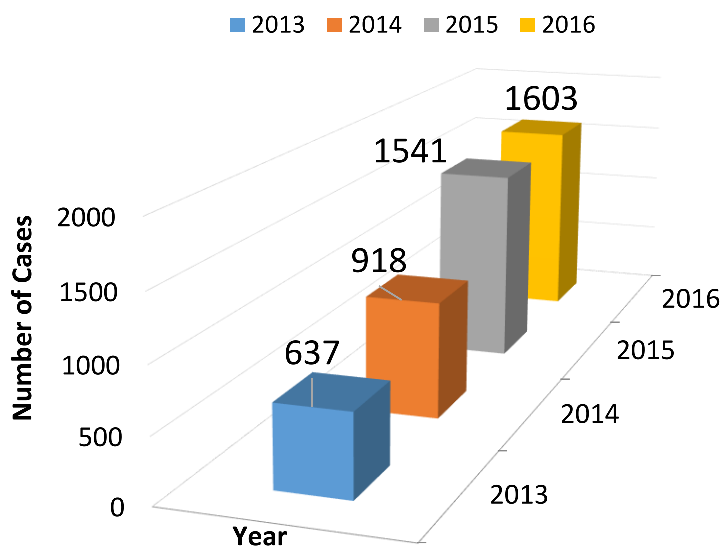
1.1.4 Vaccine Refusal Cases

Obviously, high immunization coverage has resulted in drastic declines in vaccine-preventable diseases by preventing almost 6 million of death annually (Lim *et al.*, 2016). In Malaysia, the Immunisation Program is included in the Maternal and Child Health Program (MCH) and was started since 1950s under Malaysian National Immunisation Programme (NIP). The Malaysian NIP was introduced based on the World Health Organisation (WHO) Expanded Programme on Immunisation (EPI) which consists of list of vaccinations including BCG, Hepatitis, DTaP, Hib, IPV, MMR and also HPV.

The vaccination is given free for all children while the non-Malaysian had to pay a minimal fee since 2015. Annual data from MOH, showed the immunization coverage in Malaysia for 2016 was more than 90% which comprise of BCG, 98.26%; DPT – Hib (3^{rd} Dose), 97.97%; Polio (3^{rd} Dose), 97.97%; MMR, 94.37%; Hepatitis B, 97.97% and HPV (2^{nd} Dose), 83.02% (MOH, 2018). The successful and high immunization coverage will ensure the sustaining the communicable disease control especially to the vaccine related diseases.

Unfortunately, according to the unpublished data collected from government clinics and hospitals in Malaysia, despite of high immunization coverage, there is an increasing number of vaccine refusal cases started from 2012 to 2013. Initially, it was a small movement and then the anti-vaccine movements started to spread especially in social media. It is not the new issue as vaccine hesitancy had started since vaccination was first introduced in Europe against smallpox.

Similar rejection was encountered in United States in 1850s (Taib *et al.*, 2017). A study by Ahmad *et al*., (2017) revealed that the numbers of vaccine refusal and hesitancy increased in Muslim countries including Afghanistan, Pakistan and also Malaysia. Then, it was identified as contributing factor in increase of vaccine-preventable diseases. Surprisingly, these groups have emerged in both developed and developing countries.



Source: MOH, *CDC Division 2016.*

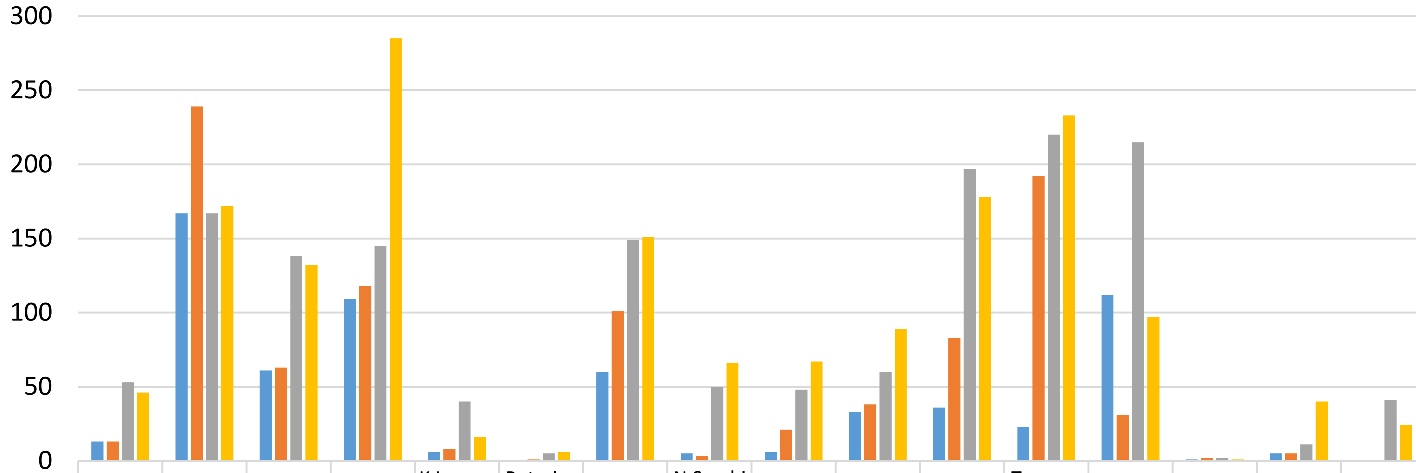
Figure 1.2 Vaccine Refusal Cases in Malaysia 2013 - 2016

