

**FACTORS ASSOCIATED WITH HAND, FOOT  
AND MOUTH DISEASE (HFMD) OUTBREAK  
CASES IN KELANTAN 2018**

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AND MOUTH DISEASE (HFMD) OUTBREAK  
CASES IN KELANTAN 2018**

**By**

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NMRR-19-3104-51280 (IIR)

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## LIST OF ABBREVIATIONS

Adj. OR	Adjusted Odds Ratio
CDCIS	Communicable Disease Control Information System
CI	Confidence interval
CV-A16	Coxsackieviruses A16
df	degree of freedom
EV-A71	Enterovirus A71
HFMD	Hand, Foot and Mouth Disease
LR	Likelihood Ratio
MOH	Ministry of Health
NMRR	National Medical Research Registry
OR	Odd Ratio
SPSS	Statistical Package for Social Sciences
WHO	World Health Organization

## LIST OF SYMBOLS

=	Equal to
$\geq$	More than and equal to
<	Less than
$\alpha$	Alpha
$\beta$	Beta
%	Percentage
n	Number of samples
m	Ratio between two groups

## ABSTRAK

**Latar Belakang:** Penyakit tangan, kaki dan mulut tetap menjadi perhatian kesihatan awam yang penting di seluruh dunia, terutamanya di Wilayah Pasifik Barat. Di Malaysia, Kementerian Kesihatan Malaysia (KKM) telah mengadaptasi sistem pemantauan, panduan, pencegahan dan program kawalan penyakit untuk mengurus kes-kes dan kejadian wabak di setiap peringkat. Walau bagaimanapun, masih terdapat banyak kes penyakit tangan, kaki dan mulut dan kejadian wabak dilaporkan walaupun program kawalan ini telah dilakukan. Oleh itu, sangat penting untuk mengenali faktor yang mempengaruhi kes wabak penyakit tangan, kaki dan mulut untuk mengatasi masalah ini.

**Objektif:** Kajian ini bertujuan untuk menerangkan kriteria kes-kes penyakit tangan, kaki dan mulut, peratusan kes wabak dan mengkaji faktor-faktor mempengaruhi kes wabak penyakit tangan, kaki dan mulut di negeri Kelantan pada tahun 2018.

**Metodologi:** Kajian ini terdiri daripada dua bahagian. Bahagian I menggunakan kajian keratan rentas deskriptif sementara di Bahagian II, kajian keratan rentas perbandingan digunakan. Data pesakit penyakit tangan, kaki dan mulut di Kelantan pada tahun 2018 menggunakan data sekunder yang diperoleh dari Unit Kawalan Penyakit Berjangkit, Jabatan Kesihatan Negeri Kelantan.

**Results:** Lebih separuh daripada kes penyakit tangan, kaki dan mulut di Kelantan pada tahun 2018 berumur 5 tahun ke atas (53.1%) dan lelaki (55.8%). Majoriti daripadanya adalah orang Melayu (96.4%), tinggal di kawasan luar bandar (78.6%) dan telah menerima rawatan sebagai pesakit luar (95.4%). Sebilangan besar dari mereka bersekolah di tadika (38.3%) diikuti oleh yang lain seperti penjagaan di rumah dan

tempat kerja yang berbeza (27.1%), sekolah (18.2%) dan taska (16.4%). Kes penyakit tangan, kaki dan mulut yang dinotifikasi juga lebih tertumpu pada musim cuaca panas antara Mei dan Ogos (40.9%). Di antara 1026 pesakit penyakit tangan, kaki dan mulut, 70 pesakit adalah kes wabak, bersamaan dengan 6.8%. Faktor-faktor signifikan yang mempengaruhi kes wabak penyakit tangan, kaki dan mulut dalam kalangan kanak-kanak berumur kurang dari 5 tahun adalah mereka yang bersekolah di tadika (Adj. OR 0.330; 95% CI: 0.114, 0.957,  $p$ -value=0.041) dan dijaga di rumah (Adj. OR 0.008; 95% CI: 0.001, 0.067,  $p$ -value<0.001) berbanding dengan mereka yang dihantar ke taska dan kejadian berlaku semasa musim panas (Adj. OR 0.154; 95% CI: 0.043, 0.557,  $p$ -value=0.004) berbanding yang berlaku di musim hujan.

**Kesimpulan:** Kajian ini melaporkan bahawa faktor-faktor signifikan yang mempengaruhi kes wabak penyakit tangan, kaki dan mulut di Kelantan dalam kalangan kanak-kanak di bawah 5 tahun adalah yang bersekolah di tadika, yang dijaga di rumah dan kejadian berlaku semasa musim panas. Oleh itu, kami mengesyorkan kerjasama pelbagai agensi untuk terus memantau dan menambah baik program yang sedia ada yang berkaitan dengan penyakit tangan, kaki dan mulut di taska, tadika dan sekolah untuk meningkatkan pengetahuan, sikap dan amalan di kalangan pengurus institusi, guru dan kakitangan tentang penyakit ini. Selain itu, kami juga mencadangkan untuk membangunkan intervensi yang terarah termasuk pengesanan awal penyakit, meningkatkan kebersihan persekitaran, penjagaan pintu masuk yang berkesan dan amalan yang baik dalam penyediaan makanan di pusat jagaan harian untuk mengurangkan kejadian dan beban wabak.

**KEYWORDS:** Penyakit tangan, kaki dan mulut, wabak, faktor yang berkaitan

## ABSTRACT

**Background:** Hand, foot and mouth disease (HFMD) remains a significant public health concern worldwide, especially in the Western Pacific Region. In Malaysia, the Ministry of Health (MOH) had adopted the HFMD surveillance system, guideline, prevention and control program for managing the HFMD cases and outbreak occurrence at any level. However, there are still high cases of HFMD and outbreak occurrence reported despite these control program had been made. Therefore, it is vital to recognise the factor associated with the HFMD outbreak cases to overcome this problem.

