TREND AND SPATIAL ANALYSIS OF HAND, FOOT AND MOUTH DISEASE (HFMD) IN PULAU PINANG BETWEEN 2017-2022

DR. MOHAMAD AFIQ AMSYAR BIN HAMEDIN

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by

DR. MOHAMAD AFIQ AMSYAR BIN HAMEDIN

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DECLARATION

I declare this research project is my own work and has not been submitted for award of higher degree elsewhere.

Mohamad Afiq Amsyar Bin Hamedin

Student ID: PUM 0116/22

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2. Mohamad Afiq Amsyar B Hamedin, Kamarul Imran Musa, Noor Farhana M Fathil, Rozaini M Shah, Paula Moraga. ***Spatial Autocorrelation and Hotspot Analysis of Notified HFMD Infections in Pulau Pinang, Malaysia between 2017 and 2022.*** (Prepared for submission to the International Journal of Geoinformatics)

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CA-16	Coxsackie A-16
CA-6	Coxsackie A-6
CDCIS	Communicable Disease Control Information System
DOSM	Department of Statistic Malaysia
EV -71	Enterovirus - 71
GIS	Geographical Information System
HFMD	Hand Foot Mouth Disease
JePem	Jawatankuasa Etika Penyelidikan Manusia
MOH	Ministry of Health, Malaysia
MREC	Medical Research Ethical Committee
NNI	Nearest Neighboring Index
NPIs	Non-Pharmacological Interventions
SD	Standard Deviation
USM	Universiti Sains Malaysia
WHO	World Health Organisation

ABSTRAK

ANALISIS TREND DAN SPATIAL PENYAKIT TANGAN, KAKI, DAN MULUT (HFMD) DI PULAU PINANG ANTARA 2017-2022

Latar Belakang: Penyakit tangan-kaki-mulut (HFMD) merupakan isu kesihatan awam global yang utama, terutamanya di Asia Pasifik termasuk Malaysia, dan lebih kerap menyerang kanak-kanak. Mengenal pasti kawasan berisiko tinggi dengan lebih awal dan memahami cara penyebaran penyakit ini dapat membantu pihak berkuasa kesihatan awam mencegah berlakunya wabak HFMD.

Objektif: Kajian ini bertujuan untuk menentukan kadar insiden HFMD di Pulau Pinang, memetakan kejadian di peringkat mukim, menganggarkan keamatan spasial jangkitan HFMD, menguji kehadiran *spatial autocorrelation*, dan mengenal pasti kawasan hotspot jangkitan HFMD.

Metodologi: Ini adalah satu kajian *cross sectional* menggunakan data sekunder dari Communicable Diseases Control Information System (CDCIS) E-Notification Versi 2011yang dikendalikan oleh Jabatan Kesihatan Negeri Pulau Pinang. Data populasi di Pulau Pinang diperoleh dari Jabatan Perangkaan Malaysia. Koordinat bagi setiap kes ditukarkan kepada format sistem projeksi Kertau RSO Malaya (EPSG:3168). Kadar insiden HFMD dikira pada peringkat mukim dan analisis *point pattern* dijalankan menggunakan Perangangan Ketumpatan Kernel (KDE) dan Indeks Jiran Terdekat (NNI). Kajian juga menganalisis kehadiran *spatial autocorrelation* dan analisis hotspot untuk mengenal pasti risiko spasial pada peringkat mukim. Analisis dilakukan

menggunakan pakej ***gtsummary, tmap, spdep, spatialeco***, dan ***spastat*** dalam perisian R Versi 4.2.3.

Keputusan: Terdapat 15,586 kes HFMD yang dilaporkan antara tahun 2017 hingga 2022. Kecuali tahun 2020 dan 2021, peningkatan kejadian HFMD dilihat dengan kejadian tertinggi dilaporkan pada tahun 2022 dengan kadar 24.81 kes setiap 1000 penduduk. Analisis Perangangan Ketumpatan Kernel (KDE) menunjukkan kes HFMD terpusat di Daerah Timur Laut, terutamanya di mukim Bandar Georgetown dan Mukim 13, dan mulai merebak ke Kawasan Daerah Barat Daya dan beberapa kawasan di Seberang Perai. Terdapat bukti kluster spasial HFMD berdasarkan julat NNI (0.21-0.50) untuk semua tahun yang dikaji. Statistik Global Moran I, yang berkisar antara 0.21 hingga 0.38, menunjukkan kehadiran *spatial autocorrelation* dalam semua tahun yang dikaji. Peta Indikator Tempatan Autokorelasi Spasial (LISA) menunjukkan bahawa kawasan dengan nilai tinggi-tinggi (H-H) terutamanya terkumpul di sepanjang pantai timur Pulau Pinang, menunjukkan hotspot bagi HFMD. Selain itu, terdapat penurunan jumlah kawasan rendah-rendah (L-L) yang digantikan oleh kawasan tinggi-rendah (H-L), terutamanya di kawasan Seberang Perai. Ini menunjukkan peningkatan risiko jangkitan HFMD di kawasan tersebut.