World Health Organization (WHO) has defined the vaccine hesitancy as a delay in acceptance or refusal of vaccine despite of availability of vaccination services. While in Malaysia setting, the vaccine refusal is referred to the cases who had refused some or all vaccines scheduled in the Malaysian NIP (Lim *et al.*, 2016). Number of parents who refused to get their children vaccinated in Malaysia has almost increased three-fold, from 637 cases in 2013 to 1054 cases in middle year of 2015 (Ahmed *et al.*, 2017).

It is also supported by the unpublished data from the surveillance system done by MOH in 2016 which reported the numbers of vaccine refusal cases in Malaysia were increasing as shown in Figure 1.2. In year 2013, there were 637 cases followed by 2014 with 918 cases; 2015 with 1541 cases and subsequently year 2016 was accounted total of 1603 cases.

Meanwhile in 2016, five states with the highest numbers of not immunized children were Perak followed by Terengganu, Pahang, Kedah and Selangor. Refer to Figure 1.3.

The reasons of parental refusal to vaccines included the traditional and religious beliefs, safety issues and they may have received incorrect health messages through various news and sources from the internet and mass media (Syafinaz *et al.*, 2013). Furthermore, according to the herd immunity concept, vaccine refusal cases not only increase the individual risk of disease but also increase the risk for the whole community as well (Omer *et al.*, 2009).



	Perlis	Kedah	P.Pinang	Perak	K.Lumpur	Putrajaya	Selangor	N.Sembilan	Melaka	Johor	Pahang	Terengganu	Kelantan	Labuan	Sabah	Sarawak
2013	13	167	61	109	6	0	60	5	6	33	36	23	112	1	5	0
2014	13	239	63	118	8	1	101	3	21	38	83	192	31	2	5	0
2015	53	167	138	145	40	5	149	50	48	60	197	220	215	2	11	41
2016	46	172	132	285	16	6	151	66	67	89	178	233	97	1	40	24

2013 2014 2015 2016

Source: MOH, *CDC Division 2016.*

Figure 1.3 Number of Vaccine Refusal Cases in Malaysia 2013 - 2016 (by states)

1.1.5 Spatial Epidemiological Study

Geographical information systems (GIS) have been widely used to visualize the epidemiological data specifically the spread and clustering as well as ongoing trends. Historically, the approach was started to gain acceptance in the 1990s and becoming a vital tool for scientists and also public health officials in investigating the causes and spread of potentially deadly diseases, new or reemerging, around the world.

In epidemiology and outbreak investigations, there are three basic elements which are person, place and time and by using GIS, it allows the integration of all these elements onto a single platform. This is why the potential applications of GIS in spatial epidemiology are limitless and await further exploration and research (Lai *et al.*, 2009). While the objectives of spatial epidemiological are the description of spatial patterns, identification of disease clusters, explanation or prediction of disease risk and identification of the causes of diseases by correlating or relating spatial disease patterns to geographic variation in health risks (Pfeiffer *et al.*, 2008).

The globalization of infectious disease has made the use of GIS and spatial epidemiology a necessity across the global health care system because outbreaks of infectious diseases such as SARS, avian influenza and many more can be quickly analyzed by using GIS tools. Recently GIS have been used for various infectious diseases including dengue fever, food poisoning and diarrhea which have been done in Thailand (Chaikaew *et al.*, 2009; Nakhapakorn and Jirakajohnkool, 2006).

Meanwhile in Malaysia, the method was used in exploring the distribution pattern of the dengue fever such done in Selangor, while in Sarawak, the spatial distribution and analyses were used to facilitate public health team responses upon HFMD outbreaks (Sham *et al.*, 2014).