**Objective:** This research aims to describe characteristics of HFMD cases, the proportion of HFMD outbreak cases and to study the associated factors of HFMD outbreak cases in Kelantan state in 2018.

**Methodology:** This study consists of two parts. Part I adopted the descriptive cross-sectional study while in Part II, the comparative cross-sectional study design was used. The data of HFMD patients in Kelantan in 2018 were using the secondary data obtained from Communicable Disease Control (CDC), Unit Kelantan State Health Department.

**Results:** More than half of HFMD cases in Kelantan in 2018 were aged 5 years and above (53.1%) and male group (55.8%). Majority of them were Malays (96.4%), resided in rural areas (78.6%) and had been treated as outpatients (95.4%). Many of them attended kindergarten (38.3%) followed by others such as home care and different working places (27.1%), school (18.2%) and nursery (16.4%). Notified HFMD cases also more concentrated during warm weather season between May and

August (40.9%). Among 1026 HFMD patients, 70 patients were HFMD outbreak cases, equivalent to 6.8%. The significant association found between HFMD outbreak cases among children aged less than 5 years old were those who attended the kindergarten (Adj. OR 0.330; 95% CI: 0.114, 0.957,  $p$ -value=0.041) and were taken care at home (Adj. OR 0.008; 95% CI: 0.001, 0.067,  $p$ -value<0.001) compared to those who attended the nursery and the disease occurred during the warm season (Adj. OR 0.154; 95% CI: 0.043, 0.557,  $p$ -value=0.004) compared to the rainy season.

**Conclusion:** This study reported that the significant factors associated with HFMD outbreak cases in Kelantan among the children below than 5 years were the children who attended the kindergarten, home-care children and disease occurred during the warm season. Therefore, we recommend the collaboration of multi agencies to continuously monitor and improvise the current particular program related to HFMD in nurseries, kindergartens and schools to improve knowledge, attitude and practice among institution managers, teachers and staff towards HFMD. Other than that, we also suggest to develop targetted interventions including early detection of disease, improve the environmental hygiene, effective gatekeeping and good practice in preparation of food in daycare centres to reduce the incidence and burden of the outbreaks.

**KEYWORDS:** Hand,foot and mouth disease, HFMD, outbreak, factor associated



# CHAPTER 1

## INTRODUCTION

### 1.1 Background

Hand, foot and mouth disease (HFMD), is a viral illness commonly affects in infants and children younger than five years old (Gui *et al.*, 2015). However, there is no exception that HFMD also can infect children more than five years old and among the adult age group. An individual who is exposed to HFMD viruses after three to seven days should develop the symptoms. This is called HFMD's incubation time. HFMD symptoms typically begin with fever, lower appetite, sore throat and feeling of ill. Then, it is followed by the appearance of soreness small red spots in the mouth and skin rash on palms and soles. Skin rash also can develop at knees, elbows and buttocks. Naming hand, foot, and mouth disorder (HFMD) is a clinical explanation of a disease describing the anatomic presentation and function of lesions that affecting parts of the human body. Nevertheless, for individuals to be classified as hand, foot and mouth disease (HFMD), they do not have to complete all the clinical manifestations.

HFMD is usually a harmless and self-limiting disease, but it can also be dangerous. (Centers for Disease Control and Prevention, 2019). As HFMD is usually mild and self-limiting illness, many cases of HFMD typically do not require hospitalisation and can be treated as outpatients. Almost all HFMD patients will get better within 7 to 10 days with no or limited medical care (MOH Malaysia, 2007). HFMD also can be severe when the illness is related to some complications such as pulmonary oedema, meningitis and encephalitis that even can cause fatality.

Main etiological agents that can cause HFMD are human enterovirus A (HEV-A) pathogens. HEV-A pathogens consist of coxsackievirus A (CV-A) 2–8, 10, 12, 14, 16 and human enterovirus 71 (EV71) (Bian *et al.*, 2015). Overall, human enteroviruses A71 (EV-A71), coxsackieviruses 10 (CV-A10) and 16 (CV-A16) were usually related to the HFMD outbreak cases. EV-A71 can cause more severe outcomes compared to other human enteroviruses (Koh *et al.*, 2018).

According to the Ministry of Health Malaysia, the diagnosis for HFMD is based on two case descriptions which are the definition of a clinical case and diagnostic laboratory criteria. Clinical case definition of HFMD is any child (10-year-old and below) with mouth or tongue ulcer and maculopapular rashes and OR or vesicles on palms and soles with or without history of fever. Laboratory criteria for diagnosis is any case that has clinical symptom and positive for virus (Coxsackieviruses (CV) A16, A5, A9, A10, B2, B5; and Enterovirus A71 and other enteroviruses) which could cause HFMD, isolated or detected from stool or vesicle fluid or mouth ulcer or saliva.

HFMD was first registered in 1957 in Canada and New Zealand (Gui *et al.*, 2015). Previously, HFMD outbreaks had been sporadic and local, but this trend had shifted. In 1997, Malaysia had recorded 2628 cases, followed by thousands of cases in Taiwan, Singapore and Australia (Wang *et al.*, 2011). After that, small to medium-sized epidemics have been reported persistently in the Asia-Pacific region. The number of HFMD cases in mainland China has gradually increased since 2007, reflecting a period of unprecedented large-scale outbreaks in the Asia-Pacific region. Therefore, HFMD had been recognised as a public health threat worldwide, especially in the Western-Pacific Region (Bian *et al.*, 2015).