Kesimpulan: Keamatan spasial, *spatial autocorrelation*, dan kawasan *hotspot* yang signifikan secara utamanya terletak di kawasan bandar yang terurbanisasi dan yang baru dibangunkan di negeri Pulau Pinang. Kawasan-kawasan ini mempunyai dengan kepadatan penduduk yang tinggi, aktiviti industri, dan penempatan utama penduduk. Penemuan daripada kajian mengenai kejadian dan corak spasial jangkitan HFMD dapat digunakan sebagai parameter tambahan untuk aktiviti pemantauan HFMD dan merumuskan tindakan pencegahan yang lebih fokus.

Kata Kunci: HFMD, Spatial Intensity, Spatial Autocorrelation, Hot Spots, Pulau Pinang

ABSTRACT

TREND AND SPATIAL ANALYSIS OF HAND, FOOT AND MOUTH DISEASE (HFMD) IN PULAU PINANG BETWEEN 2017-2022

Background: Hand-foot-mouth disease (HFMD) is a major global public health issue, especially in Asian Pacific Region including, Malaysia and particularly affects children. Recognizing high-risk areas early on and understanding how the disease spreads can help public health authorities effectively prevent HFMD outbreaks from occurring.

Objective: This study aimed to determine incidence of HFMD in Pulau Pinang, map the incidence at subdistrict level, estimate the spatial intensity of HFMD infections, test for presence of spatial autocorrelation and identify hotspots of HFMD infections.

Methodology: This was a cross sectional study using secondary data from Communicable Diseases Control Information System (CDCIS) E-Notification Version 2011 governed by State Health Department of Pulau Pinang. Data on population in Pulau Pinang was obtained from Department of Statistic Malaysia. The coordinates were converted into the format of projected system Kertau Rectified Skewed Orthomorphic (RSO) Malaya (EPSG:3168). Incidence of HFMD was calculated at subdistrict level and point pattern analysis conducted using Kernel Density Estimates and Nearest Neighboring Index (NNI). The study also analyses presence of spatial autocorrelation and hot spot analysis to distinguish spatial risk at

subdistrict level. Analyses were done using ***gtsummary, tmap, spdep, spatialeco*** and ***spastat*** package in R Software Version 4.2.3

Result: There was total of 15 586 reported HFMD cases between 2017 until 2022. Except year 2020 and 2021, increment of incidence of HFMD was seen with highest incidence reported in 2022 at 24.81 cases per 1000 population. Kernel Density Estimates (KDE) analysis revealed HFMD cases centered at District of Timur Laut, particularly in the subdistrict of Bandar Georgetown and Mukim 13, and began to spread over Barat Daya and pockets of the Seberang Perai area of the state. There was evidence of spatial cluster of HFMD based on NNI (0.21-0.50) for all studied years. The Global Moran I statistic, ranging from 0.21 to 0.38, suggests the presence of spatial autocorrelation in all the years studied. The Local Indicator of Spatial Autocorrelation (LISA) map revealed that the areas with high-high (H-H) values were mainly clustered along the eastern coast of Penang Island, indicating hotspots for HFMD. Additionally, there was a decrease in the number of low-low (L-L) regions, which were replaced by high-low (H-L) regions, particularly in the Seberang Perai area. This indicates a growing risk of HFMD infections in that region.

Conclusion: The spatial intensity, spatial autocorrelation, and significant hotspot regions primarily located in urbanized and newly developed areas in Pulau Pinang. These areas are characterized by high population density, industrial activities, and settlements. The findings from studying the incidence and spatial patterns of HFMD infections can serve as an additional parameter for HFMD surveillance activities and formulating targeted preventive actions.

Keywords: HFMD, Spatial Intensity, Spatial Autocorrelation, Hot Spots, Pulau Pinang

CHAPTER 1

INTRODUCTION

1.1 Study Background

HFMD is a visible illness that primarily affects children and infants, and it is characterized by symptoms such as fever, mouth ulcers, and a skin rash (Solomon *et al.*, 2010). While the disease is typically self-limiting, some children may develop more serious complications, such as myocarditis, aseptic meningitis, or even death (Ooi *et al.*, 2010). In recent years, the Western Pacific Region, including Malaysia, has experienced increasing trend of HFMD outbreaks (Huang *et al.*, 2012).