Spatial analysis involves few operational steps to achieve the main objective which is GIS-based health analysis. Firstly, need to identify the study area. Next, the sources of spatial and disease data must be included in the study. Then, the appropriate spatial analysis to be used will be selected and finally, to conclude and determine if the chosen method is adequate to summarize our data. Once completed, it can provide sufficient information that helps the health authorities to choose the right timing and strategy for the implementation of control activities (Noraishah and Krishnarajah, 2016).

However, the GIS studies on HFMD in Malaysia are still very few and limited. One of the studies was HFMD cases in Sarawak which used GIS to investigate the spatial relationship between reported HFMD cases in Sarawak, Malaysia. The study used data over 7 years period provided by the Sarawak Health Department from 2006 to 2012 and concluded the HFMD is a serious infection, for which GIS had not been applied before, thus providing expectation of finding disease patterns that could indicate suitable control measures (Sham *et al.*, 2014).

Finally, from the perspective of public health, the spatial analysis of disease incidence can be of great benefit in reassuring citizens' concerns over local hazards and in monitoring the progress of prevention or intervention programs.

The primary strategy of public health is the prevention of disease and injury by changing the underlying conditions or the environment that place populations at risk through timely alerts of possible outbreaks and suitable intervention measures.

1.2 Problem Statements

1.2.1 There is a progressively increment of HFMD cases in Malaysia since 2005 and since 2010 in Terengganu. Conducting a high quality research is a part of preventive measure and long term plan in order to understand the nature, pattern and complication of HFMD cases in Malaysia.

1.2.2 Very limited study done regarding HFMD cases especially involving the application of GIS in spatial epidemiology. To our best information, there was only a study on HFMD using GIS in 2012 involving 11 districts of Sarawak.

1.2.3 Numbers of vaccine refusal in Terengganu are increasing by time yet no proper analysis is done towards the implication. Comparing to developed countries, research related to the vaccine refusal is still lacking and also covering very narrow scope especially involving the other common infectious disease in children.

1.3 Study Rationale

The result from the study will provide map or spatial distribution indicates the area of risk to HFMD cases and vaccine refusal cases. Furthermore the study on HFMD using GIS in Malaysia is very limited (Noraishah and Krishnarajah, 2016).

Apart from that, the information may guide the appropriate control strategies in future by understanding the interaction of infectious disease in relation with environment and behavior factors.

It proven in existing studies by Nakhapakorn and Jirakajohnkool (2006) which explored the analysis of spatial factors with the dengue fever and dengue hemorrhagic fever while Chaikaew *et al.*, (2009) conducted study of spatial patterns and hotspots of diarrhea in Thailand.

By estimating the area of vaccine refusal cases, we can predict the chance and possible risk of having the vaccine preventable disease as well as other possible infectious disease related including the HFMD cases. Indirectly, study will promote the benefits of the current vaccination to the target groups and also through the herd effect extending to other populations at risk (Kim *et al.*, 2011).

1.4 Research Questions

1.4.1 What is the prevalence of HFMD cases in Terengganu for the year 2016?

1.4.2 What are the characteristics of HFMD cases in Terengganu for the year 2016?

1.4.3 What is the spatial distribution of HFMD cases in Terengganu for the year 2016?

1.4.4 Is there any spatial association between HFMD cases and the vaccine refusal cases?

1.5 Objectives

1.5.1 General Objective

To estimate the prevalence, map the spatial distribution of HFMD cases and assess its spatial association to the vaccine refusal cases.

1.5.2 Specific Objectives

1. To estimate the overall prevalence, age, gender and district specific prevalence of HFMD cases in Terengganu for the year 2016.

2. To map spatial distribution of HFMD cases in Terengganu for the year 2016.

3. To estimate the spatial relationship between HFMD cases and the vaccine refusal cases in Terengganu.

1.6 Hypothesis

There is a significant spatial association between HFMD cases and vaccine refusal cases in Terengganu for the year 2016.

CHAPTER 2

LITERATURE REVIEW

This study uses spatial distribution and analysis to further explore the HFMD and possible relationship to the vaccine refusal cases.

2.1 Nature of HFMD

HFMD as mentioned earlier, often affects the infants and children. In Singapore, most of outbreaks occurred in childcare centers where children aged between 2 and 6 years old comprised of 44.8% to 86.4% of reported cases, followed by children in kindergartens aged between 5 and 6 years old (13.0% to 34.1%) (Ang *et al.*, 2009). While in Malaysia, it notified almost the same finding where young children, especially those below the age of 4 years old, were mainly affected by the illness (Hooi *et al.*, 2002).