Nearly three million children were reported to have HFMD by World Health Organisation (WHO) in 2014. They were mostly from the Western-Pacific Regions such as China, Japan, Malaysia, North Korea, Singapore and Vietnam (Qiu *et al.*, 2019). Recently, as the burden of this illness is increasing in trend worldwide, especially in Western-Pacific Regions, more further control measures and interventions are needed as public health responses to limit the circulating infectious agents in the populations and minimise the complications of HFMD (Wang *et al.*, 2018).

The establishment of the surveillance system for HFMD cases in most countries in the Asia-Pacific region such as China, Taiwan, Singapore, Malaysia and Vietnam was due to the significant incidence of several large HFMD outbreak cases recorded in Asia-Pacific region countries since 1997 (Hoang *et al.*, 2019). At that moment, millions of HFMD cases were reported, including several percentages of the cases progressed to severe manifestations and even caused death. HFMD surveillance in Malaysia began in 1997 with sentinel surveillance. The surveillance started after a major outbreak of HFMD emerged in Sarawak state in 1997.

Previously, HFMD notification was administratively necessary and had commenced since October 2005. However, the death of HFMD and cases admitted to the ward of children aged ten years and under are mandatory for notification. Sarawak State has mandated notification of all HFMD cases in the state because of repeated outbreaks and fatalities in Sarawak. Later on, HFMD's notification came into enforcement under the PU.A 374/2006 on 12 October 2006 (MOH Malaysia, 2007).

There are two types of surveillance practising in the Ministry of Health for HFMD, which are clinical surveillance and laboratory surveillance (MOH Malaysia, 2007).

For clinical surveillance, notification of HFMD is mandatory under the National Notification of Infectious Diseases. Notification must be done by phone within 24 hours of diagnosis, then notification form must follow. All confirmed HFMD cases must be entered into CDCIS eNotifikasi. Meanwhile, for laboratory surveillance, two sentinel sites must be selected by the state health department per state. At least five specimens should be taken from five patients per centre and sent to the specified laboratories. There will be designated laboratories appointed by MOH involve in enterovirus surveillance.

Surveillance for HFMD will help to explain the transmission rate, risk factors and outcome of these infectious diseases, which will provide guidelines for treatment and prevention of the disease. It is also useful to predict potential outbreaks, monitor spreading infectious agents, approximate the degree of HFMD in the population at risk and also evaluate the extent of HFMD complication in the population at risk (MOH Malaysia, 2007).

## **1.2 Statement of the problem**

Although the HFMD surveillance program undertaken, the establishment of HFMD guidelines, control and preventive measures adopted by MOH in Malaysia, there are still high cases of HFMD outbreak and has higher incidence rate compared to other infectious diseases. Low compliance and poor level of practice on HFMD either in preventive or control measures are major issues in the HFMD outbreak control program (Inta *et al.*, 2017). Therefore it is crucial to understand the spread of the disease in term of factors that are associated with the HFMD outbreak cases.

Besides, the constant occurrence of new cases and outbreaks of HFMD in Malaysia in recent years also requires study to be undertaken because the published article explaining the outbreak of HFMD in Malaysia is limited, including factors associated with the outbreak.

According to Kelantan State Health Department reports, HFMD outbreak cases were increasing from the past five years in Kelantan and HFMD is one of Kelantan's five most recorded outbreaks in 2018 (CDC Kelantan State Health Department, 2019). Therefore, a study is required to determine the source of the problem, including factors associated with HFMD outbreak cases in Kelantan.

### **1.3 Rationale of the study**

The findings of this study will benefit by providing information and database on HFMD, especially for stakeholders towards prevention and control programs of the HFMD outbreak. Besides, the information can also be used to enhance the surveillance system operated by MOH Malaysia. By predicting the associated factors of HFMD outbreak, appropriate action and strategies can be taken by the Disease Control Division in MOH Malaysia to reduce numbers of HFMD outbreak cases and the morbidity during the HFMD outbreak.

### **1.4 Research questions**

- 1) What are the characteristics of HFMD cases in Kelantan in 2018?
- 2) What are the factors associated with HFMD outbreak cases in Kelantan 2018?

## **1.5 Objectives**

### **1.5.1 General objective**

To study the characteristics of HFMD cases and associated factors of HFMD outbreak cases in Kelantan 2018

### **1.5.2 Specific objectives**

- 1) To describe characteristics of HFMD cases in Kelantan State in 2018
- 2) To describe the proportion of HFMD outbreak cases among HFMD cases in Kelantan in 2018
- 3) To identify factors associated with HFMD outbreak cases in Kelantan 2018

## **1.6 Research hypotheses**

There are significant factors associated with HFMD outbreak cases in Kelantan 2018.

## CHAPTER 2

### LITERATURE REVIEW

The search of papers in this study was done using online search engine and database including PubMed, Science Direct, Scopus, Springer link and Google Scholar. Several search strategies were applied, including the use of Boolean operators, “AND”, “OR” and “NOT”. The keywords used were hand, foot and mouth disease, HFMD, factor associated outbreak and epidemiology.

#### 2.1 Epidemiology of HFMD

The first diagnosis of hand, foot and mouth disease (HFMD) came in 1948. Later on, HFMD case was registered in New Zealand in 1957. Subsequently, in 1958, the Cox Virus was isolated in Canada. In 1959, that disease that was caused by Cox Virus was called HFMD in America (Li *et al.*, 2014). HFMD has gained new attention over the last two decades because of evidence that clinical, epidemiological and aetiological features of this disease may be significantly different from those believed initially (Esposito and Principi, 2018).

The incidence rate of HFMD cases reported to the National Notifiable Disease Surveillance System (NNDSS) in China was increased from 40 in 100,000 in 2008 to 198 in 100,000 population in 2014 (Qiu *et al.*, 2019). While in Vietnam, from February 2011 to July 2012, about 174,677 HFMD cases were noted, together with 200 deaths reported (Khanh *et al.*, 2012). From January to July 2018, Japan reported 47,930 HFMD cases, which were about the same persistent pattern that was seen from 2013

to 2017 (WHO, July 2018). Meanwhile, in Thailand, between the years 2007 to 2011, the Thai Ministry of Public Health had reported about 12,000 to 18,000 HFMD sporadic cases annually (Linsuwanon *et al.*, 2014). From 2003 to 2012, a total of 197,207 cases of HFMD were reported to the Singapore Ministry of Health (Chen *et al.*, 2018).