1.1.1 Epidemiology of HFMD

HFMD was first identified in 1948 during an outbreak of febrile illness with pharyngeal lesions and a skin rash in the Toronto region of Canada (Robinson *et al.*, 1958). However, the first recorded case of HFMD occurred in 1957 in New Zealand. Despite these early reports, little attention was given to understand the epidemiological and clinical characteristics of the disease for many years. Over the past two decades, research on HFMD has experienced a surge in activity, primarily driven by its escalating prevalence in the Asia Pacific region. This rise has surpassed that of other epidemics, rendering HFMD a critical public health concern (Huang *et al.*, 2012).

HFMD outbreaks have been reported globally for over four decades, but in recent years, they have been more prominent in the Western Pacific Region (Samphutthanon *et al.*, 2014). China has been particularly affected, with more than 22 million cases reported between 2009 and 2019 and an average monthly incidence rate

of 12.309 per 100,000 people (Yu *et al.*, 2021). Furthermore, a time series analysis conducted in China has forecasted that the number of cases will continue to increase in the immediate future (Yu *et al.*, 2021). Study in Japan revealed increment of cases between year 2000 until 2015 with more than 2 million infections recorded during this period. The trend in some years showed bimodal characteristics, indicating that HFMD can occur in multiple waves within a single year (Sumi *et al.*, 2017).

In Malaysia, HFMD was included as one of statutory notification nationally in October 2006. However, HFMD was first reported in Malaysia in the state of Sarawak in 1997 and was found to be associated with the emergence of the Enterovirus A71 (EV-A71) virus. The outbreak during that time caused 28 deaths among infected children (NikNadia *et al.*, 2016). Since then, HFMD outbreak with larger amplitude tend to occur 2-to-3-year cyclical pattern in Malaysia along with molecular analysis that revealed presents of more than 1 prominent type of Enteroviruses co-circulating together within community (Lee *et al.*, 2021).

1.1.2 Nature of HFMD

Various types of human enteroviruses known to be causative pathogen for HFMD infections. The most known HFMD-associated viruses were EV-A71 and CV-A16; however, increasing cases of HFMD due to other viruses such as CV-A6 and CV-A10 have been reported (Lu *et al.*, 2012). Presence of multiple type of entroviruses at large scale within particular community known to be one the major reason for large occurrence of HFMD outbreak in recent decades (Lee *et al.*, 2021).

CV-A16 HFMD infections usually causing mild infections and resolved without major events, however there has been report that conclude its ability to cause

complication such as temporary and permanent neurological deficits (Xu *et al.*, 2012). Another common pathogen, EV-A71 were more commonly associated with large outbreak and cause major complications including cardiorespiratory collapse, encephalitis and even causing fatality (Ooi *et al.*, 2010).

Common clinical features of children infected with HFMD were present of herpes, eczema and ulcerated lesion in the hands, feet, mouth, and hips (Solomon *et al.*, 2010). Commonly, Transmissions occur via fecal oral route or contact with objects contaminated with fluids from infected patient. Proximity between children especially during outdoor playing time and crowded child-care facilities usually among the main reason for large outbreak of HFMD (Sun *et al.*, 2016). HFMD known to predominantly infect children, however the transmission was more advance if the outbreak involve smaller children (Koh *et al.*, 2016). The household transmission rate can extend up to 52% in EV-A71 outbreaks and particularly high at 84% among children under 6 years of age (Chang *et al.*, 2004).

With absent of definitive treatment and widely available vaccines, HFMD may exerts pressure to various sectors. In health sector, countries are still monitoring HFMD outbreak trough systematic surveillance system (Xing *et al.*, 2014b; NikNadia *et al.*, 2016). In addition, phylogenetic analysis to develop effective vaccines for worldwide distributions also actively being initiated along with development of antiviral medications (Pourianfar *et al.*, 2015). In order to immediately response to epidemic of HFMD, education sector will need to adopt for preventive policy such as school and premises closure to break the transmission chain among children. While it would help to reduce disease occurrence, such policy exposed school children towards mental and psychosocial issues upon prolonged implementations (Bahn and Psychiatry, 2020).