Immunity wise, HLA-A33 was strongly associated with EV-71 infection while HLA-A2 was found more frequently in EV-71 cardiopulmonary failure patient. Both of genetic types commonly seen in 17 - 35% of Asian population, including Taiwan and Malaysia (Chan *et al.*, 2011). The facts explained why most of HFMD cases and outbreaks occur in Asian population even though the numbers are also increasingly in European countries. However, the study on specific ethnicity was still lacking as most of studies discussed the incidence of HFMD as a whole population or between the genders.

The HFMD is predominantly occurs in male gender as suggested in most of the studies. For example in Shenzhen, China, the male-to-female ratio between 1.69:1 and 1.85:1 and the study suggested that males have relatively higher chance to be infected by HFMD viruses than females. However, the same study reported more female fatal cases than boys cases in HFMD (Wang *et al.*, 2013). Similar finding also shown by other study with male to female ratio from 1.5:1 to 2.5:1. The results might suggest of susceptibility at the host genetic level (Chang *et al.*, 2012).

The infection of HFMD are considered as cyclical pattern as reported by national based study which established sentinel and laboratory-based surveillance of HFMD clearly showed recurrent HFMD epidemics rates occurring at 2–3 year intervals (NikNadia *et al.*, 2016). A study done in Singapore postulated that the cyclical pattern in HFMD actually due to the accumulation of immunologically especially in preschool children between epidemics until a critical threshold level is breached (Ang *et al.*, 2011).

The pattern occurred without any specific month of distribution. However, study by Wang *et al.*, (2013) represented cases in China reported that most of the severe and fatal cases were most frequently seen in June, July and August while an equal number of fatalities occurred in June and July. This is why they were practice routine epidemiological surveillance and more preventive actions during that period each year (Wang *et al.*, 2013). In other study found that HFMD occurred predominantly during the summer months especially for EV-71 but that infections were closely associated with humid periods during those months (Chang *et al.*, 2012).

The same findings were suggested by other studies in USA and Taiwan where the HFMD epidemics occur during summer and autumn months (Chang *et al.*, 2004). In general, the overall of an HFMD epidemic was influenced by the climatic factors including the temperature, humidity and rainfall. The effect of those factors are demanding in further study of HFMD especially in Malaysia (NikNadia *et al.*, 2016).

Other than demographic factors and climatic factors, the geographical or environmental factors have a strong influence on the spread of HFMD in Malaysia and worldwide. A study done in China, used the geographically weighted regression (GWR) model to investigate the associations between the HFMD and the selected factors (child population density, temperature, relative humidity and precipitation) found spatial heterogeneity of the strength and direction of association between these factors and the incidence of HFMD (Hu *et al.*, 2012). Moreover, earlier study done in 2008, showed that the population density greatly affects HFMD (Huang *et al.*, 2014). The population density are including the population in the states or districts and also the population density among the household. The household setting, as well as schools and communities, play important roles in the transmission of HFMD (Chang *et al.*, 2004). In Malaysia setting, the high risk area of HFMD were found in urban area which is high population density as the ratio of urban to rural area was 1.12:1 (Noraishah and Krishnarajah, 2016).

2.2 Rising of Vaccine Refusal Cases in Malaysia

Coming to the vaccine refusal cases, it actually refer to the cases who had refused some or all vaccines scheduled in the Malaysian National Immunization Program (NIP) that was introduced in the early 1950s. As we concerned, Malaysian NIP was designed based on the World Health Organisation (WHO) Expanded Programmed on Immunization (EPI). It consists of list of vaccinations including BCG, Hepatitis, DTaP, Hib, IPV, MMR and also HPV. Most of the vaccinations are given during the childhood except for the HPV which is given to the 13 year old adolescent. The EPI recommends that all countries immunise against 6 childhood diseases, however our Malaysian NIP has expanded protection against 12 major childhood diseases.

Data from Ministry of Health (2017) showed there is an increasing number of vaccine refusals based on the surveillance from government clinics and hospitals. However the data does not include private clinics and hospitals which can be more. A study was done involving 10 health clinics in Perak 2016 revealed that the immunization refusal and defaulter rates were 8 and 30 per 10,000 children immunized per year respectively and the three main reasons for refusing immunization were a preference for alternative treatment, assumption that vaccines have no effect and doubt regarding vaccine contents (Lim *et al.*, 2016).

Looking at the NIP, HFMD is not part of the vaccine preventable diseases then why it is more interested compared to other diseases related such as measle, pertussis, diphtheria or tuberculosis?