Ministry of Health Malaysia (MOH) data showed the incidence rate of HFMD in 2007 and 2008 was as high as 56.1 and 60.6 per 100,000 populations, respectively. It may be because, in 2006, HFMD was declared as a reportable disease (Chan *et al.*, 2011). In 2014, the incidence rate of HFMD cases in Malaysia recorded as 104.07 per 100,000 populations, and there were consistently increasing of HFMD cases in 2016 (148.47 per 100,000 population) and 2018 (232.62 per 100,000 population). However, there were slightly decreased in the trend of HFMD cases in 2015 and 2017 with the incidence rate of 74.09 per 100,000 populations and 90.64 per 100,000 populations, respectively. Even though the incidence rate of HFMD in Malaysia dropped from in 2015, HFMD is still one of the diseases with the highest incidence rate. As the HFMD incidence rate increased nationwide, the incidence rate in Kelantan state also drastically increased from 2017 (31.78 per 100,000 populations) to 2018 (203.18 per 100,000 populations). The incidence rate and total cases of HFMD cases in Kelantan in the last five years, from 2014 to 2018, are illustrated in the following Figure 2.1.



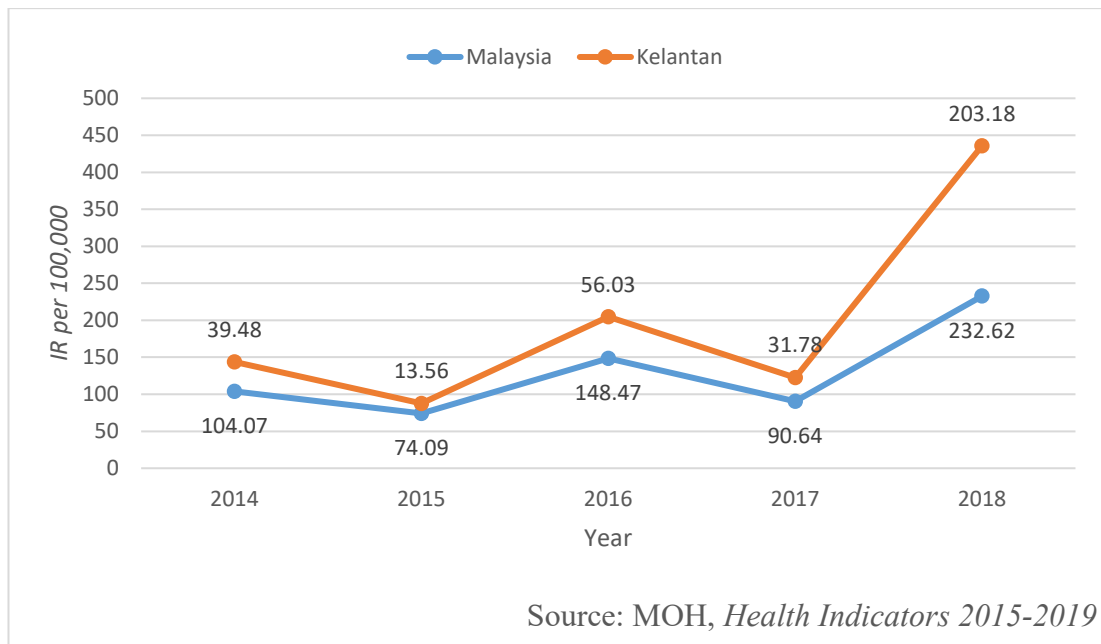


Figure 2.1: Incidence Rate of HFMD in Malaysia and Kelantan 2014-2018

From 3 January to 6 August 2016, a total of 23,454 cases of HFMD were reported nationally, with an average of 757 cases per week, increasing 17.8% from 19,916 cases reported in 2015 (Mahadzar and Abdul Rahman, 2019). Overall from the recent five years, the HFMD cases showed a clear upward trend from 2017 to 2018. HFMD cases in Malaysia had increased from 29,358 cases in 2017 to 76,446 cases in 2018, accounting for a 160% increment (Health Informatics Centre MOH Malaysia, 2018). Therefore, that increment was proportionate with the increased pattern of total HFMD outbreaks in Malaysia from 926 in 2017 to 1,932 in 2018 (Sektor Zoonosis KKM, 2019). There was no mortality of HFMD reported in 2017; however, in 2018, there were a total of three death recorded in Malaysia (Sektor Zoonosis KKM, 2019). Meanwhile, in Kelantan, HFMD cases had increased six times higher from 587 cases in 2017 to 3,829 cases in 2018 (Health Informatics Centre MOH Malaysia, 2018). The

total cases of HFMD cases in Malaysia and Kelantan state in the last five years, from 2014 to 2018, as illustrated in the following Figure 2.2.