1.1.3 Spatial Analysis in Communicable Disease

The utilization of spatial analysis as an integral part of epidemiological investigations has been a longstanding practice within the field. Its application can be traced back through a significant historical timeline, highlighting its importance in understanding and addressing public health concerns. One of the most famous examples of this is John Snow's map of a cholera outbreak in 1854. Snow's map was instrumental in identifying a water pump as the source of the infection, providing compelling evidence for the importance of incorporating spatial data in controlling communicable disease outbreaks (Hajna *et al.*, 2015). In recent decades, guidelines on prevention of communicable diseases had include use of spatial locations as part of monitoring elements to guide for control actions (Auchincloss *et al.*, 2012). While investigations and reports on disease outbreaks often prioritize analyzing factors related to time and individuals involved, less attention is typically given to the importance of spatial elements. This can result in important associations, such as those related to geography and environmental factors, being overlooked as potential contributors to the emergence of outbreaks. Incorporating spatial data into epidemiological investigations can help to identify and better understand these important factors and ultimately improve our ability to prevent and control communicable diseases (Moore and Carpenter, 1999).

The availability and accessibility of spatial tools and software, such as ArcGIS, Quantum GIS (QGIS), and R-software, have significantly advanced the field of spatial analysis. These technological developments have facilitated the process of conducting spatial analyses, enabling researchers to swiftly identify and differentiate high and low-risk areas through molecular analysis and pathogen identification. This advancement has substantially reduced the time required for such assessments.

Additionally, one of the key strengths of spatial analysis is its adaptability to various types of infectious diseases, irrespective of their clinical features or potential for transmission. This adaptability underscores the versatility and utility of spatial analysis as a valuable tool in the investigation and management of infectious diseases. (Auchincloss *et al.*, 2012). Recently, spatial analysis have been used to map and analyze multiple communicable disease including food poisoning, Legionnaires' disease, Cryptosporidiosis, Q fever, Measles and Leishmaniasis (Smith *et al.*, 2015).

Spatial analysis in epidemiology typically starts with identifying the location of disease outbreaks, which can be specified using information such as residential addresses, outbreak sites, or postal addresses as reference points. From there, appropriate spatial analysis techniques can be applied, along with effective data visualization and mapping, to gain valuable insights into disease occurrence and inform efforts to control and prevent the spread of communicable diseases. By leveraging the power of spatial data analysis, public health professionals can more effectively identify and target areas of high disease prevalence, assess potential environmental or geographic factors that may be contributing to the spread of disease, and ultimately develop more effective interventions and prevention strategies to protect the health of communities (Pfeiffer *et al.*, 2008).

In relation to HFMD infections in Malaysia, use of spatial analysis in investigations and published reports are still scarce. A study in Sarawak used spatial analysis to map HFMD infections in the state and able to provide proper guide to control actions against the disease (Sham *et al.*, 2014). Another state-wide study in Terengganu emphasized clustering and hotspots identification of HFMD infections using the GIS software and various method of spatial analysis (Said *et al.*, 2021).

Spatial analysis can serve as additional parameter towards surveillance activity of communicable disease including HFMD. It can provide great benefit in the form of visualization of cases according to geographical area, identifying spatial relationship between cases and surrounding factors and evaluating progress of prevention actions against the disease.

1.2 Problem Statement

The increase in cases of HFMD has become a significant issue for public health authorities in Malaysia, causing both health and economic burdens. Conducting thorough epidemiological analysis at both local and national levels can aid in identifying the underlying causes of the disease's occurrence and how it spreads. Such analysis is crucial for understanding and managing the outbreak effectively.

The epidemiology of HFMD in the country has been extensively researched, with studies focusing on various aspects such as clinical, pathological, molecular characteristics, and human behavior towards HFMD infections (Ooi et al 2010; Yogambigai Rajamoorthy et al 2022). However, there have been only a few local studies on the application of spatial epidemiology for HFMD in Malaysia. The previous research conducted in Sarawak and analyzed up to the district level was deemed too broad to be used for mitigation actions (Noraishah M Sham et al. 2014). Similarly, a study conducted in Terengganu using single-year data from 2018 was not comprehensive enough (Said et al 2021). Therefore, further research on spatial epidemiology for HFMD in Malaysia is needed to develop effective mitigation strategies.

To improve the HFMD surveillance system, an additional parameter is necessary to aid in the implementation of more strategic human resources and

prevention activities. This can be achieved through inclusive and focused spatial analysis, which can serve as an early warning parameter to anticipate potential large outbreaks of HFMD. Such an approach will enable timely and effective intervention to mitigate the spread of the disease, and ultimately reduce its impact on public health.

1.3 Study Rationale

The study will develop geographical map and analyze spatial distribution of HFMD infections in Pulau Pinang, which will enable public health authorities to differentiate between high and low-risk areas for infections. This will allow for more strategic and appropriate resource management in response to potential large outbreaks. Additionally, the study will explore the sociodemographic characteristics of HFMD infections in Pulau Pinang over a period of 6 years. This will further help in understanding the characteristics of infections for specific population groups and guide in planning prevention strategies against them. Overall, this study will provide valuable insights for the development of effective intervention measures to control the spread of HFMD in Pulau Pinang.