As mentioned earlier in the problem statement of the study, instead of very rapid increment of HFMD cases in Malaysia since 2005 and since 2010 in Terengganu but the study related is still limited especially involving the application of GIS in spatial epidemiology. Comparing to the other vaccine preventable diseases, a lot of studies done including in Michigan, USA which showed a significant overlap between geographic clusters of non-immunised cases and pertussis clusters was documented (Omer *et al.*, 2008). While other study (Phadke *et al.*, 2016) concluded that the phenomenon of vaccine refusal was associated with an increased risk for measles among people who refuse vaccines and among fully vaccinated individuals.

Apart from that, in 2016 the death of two children with diphtheria in Malacca and Kedah were very surprising as diphtheria had been eradicated since a decade ago after vaccination program was introduced. Based on the investigation done, both cases had a similar root cause where the children did not receive a complete set of vaccination and they died because of infection complication. Based on some study discussed, the relationship between the vaccine preventable diseases and the vaccine refusal cases are quite well and broad studied however the relationship and effect of the vaccine refusal cases towards other non-vaccine preventable diseases such as HFMD is still limited.

By using the epidemiological triad, the relationship of the vaccine refusal cases to the HFMD are more likely due to the low immunity condition created by vaccine refusal cases.

Big scale study by Hu *et al.,* (2012) summarized that other than the factors of climate and child population density, the population immunity and environmental hygiene can contribute to the occurrence, transmission and spread of HFMD (Hu *et al.*, 2012). The population immunity due to the vaccine refusal cases is part of study issue that need to be emphasized.

Important to note that a retrospective study from the 1970s in Kuala Lumpur, Malaysia revealed the prevalence of total enteroviruses (including EV-71 and CA-16), besides Poliovirus per se, sharply decreased shortly after a mass poliovirus vaccination campaign (Tan and SK Lam, 1978). Similarly, a coincidence of poliovirus vaccination and decline of HFMD occurred during the Bulgarian HFMD epidemic, suggesting a possible of protective role of poliovirus vaccination against HFMD (McMinn, 2002).

Those studies indirectly showed the relation of vaccination used in poliovirus vaccination campaign had also reduced the prevalence of common causative agent for the HFMD. Besides, concept of the herd immunity is important to explained the extend vaccine benefits beyond the directly targeted population, whereby an increase in the prevalence of immunity by the vaccine prevents circulation of infectious agents in susceptible populations (Kim *et al.*, 2011).

2.3 Spatial Epidemiological Analysis

Next is the justifications of using the spatial distribution and analysis in conducting study are proved by a lot of studies such as, Bie *et al.*, (2010) had revealed the relationship between geographical factors and HFMD incidence rate were important factors in order to control and prevent HFMD outbreak and epidemic. Besides, GIS and spatial epidemiological analysis have been used for various infectious diseases, for example study done in Sukhothai province, Thailand in 2006 explored the potential of analysis of spatial factors related to dengue fever and dengue hemorrhagic fever, while other study done in Chiang Mai province, Thailand between the years 2001 and 2006 revealed the spatial patterns and hotspots of diarrhea using the spatial analysis methods in GIS (Nakhapakorn and Jirakajohnkool, 2006) (Chaikaew *et al.*, 2009).

Then, a study used GIS in Subang Jaya, Malaysia showed there was no significant distribution pattern for the dengue intensity index as the higher values tend to stay at the same locality throughout the year in study area. Furthermore the study also recommended to utilize the temporal risk indices to characterize dengue rather than relying on the traditional case incidence data (Dom *et al.*, 2010).

Regarding cases of HFMD, study done in China using spatial and temporal statistical modeling revealed the incidence rate of HFMD was associated with geographical factors, social factors and meteorological factors but it was different in some areas (Ma *et al.*, 2015).

While in Malaysia, spatial distribution and analysis facilitates public health responses upon HFMD outbreaks; isolation according to districts and implement general control measures; helps to choose the right timing and strategy for the implementation of control activities (Sham *et al.*, 2014).

Apart from that, Noraishah *et al.*, (2016) had proven that a study using GIS regarding HFMD in year 2012 which was the outbreak year had shown that spatial autocorrelation exist in 11 district of Sarawak due to HFMD. On the other hand, the spatial statistical analysis useful in identifying the cluster of the studied disease as well as determining at what spatial distance the cluster occurs. It was proven in a study done by Safian *et al.*, (2008), which able to investigate the pattern of typhoid cases in Kelantan by using the Nearest Neighboring and Ripley's K-function analysis (Safian *et al.*, 2008). The same method was used in studying the clustering phenomena of tuberculosis in Singapore among various categories (Das *et al.*, 2017).

This is why most of study related to the infectious diseases are using the spatial method particularly to identify the diseases cluster and assess the significance of potential exposure.