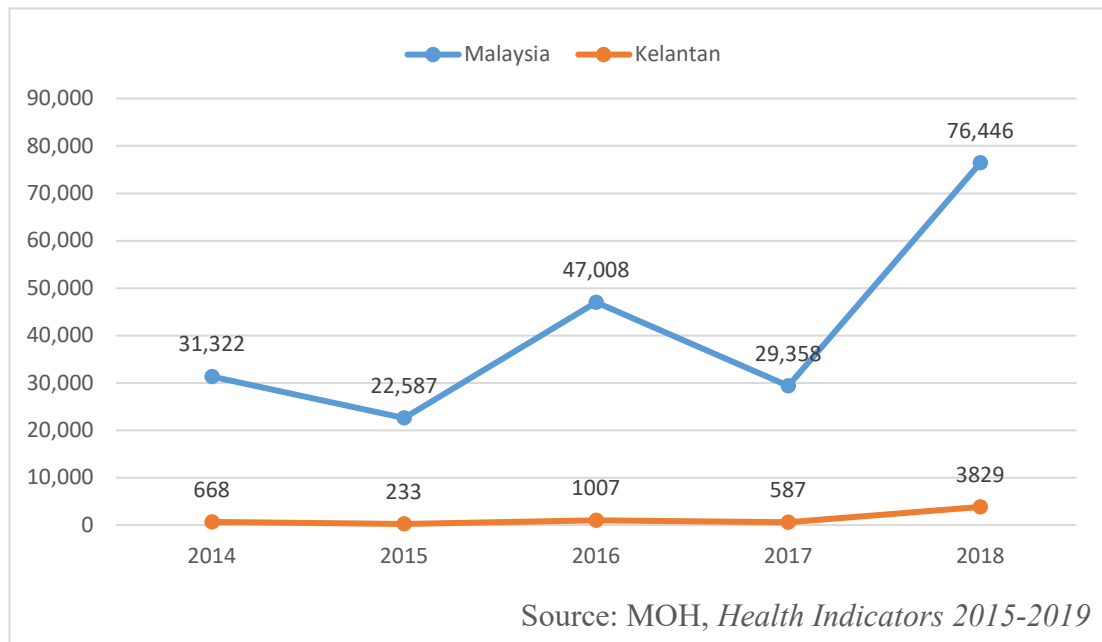


Figure 2.2: Total Cases of HFMD in Malaysia and Kelantan 2014-2018

## 2.2 HFMD Outbreaks

HFMD outbreaks had occurred in many parts of the world, including the United States of America, Australia, Europe, Brazil, Japan and Malaysia. The increasing number of HFMD outbreaks worldwide had brought HFMD to international attention due to complications caused by death. In 1975, an HFMD outbreak in Bulgaria emerged, 750 people were infected, 149 people were paralysed and 44 people died. In 1998, there was a wide-scale HFMD outbreak in Taipei, 129,106 people were diagnosed with HFMD and 405 people had developed complications such as neurological problems or pulmonary oedema. A total of 78 children death also was reported in this HFMD outbreak (Li *et al.*, 2014).

There also had a record of HFMD outbreak in Fuyan Anhui Province, China in 2008 where 25,000 people were diagnosed with HFMD in a short period, including 42 children death. Since that, HFMD was listed as a reportable disease in China (Ni *et al.*, 2012). According to the “Protocol of control practice for the clustered cases and outbreaks of hand, foot and mouth disease” established in 2012 in China, HFMD outbreak was defined as more than or equal to 10 cases of HFMD occurring in a kindergarten or school within a week (Li *et al.*, 2018).

Taiwan recorded the largest HFMD outbreak in 1998 that involved more than 100,000 cases. During that outbreak, about 400 children were hospitalised due to central nervous system (CNS) complications. Out of them, 78 patients died with brainstem encephalitis and neurogenic pulmonary oedema (Ho *et al.*, 1999). During the HFMD outbreak in 2010 in Taiwan, HFMD patients diagnosed with CV-A6 were hospitalised more often than those diagnosed with other enterovirus infections, such as CV-A16 and CV-A5, suggesting more severe CV-A6 related symptoms (Bian *et al.*, 2015).

The first HFMD outbreak in Vietnam was reported in Ho Chi Minh City in 2003, and the report showed a rise in HFMD cases in Daklak Province, which is situated in the Central Highlands area of Vietnam. (Van Pham *et al.*, 2017). In another HFMD outbreak occurred in Vietnam in 2005, CV-A16 and EV-A71 were identified as the primary pathogens related to the outbreak (Hoang *et al.*, 2019).

The earliest occurrence of HFMD outbreak in Singapore took place in 1970 without known pathogen, followed by another two outbreaks in 1972 and 1981 with 104 and 742 reported cases, respectively. CV-A16 was found to be responsible for causing these two later outbreaks in Singapore (Chan *et al.*, 2003). In 2009, a major HFMD

outbreak occurred in Singapore with 29,686 confirmed cases, resulting in four cases developed with encephalitis and one death (Bian *et al.*, 2015).

Meanwhile, in 2012, a nationwide HFMD outbreak occurred in Thailand and a large proportion of the cases had affected the children. Coxsackie A6 (CV-A6) was the main pathogen causing a 2012 HFMD outbreak in Thailand, but severe cases that cause the deaths during this outbreak were related to the EV-A71 (Jiratchaya *et al.*, 2018).

In Malaysia, the HFMD outbreak is defined as the occurrence of two or more cases in the same locality within the incubation period (6 days) (Ministry of Health Malaysia, 2017). National surveillance data need to be evaluated to detect and identify the occurrence of HFMD outbreak. First Malaysia HFMD outbreak occurred in Sarawak state in 1997. During that time, HFMD not only emerged in Sarawak but was subsequently spread in Peninsular Malaysia with a total of 4253 HFMD cases reported by June 1997. About 49 HFMD deaths recorded which were 29 deaths in Sarawak and 12 deaths in Peninsular Malaysia. Then, the fatal HFMD outbreak occurred again in peninsular Malaysia at the end of 2000 and had claimed the life of eight young children (Chua and Kasri, 2011). Later in 2005, a similar outbreak of HFMD occurred in peninsular Malaysia, with two reported deaths in young children, followed by a larger outbreak in Sarawak in early 2006 (Chua *et al.*, 2007).