1.4 Research Question

- What are the characteristics of HFMD infection in Pulau Pinang between 2017 – 2022
- What is the spatial distribution and intensity of the infections in Pulau Pinang between 2017-2022
- Is there presents of spatial autocorrelation and hotspots of HFMD infections in Pulau Pinang between 2017-2022

1.5 Objectives

1.5.1 General Objectives

To describe the characteristics, develop geographical map of incidence and identify spatial distribution of HFMD infections in Pulau Pinang between 2017-2022

1.5.2 Specific Objectives

i) To describe the characteristic of notified HFMD infections in Pulau Pinang between 2017-2022.

ii) To develop geographical map of incidence and intensity of notified HFMD infections in Pulau Pinang between 2017 – 2022.

iii) To identify presence of spatial autocorrelation and hotspot of notified HFMD infections in Pulau Pinang between 2017 – 2022.

1.6 Research Hypothesis

- There are differences in spatial intensity of notified HFMD infections in Pulau Pinang using data from 2017 until 2022.
- There are presence of spatial autocorrelation and hotspots of notified HFMD in Pulau Pinang using data from 2017 until 2022.

CHAPTER 2

LITERATURE REVIEW

This chapter provides the review of HFMD incidence, spatial data analysis and the framework of the study.

2.1 Review on global incidence, regional and national of HFMD

Hand, foot and mouth disease (HFMD) is an acute viral infection caused by a group of human enteroviruses (EVs), such as Enterovirus A71 (EV-71), Coxsackievirus A16 (CV-Al6) and others (Lee *et al.*, 2021). It has become a significant public health concern due to emerging of frequent outbreaks and rise in its incidence, severity, and fatal complications particularly in South Asian countries in last few decades (Ho *et al.*, 1999; Wu *et al.*, 2010; Chua and Kasri, 2011).

Since introduction of HFMD as one of the mandatory notifiable diseases in China in 2008, close to 1.4 million cases reported within first 4 years involving approximately 400 annual deaths due to complication of the disease (Xing *et al.*, 2014a). In an effort to combat the spread of HFMD, Chinese authorities introduced a vaccine against EV-71 in 2016. However, recent reports indicate that the incidence of HFMD remains high in affected countries, highlighting the urgent need for a multivalent vaccine to effectively address this public health concern (Meng *et al.*, 2020). In Japan, National Epidemiological Surveillance of Infectious Diseases (NESID) also reported increasing number of infections trough routine surveillance done in the country. Japanese authority reported 3-year cyclical pattern of infections with more than 300 000 cases reported nationwide during peak year which can be attributed to the circulation nature of EV-71 (Takahashi *et al.*, 2018). However, detailed molecular study revealed the large HFMD outbreak also could be resulted from the co-circulation of other agents

such as CV-A16 (Lee *et al.*, 2021). Regionally, Singapore had established mandatory notification by medical practitioners all over the country as part of surveillance system for HFMD since year 2000. Modelling analysis published in 2018 revealed positive slope of gradient indicating increasing incidence of HFMD in Singapore and 70% of the cases did not show adequate symptomatology to help with diagnosis upon first presentation to doctors or gatekeeping screening at school (Koh *et al.*, 2016; Min *et al.*, 2021). It can be argued that the reported cases of infections in Singapore represent only the minimum number of cases in comparison to other Asian countries, due to the high intensity of Singapore's notification system (Koh *et al.*, 2016). Therefore, the actual number of unreported cases of infections in other Asian countries could be much higher.

In Malaysia, the incidence of HFMD was reported to range between 1.5 to 60.6 per 100,000 population from the year 2000 to 2008 (Chan *et al.*, 2011). However, this figure may be biased due to underreporting, as the statutory notification of HFMD cases in the country only began in October 2006. Subsequently, the total annual reported cases of HFMD from 2008 to 2014 ranged between 7,002 to 34,519 cases (NikNadia *et al.*, 2016). State-wide study in Sarawak revealed an increasing trend in the incidence of HFMD infections, with reported incidence rates ranging from 115.25 per 100,000 population to 530.1 per 100,000 population between 2006 and 2012 (Sham *et al.*, 2014). Furthermore, in 2018, several states in Malaysia recorded more than 100 cases per 100,000 populations, indicating a high burden of the disease in the country (Fong *et al.*, 2021; Said *et al.*, 2021).