Malaysia reported 1,932 HFMD outbreaks nationwide in 2018 while 926 outbreaks in 2017. It was clearly shown that there was 109% increment in a total of HFMD outbreaks from 2017 to 2018. Sarawak State had the highest HFMD outbreak reported in Malaysia in 2018, with 569 outbreaks involving 1,512 outbreak cases, followed by Wilayah Persekutuan Kuala Lumpur with 368 HFMD outbreaks involving 1,166 outbreak cases, while Perlis had 12 outbreaks with 49 outbreak cases. (Sektor Zoonosis

KKM, 2019). In Kelantan, the total confirmed outbreak cases were 61 cases in 20 HFMD outbreaks in 2018, up significantly from 2017, with only two outbreaks involving five cases registered (Kelantan, 2019).

### **2.3 Management of HFMD Outbreak**

Based on HFMD Guideline 2007 by MOH Malaysia, when reporting a suspected outbreak from a kindergarten or school, it is crucial to quickly establish if an actual outbreak exists based on the case definition. Then, district health practitioners will conduct a risk assessment of the outbreak. A minimum of five samples is expected to be obtained and tested to confirm the disease that causes the outbreak agent. It is important to evaluate the number of cases, the vulnerable population affected, the overall attack rate and the age-specific attack rate. Active case detection shall be conducted among contacts within the organisation and relatives, and all those with illness shall be referred to nearest health clinics for treatment. Swabs from oral ulcers and vesicular lesions on the hands and feet or even stool samples when the vesicles resolved shall be collected and send to identified laboratories for virus isolation. Health education for institutions supervisors on the HFMD and the control measures such as good personal hygiene and isolation of infected children need to be conducted. The institution's staffs must do gatekeeping to separate the symptomatic child from other healthy children. Keep the institution closed for ten days from the onset of the last case. Then, the disinfection procedure will be conducted for the institution.

## **2.4 The Associated Factors with HFMD Outbreak Cases**

HFMD disease has been consistently observed globally over the last three decades (Wang *et al.*, 2017). Various parameters had been used to identify the epidemiological characteristics of HFMD cases and possible risk factors that increase the HFMD outbreak cases (Wang *et al.*, 2018). Many studies around the world had established the epidemiological characteristics of HFMD outbreak cases within HFMD cases, but as far as I know, there has been no research on factors associated with HFMD outbreak cases in Malaysia or specifically in Kelantan state.

### **2.4.1 Age**

In Singapore, from 97,207 HFMD cases in 2003-2012 and 57,502 in 10,080 institutional outbreaks in 2011-2016, about 90% of cases were children under 12 years of age, and about 70% of that were children five years of age and younger (Chen *et al.*, 2018). During the HFMD outbreak in Sarawak in 1997, children aged less than five years accounted for more than 80% of cases, with more than 50% of children under two years of age affected. Similar to the findings in other countries, HFMD in Malaysia primarily impacted the children at a very young age, especially those aged one to two years (Chua and Kasri, 2011). Other than that, from the study that had been done on HFMD outbreak cases in Singapore in the late year 2000, out of 129 patients, 87% of the cases were less than five years old (Shah *et al.*, 2003). Meanwhile, in the province of Zhejiang during 2008 to 2012, from 454,339 cases of HFMD were registered, children under the age of three and five accounted for nearly 60% and 90% respectively (Gui *et al.*, 2015).

### **2.4.2 Seasonal**

A research was carried out in Singapore on the effect of short-term weather changes on the incidence of HFMD from 2001 to 2008 found that outbreaks of HFMD peaks in the warmer season of the year (Hii *et al.*, 2011). The data of HFMD outbreaks in Malaysia from 2006 to 2012, also follow the seasonal pattern of the study that carried out in Singapore, which was most outbreaks occurred between March and May. Two seasons which are intermonsoon seasons and southwest monsoon seasons included between March and May. Throughout Peninsular Malaysia, the southwest monsoon season is a dry time while in the intermonsoon season, the west coast is usually wetter than the east coast region. Kelantan is a state that includes in the East Coast Region of Peninsular Malaysia (Jamaludin Suhaila *et al.*, 2010). However, in Northern Thailand, HFMD occurred mainly during the rainy season and in winter, same with the occurrence in Yunnan in southern China, where peaks of the outbreak were also recorded in winter (Samphutthanon *et al.*, 2013).

### **2.4.3 Institution**

There were a total of 10,080 outbreaks at the school level in Singapore from 2011 to 2016 affecting a total of 57,502 HFMD cases in childcare centres and kindergartens, 105 of which resulted in the closure (Chen *et al.*, 2018). In Thailand, children under five years of age were at high risk of infection and disease outbreak since many children of this age attend nursery school or kindergarten, where they play with their classmates in the same age group (Samphutthanon *et al.*, 2013). Besides, kindergartens were highly susceptible area for HFMD outbreaks because a large proportion of

children with close contact could provide an ideal HFMD incubation place. Children get infected quickly and are more likely to transmit this disease (Li *et al.*, 2018).

#### **2.4.4 Gender**

A study conducted in Northern Thailand, HFMD outbreaks have been shown to affect males more than females, which is consistent with earlier China research that found boys more vulnerable to enterovirus than girls (Samphutthanon *et al.*, 2013). Most of the research on HFMD outbreak cases among pre-school children done in China had resulted that clustered male case rate was 60%, whereas the clustered female case rate was 40%; thus the male proportion was 1.5 times more than female (Wang *et al.*, 2018). Furthermore, during the enterovirus outbreak in Taiwan in 2008, the male was also more affected than female, which the ratio was 1.6:1 (Wu *et al.*, 2010).

#### **2.4.5 Residence**

In a study done on HFMD outbreak cases in China among pre-school children from 2009 to 2013, the cumulative rate of HFMD outbreaks in urban areas is high, with a value of 65%. Whereas in rural areas, the rate is lower, which was 35% (Wang *et al.*, 2018). In urban areas of China, pre-school children typically crowd in limited space, creating a reservoir for rapid virus transmission. In Shandong province, China, the incidence of HFMD was higher in urban areas compared to rural areas. Even though the rates of occurrence in urban areas were slightly higher than those in rural areas, the rates of case-severity and case-fatality in rural areas were equivalent to those in urban areas (Wang *et al.*, 2017).