2.2 Review of spatial data analysis methods for infectious diseases

2.2.1 Motivation for Spatial Analysis

Spatial epidemiology emphasizes the importance of geographical patterns in understanding disease risk factors, incidence, and outcomes. Application of spatial epidemiology can be done via multiple approaches. Auchincloss et al (2012) reported several spatial methods that frequently used in epidemiological studies include spatial proximity, aggregation method, cluster detection techniques and multivariable spatial regression (Auchincloss *et al.*, 2012)

2.2.2 Point Pattern Analysis in Epidemiological Studies

Spatial proximity and aggregation method were part of point pattern analysis in spatial epidemiology. For example, Nutor et al (2020) used geo-location of HIV patients in Malawi to visualize and understand the distribution of pattern of the disease at sub-regional level in the country (Nutor *et al.*, 2020). Then, a study in Malaysia adopted for Kernel Density Estimates (KDE) techniques to explore the aggregation of dengue cases in Putrajaya, Malaysia. The study also highlighted the importance of understanding proximity and aggregation pattern between cases to plan for prevention and control activities against infections (Hazrin *et al.*, 2016). In relations to HFMD infections, a study in China showed that spatial proximity and aggregation analysis in the form of KDE able to determine the spatiotemporal variation of HFMD cases and its relation to environmental variable within the area (Yi *et al.*, 2021). Such analyses can help in guiding appropriate prevention action against HFMD over accurate geographical area.

Cluster detection techniques are also commonly used to explore spatial characteristics of infectious diseases in a particular geographical area. These techniques

involve identifying areas with statistically significant clusters of cases and mapping them to help guide control efforts (Mergenthaler *et al.*, 2022). For example, Li et al (2016) identified the global spatial clustering trough Moran I statistic and findings were quantified and mapped by applying Local Indicator for Spatial Autocorrelation (LISA) technique to highlight hotspot areas for Tuberculosis infections in Beijing, China (Li *et al.*, 2016). Moran I statistic also being used by Li H et al (2020) to study on global clustering of cysticercosis in Dali, China and visualization of area with higher risk of infections were pointed out by employing spatial scanning approach (Li *et al.*, 2020) . More recently, Global Moran and Local Moran statistic were used in research to understand spatial dynamic of COVID-19 infections in Brazil (de Souza *et al.*, 2021). Similarly, cluster detection techniques were employed for research involving HFMD infections, for example Qian et al (2016) apply Moran I statistic to determine global clustering of HFMD infections in mainland of China (Qian *et al.*, 2016) . Samphutthanon et al (2013) in Thailand used Moran I for cluster detections and the outcome were quantified and mapped according to LISA to guide control actions against HFMD in Northern Thailand (Samphutthanon *et al.*, 2014).

2.2.3 Point Pattern Analysis using R-Software

A Geographic Information System (GIS) is a comprehensive framework used for creating, managing, visualizing, and analyzing spatial data. It consists of multiple components and supports various software applications, including both commercial options like ArcGIS and QGIS, as well as open-source alternatives. These applications empower researchers to conduct spatial analysis and data visualization. R-software has emerged as a valuable tool in spatial analysis, particularly in fields such as ecology, environment, and public health. It offers a wide range of spatial analysis and statistics

packages, making it a preferred choice for data analysis. Additionally, R's scripting environment enhances reproducibility, further adding to its appeal in the realm of spatial analysis {Gimond, 2019 #109}.

In R-software, researchers have access to a variety of spatial packages that facilitate the exploration of point pattern analysis from a multidimensional perspective. One such package is **spastat**, which offers an extensive collection of more than 2000 functions. These functions cover a wide range of tasks, including plotting spatial data, conducting exploratory data analysis, fitting models, performing simulations, conducting spatial sampling, diagnosing model performance, and formal inference. The **spastat** package provides researchers with several exploratory methods to analyze point patterns. These methods include quadrat counts, K-functions and their simulation envelopes, estimation of intensity through kernel smoothing of nearest neighbor distances, as well as kernel estimates of covariate effects. These functionalities enable researchers to explore various aspects of point pattern analysis and gain insights into the spatial characteristics of their data including epidemiological analysis {Baddeley, 2015 #110}.

2.3 Conceptual Framework

Based on literature review, spatial variation of HFMD infections can be analyzed by obtaining locations of the infections and georeferencing the coordinates prior to spatial analysis. Outcome of interest following spatial analysis comprises of proximity of the cases, aggregation and clustering of the cases and its relationship with other spatial factors such as environment variation over the geographical region.

Based on HFMD cases occur in Pulau Pinang between 2017-2022 incidence of cases were estimated and further analyzed for its spatial distribution pattern, intensity, clustering characteristic and hotspots profiling.