#### **2.4.6 Race**

Between August 2008 and July 2010 in Singapore, EV-A71 seroprevalence in Malay ethnic group was at 34.9%, higher than the Indians (24.6%) and the Chinese (24.3%) (Ang *et al.*, 2011). However, in another study conducted in Singapore, out of the 97,207 cases of HFMD nationwide in 2003 to 2012 and 57,502 cases in 10,080 institutional outbreaks in from 2011 to 2016, majority of cases were Chinese accounted 74%, followed by 15% Malay, 3% Indian and 8% others (Chen *et al.*, 2018).

#### **2.4.7 Admission**

Around 1.6% of HFMD cases in Singapore were hospitalised during the HFMD epidemics associated with EV-A71 between April and May 2008. It was more than twice the hospitalisation rates of CV-A16 caused epidemics, which in 2007 was 0.7 % in the same period (Ang *et al.*, 2011). In the biggest EV-A71 outbreak in Taiwan occurred in 1998, there were at least 405 children admitted to the hospital with serious neurological complications, and 78 of them died (Chang *et al.*, 2016). Patients with HFMD were hospitalised because they had signs or symptoms that indicated more severe illness. These included high fever, vomiting, tachypnea and indications of neurological involvements such as encephalitis, aseptic meningitis or acute flaccid paralysis or cardiopulmonary complications such as pulmonary oedema, pulmonary haemorrhage or myocarditis (Ho *et al.*, 1999).

## 2.5 Conceptual framework

The concept of infectious disease development or causation, including HFMD is referred to the epidemiological triangle model, which consisted of human or host, pathogen and environment. In this triad, the HFMD cases may result from the interaction between the pathogen, susceptible host in an environment that supported the transmission of the disease.

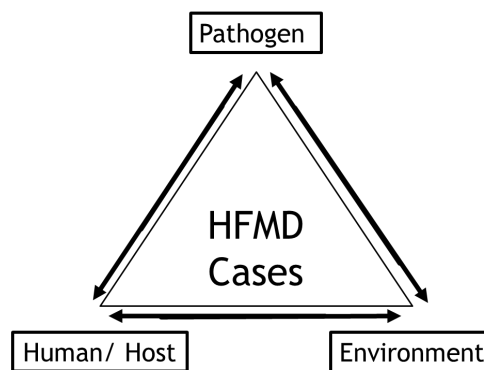


Figure 2.3: Epidemiological triangle for HFMD cases

Our conceptual research framework is actually based on this model. According to the literature review, there were several factors which influenced the association of HFMD outbreak cases and they were further categorised into the pathogen, human or host and environment factor.

In the host factor, characteristics that listed were age, gender, race, hospital admission, clinical symptoms, underlying disease, socio-economic status, education level, nutritional status, immunisation status and behaviour. In the environment factor, characteristics that included were seasonal factor, residence, institution, climate changes, sanitary condition and social contact. In the pathogen factor, features that involved were types of the virus isolated, phenotypic, serotypes and genotypic differences.

However, due to limitation of secondary data that were used in this study, age, gender, race, hospital admission, season, residence and institution only will be included as the data that available.

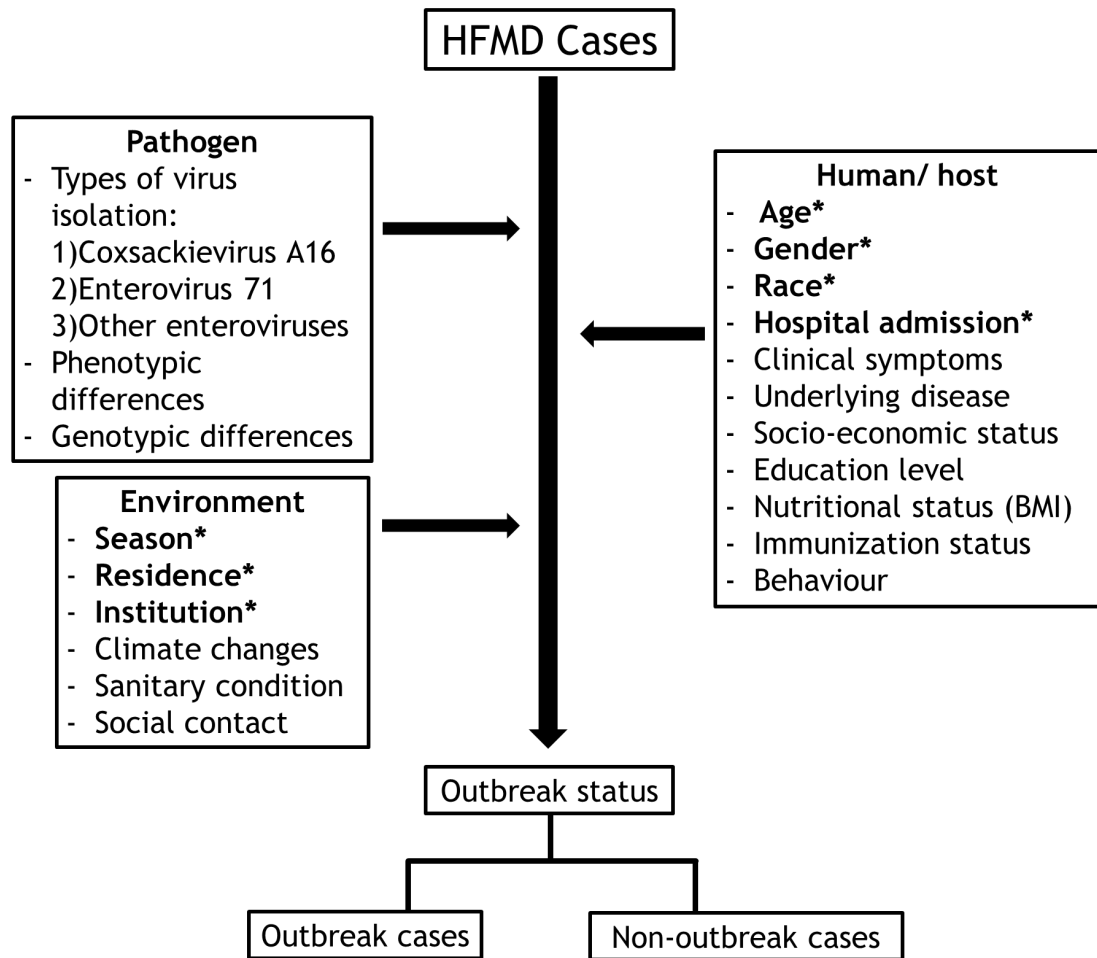


Figure 2.4: Conceptual framework of factors associated with HFMD outbreak cases. Factors with "\*" and bold are studied.

## CHAPTER 3

### **METHODOLOGY**

#### **3.1 Study design**

This study consists of two parts, which consist of descriptive cross-sectional study (Part I) and comparative cross-sectional study design (Part II).

#### **3.2 Study duration**

This study was conducted between December 2019 and April 2020.

#### **3.3 Study location**

This study was conducted in Kelantan. Kelantan is a North East state of Peninsular Malaysia, split into a total of 10 regional districts, including Kota Bharu, Tumpat, Pasir Mas, Pasir Puteh, Machang, Kuala Krai, Gua Musang, Bachok, Tanah Merah, and Jeli. The capital of Kelantan is Kota Bharu.

#### **3.4 Reference population**

The reference population were the population in Kelantan State.

### **3.5 Source population**

The source population were the HFMD cases in Kelantan State.

### **3.6 Study population**

The study population were all the notified HFMD cases in Kelantan State in 2018.

### **3.7 Sampling frame**

The sampling frame was all the notified HFMD cases in Kelantan in 2018 that fulfilled the inclusion and exclusion criteria.

### **3.8 Study criteria**

In this study, the criteria for sample selection can be categorised as follows:

#### **3.8.1 Inclusion criteria:**

The inclusion criteria were all HFMD cases which had been notified via CDCIS e-Notifikasi to Department of Communicable Disease Control (CDC) Kelantan in 2018.

#### **3.8.2 Exclusion criteria**

The exclusion criteria was incomplete data in CDCIS e-Notifikasi more than 20 % missing data which cannot be verified further.

### **3.9 Sample size determination**

Sample size was calculated based on study objective as follows:

#### **3.9.1 Objective 1**

The sample size was not calculated in Objective 1 because it was a descriptive study. There was a total of 3829 HFMD cases notified to State Health Office Kelantan in 2018. However, only 1026 cases with fulfilled criteria were included to answer Objective 1.

#### **3.9.2 Objective 2**

There was no sample size calculation done for Objective 2 because it was a descriptive study. As per in Objective 1, 1026 cases with fulfilled criteria were included to answer Objective 2.

#### **3.9.3 Objective 3**

The sample size calculation for Objective 3 was calculated for each variable of factor associated with HFMD outbreak cases in Kelantan 2018 using two proportion formula by using Power and Sample Size calculation software. Some of the variables of factor associated with HFMD outbreak are shown in Table 3.1. Table 3.1: Summary of sample size calculation for some of the factors associated with HFMD outbreak cases. The parameters used for sample size calculation were  $P_0$ ,  $P_1$ ,  $n_1$ ,  $n_2$ ,  $n$ ,  $m$ , significant level and power of test.

The sample size was calculated for each variable including an allowance of an additional 20% possibility of missing data which is 10% for HFMD outbreak cases ( $n_1$ ) and 10% for HFMD non-outbreak cases ( $n_2$ ). Description of each of these parameters are as follow:

$P_0$  = proportion of exposure among HFMD non-outbreak cases

$P_1$  = expected proportion of exposure among HFMD outbreak cases

$\alpha$  = value of standard normal distribution cutting off probability  $\alpha$  (1.96 for  $\alpha = 0.05$  (two-tailed))

$\beta$  = value of standard normal distribution cutting off probability  $\beta$  (0.8 for 80% power)

$m$  = ratio of size of exposed population to unexposed population

$n_1$  = sample size in HFMD outbreak cases

$n_2$  = sample size in HFMD non-outbreak cases

Table 3.1: Summary of sample size calculation for some of the factors associated with HFMD outbreak cases

Variables	P0	Est.P1	M	n1	n1+10 %	n2	n2+10 %	Literature review
Age (age less than 5 years)	0.71	0.90	4	45	50	180	198	(Chen <i>et al.</i> , 2018)
Gender (male)	0.49	0.70	1	85	94	85	94	(Li <i>et al.</i> , 2018)
Residence (urban area)	0.38	0.60	2	60	67	120	132	(Zeng <i>et al.</i> , 2013)
Institution (kindergarten/ pre-school)	0.24	0.50	4	31	35	124	137	(Zeng <i>et al.</i> , 2013)
Race (Malays)	0.34	0.60	1	57	63	57	63	(Ang <i>et al.</i> , 2011)

Based on the above calculations, the largest sample size used in this study were 94 for HFMD outbreak cases and 198 for HFMD non-outbreak cases. For outbreak cases, the sample was lesser, which was 70 cases than the calculated sample size; therefore, all were included. In conclusion, a total of 268 cases were included to find the associated factors for HFMD outbreak cases in answering Objective 3.