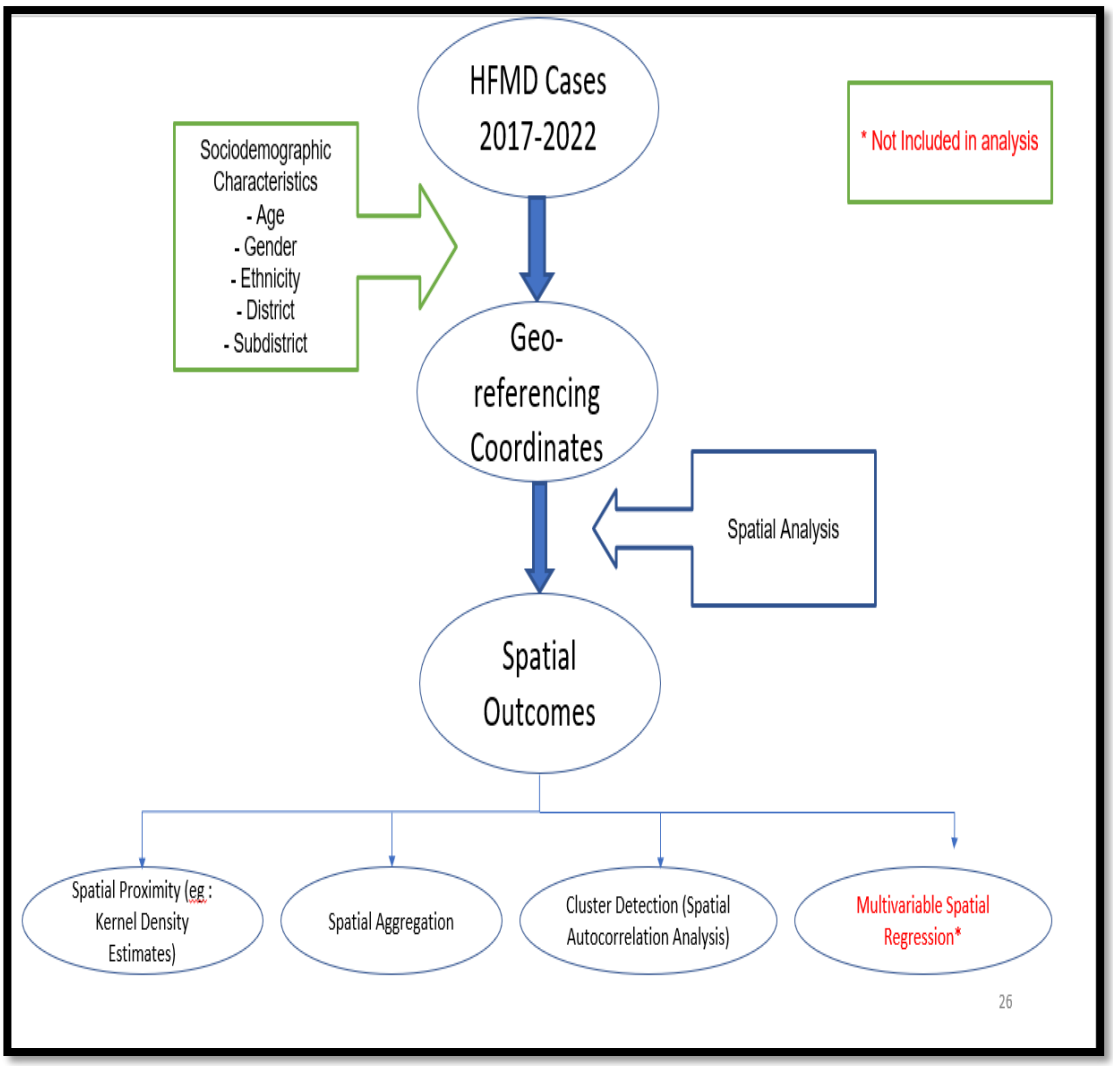

Figure 2.1 Conceptual Framework of Spatial Analysis of HFMD Infections

CHAPTER 3

Spatial and Temporal Intensity of HFMD Infections in Pulau Pinang between 2017-2022

Mohamad Afiq Amsyar B Hamedin, Kamarul Imran Musa, Noor Farhana M Fathil, Rozaini M Shah, Paula Moraga.

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3.1 Abstract

Background: Hand, foot and mouth disease (HFMD) remains a major public health issue in Malaysia, persisting despite existing control measures. The incidence of HFMD cases has shown a steady rise in Malaysia, particularly in the aftermath of the COVID-19 pandemic, necessitating a comprehensive epidemiological examination to comprehend the disease transmission dynamics.

Objective: To assess shifts in the spatial and temporal intensity of HFMD in Pulau Pinang, a north-western state of Malaysia using HFMD Notifications data from 2017 to 2022.

Methodology: Data were retrieved from the Communicable Diseases Control Information System (CDCIS) E-Notification Version 2011. The data were provided by the State Health Department of Pulau Pinang, Malaysia, and included all cases notified between 2017-2022. We estimated the number of HFMD cases for each district using the ***points-in-polygons*** function from in ***sf*** package in RStudio IDE. We tested the intensity and clustering of cases using Kernel Density Estimates (KDE) and nearest neighbor index (NNI) analysis.

Results: The district of Timur Laut had the highest proportion of notified cases (33%) followed by Barat Daya (22%) from 2017 until 2022. The intensity of infections was

centered in district of Timur Laut, particularly in the subdistrict of Bandar Georgetown and Mukim 13, and began to spread over Barat Daya and pockets of the Seberang Perai part of the state. We also found evidence of spatial cluster of HFMD based on NNI (0.21-0.50) for all studied years.

Conclusion: High intensity and clustering of HFMD cases were noted between 2017 and 2022 in regions characterized by denser populations and newly established settlements. Incorporating details about urbanization strategies within the state can enable public health authorities to effectively prioritize targeted control and prevention measures against the spread of the disease in specific areas.

Keyword*:* HFMD, Spatial Analysis, Spatial Intensity, Pulau Pinang

3.2 Introduction

Hand, foot, and mouth disease (HFMD) is a common infectious disease in childhood caused by various enteroviruses (Lee *et al.*, 2021). HFMD transmitted through close contact with virus-contaminated objects or contaminated respiratory droplets, water, and food from infected individuals (Hu *et al.*, 2012). Patients typically presented with fever, malaise, rashes, skin eruptions on the hands and feet, and vesicles in the mouth which usually mild and self- limiting (Solomon *et al.*, 2010). However, few infected children develop systemic complications includes neurological complications, cardiorespiratory problem and even death (Long *et al.*, 2016).

In last decades, HFMD infections had been widely spread in Asian region with multiple major outbreaks reported (Chen *et al.*, 2007; Ang *et al.*, 2009; Ma *et al.*, 2010). Apart from clinical treatment given to the patient, various public health measures such as isolation of infected children, school closure and social distancing being implemented as response towards large HFMD outbreak (Bahn and Psychiatry, 2020). As preparedness measure, several countries develop surveillance system to continuously monitoring trend of HFMD infections locally (Ma *et al.*, 2010; Cho *et al.*, 2014; Zhao *et al.*, 2022). Laboratory advancement also increase ability to detect responsible pathogen such as EV-71 and Coxakie A-6 that potentially causing major outbreak to assist in control measure (NikNadia *et al.*, 2016; Luchs *et al.*, 2022). Despite careful attention given to distribution of HFMD infections, the incidence of HFMD continue to rise particularly in Western Pacific Region including Malaysia (Koh *et al.*, 2016).

Since 1st outbreak in 1997, Malaysia has been facing with endemicity nature of HFMD infections in various part of the country (Podin *et al.*, 2006). According to report published in 2016, large outbreak in Malaysia tend to occur in cyclical pattern for every

2- 3 year (NikNadia *et al.*, 2016). Pulau Pinang, one of the states in Northwest part of Malaysian Peninsula also contribute to the rising number of cases in national tally. In 2016, 47 008 cases of HFMD reported nationwide and Pulau Pinang account for 2399 cases (5.1%) of the tally, an increment of about 300% from data in 2015, 598 cases (2.6%) of national tally in Pulau Pinang (MOH; 2016). This has necessitated immediate improvement towards pre-existing surveillance system towards HFMD infections.

Application of spatial and temporal analysis can assist public health authorities to differentiate intensity of infections between different geographical areas (Bhunia *et al.*, 2013). Besides, it can serve as additional early warning parameter towards large outbreak of infectious disease including HFMD (Noraishah and Krishnarajah, 2016). However, there has been lacking of studies that analyze the geographical locations of HFMD and the temporal trend of HFMD in Malaysia. The lacking of such studies will hinder our understanding of the spread and patterns of HFMD in Malaysia, impede effective preventive measures, and limit our ability to allocate resources and target interventions in the most affected areas. This knowledge gap may lead to delayed responses, increased transmission, and greater burden on healthcare systems, ultimately impacting the overall management and control of HFMD outbreaks. Therefore, we conducted this study to analyze the spatial and temporal intensity of HFMD infections in Pulau Pinang, Malaysia to provide useful insights into local epidemic control against the disease.