Spatial and Temporal Intensity of HFMD Cases in Pulau Pinang, Malaysia between 2017 and 2022

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ABSTRACT

INTRODUCTION: Hand, foot and mouth disease (HFMD) remains a significant public health concern in Malaysia, persisting despite existing control measures. This study aimed to assess the spatial and temporal dynamics of HFMD in Pulau Pinang, a north-western state of Malaysia. **MATERIALS AND METHODS:** Data were retrieved from the Communicable Diseases Control Information System (CDCIS) E-Notification Version 2011, including all notified HFMD cases in Pulau Pinang from 2017 to 2022. The number of cases by district was estimated using the points-in-polygons function in the sf package in RStudio. Kernel Density Estimates (KDE) were used to assess spatial intensity, while spatial clustering was evaluated using the nearest neighbor index (NNI). **Results:** A total of 15 586 notified HFMD cases reported in Pulau Pinang between 2017 -2022. Temporally, the spatial intensity of cases fluctuated, with a peak in 2018, followed by a marked decline in 2020 and 2021 and a resurgence in 2022. Spatially, the highest intensity of infections was consistently observed in the district of Timur Laut, particularly in urban subdistricts such as Bandar Georgetown and Mukim 13 (Paya Terubong). Over time, high-intensity areas expanded to include Barat Daya and parts of Seberang Perai, including Mukim 12 (Bayan Lepas) and central areas of Seberang Perai Tengah, Utara, and Selatan. Evidence of significant spatial clustering was detected across all years based on nearest neighbor index values (NNI: 0.21–0.50). **CONCLUSION:** HFMD cases in Pulau Pinang showed marked spatial clustering and shifting intensity patterns, especially in densely populated and newly developed areas. These findings highlighted the need for targeted, locality-specific prevention strategies to curb HFMD transmission.

INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a common infectious disease in childhood caused by various enteroviruses.[1] Patients typically presented with fever, malaise, rashes, skin eruptions on the hands and feet, and vesicles in the mouth which are usually mild and self-limiting.[2] However, few infected children develop systemic complications including neurological and cardiorespiratory complications, and even death. [3]

In the last decades, HFMD infections have widely spread in Asian region with multiple major outbreaks reported.[4-6] Apart from clinical treatment given to the patient, various public health measures such as isolation of infected children, school closure and social distancing implemented as response towards large HFMD outbreak.[7] Several countries develop surveillance system to continuously monitoring the trend of HFMD infections locally.[4, 8, 9] Despite careful attention given to distribution of HFMD infections, the incidence of HFMD continue to rise particularly in Western Pacific Region including Malaysia.[10]

According to report published in 2016, large outbreaks in Malaysia tend to occur in cyclical pattern for every 2 to 3

years.[11] This has necessitated improvement to the existing surveillance system towards HFMD infections. The application of spatial and temporal analysis can assist public health authorities to differentiate intensity of infections between different geographical areas.[12] However, there has been a lack of studies that analyze the geographical distribution and temporal trend of HFMD in Malaysia. This knowledge gap may lead to delayed responses and impacting the overall management of HFMD outbreaks. This study aimed to analyze the spatial and temporal intensity of HFMD infections in Pulau Pinang, Malaysia.

MATERIALS AND METHODS

Study Area

The study was conducted in Pulau Pinang, Malaysia. Pulau Pinang located at Northwest part of Malaysian Peninsula between 5 8' and 5 35' in latitude and between 100 8' and 100 32' in longitude. The state comprises two halves: Penang Island, where the capital city of George Town is located; and a strip of land on the peninsula, named Seberang Perai. The estimated population in Pulau Pinang is about 1,740,405 individuals.[13] Pulau Pinang has 5 administrative districts where 2 districts are located in Penang Island (Timur Laut and Barat Daya) and the other 3 districts in Seberang Perai (Northern, Middle and Southern Seberang Perai) (Figure 1). The ethnic composition in Pulau Pinang shows that 42% are of Malay and Chinese, 9% are of Indian and 0.6% are of other races. About 13% or 225 000 of the whole population are children under the age of 10 years.

Data Source

This study was a state-wide retrospective secondary data review involving 6 years of quantitative data from 2017 to 2022. Data were obtained from national electronic communicable disease notification system known as Communicable Diseases Control Information System (CDCIS) E-Notification Version 2011. It contained variables from age, age group, gender and ethnicity for each notified HFMD case. The data of geographical location of the notified cases was captured in WGS 84 coordinate reference system (CRS). The CRS were then converted into the projected coordinate system, the
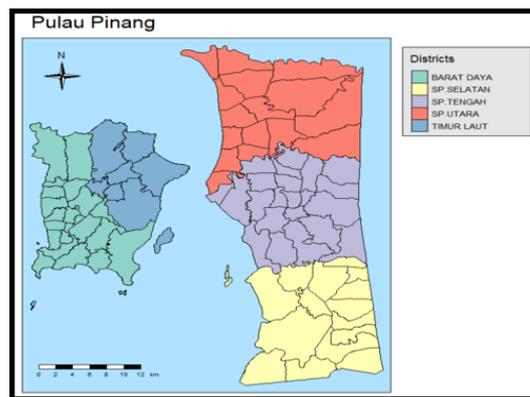

Figure 1 Map of Pulau Pinang, Malaysia, showing the five administrative districts: Barat Daya, Seberang Perai Selatan (SP Selatan), Seberang Perai Tengah (SP Tengah), Seberang Perai Utara (SP Utara), and Timur Laut

Kertau Rectified Skewed Orthomorphic (RSO) Malaya (EPSG:3168). Census tract data contain the variables for yearly population census for state, district and subdistrict of Pulau Pinang were obtained for comparison and analysis purposes.

Data Analysis

The coordinates of each notified HFMD cases were entered to R-Software for data cleaning and analysis using *sf package*.[14] Spatial point distribution was performed to show distribution of notified HFMD cases in Pulau Pinang. Each point will represent geographical coordinates projected in RSO format for each notified HFMD cases. Subsequently, a series of spatial point maps indicating the yearly distribution of data point data from 2017 until 2022 were projected using tmap package in R-software version 4.2.3.[14]

Kernel Density Estimates (KDE) was one of the density-based approach (first-order effect) in spatial point pattern analysis.[15] KDE refers to the probability density function that follow this equation.

$$\hat{f}(x) = \hat{f}(x,y) = \frac{1}{nh_x h_y} \sum_i k \left[\frac{x - x_i}{h_x}, \frac{y - y_i}{h_y} \right]$$

Where,
(x,y)- projected coordinate reference system of HFMD cases using Kertau RSO/RSO Malaya (m) or EPSG:3168 as the coordinate reference system.
hx and hy: referred as the fixed bandwidths in the x and y direction.

KDE functions were used to estimate the intensity of HFMD infections in Pulau Pinang according to specific bandwidths. In this study, the bandwidths smoothing was adjusted to 2 Kilometers radius giving better visualization of the kernel smoothing effect. KDE analysis was performed using spastat package in R-software 4.2.3 and the outcomes of the analysis were visualized using series of maps representing spatial intensity of HFMD infections in Pulau Pinang.[16] The sequential Kernel maps were produced according to KDE analysis were plotted using raster package in R-software.[14]

Next, we used the point pattern analysis to examine the spatial spread (clustered, dispersed, or random) based on the Nearest Neighbour Index (NNI) analysis.[17] The NNI measures the spatial distribution from zero (clustered pattern) to one (randomly dispersed pattern) to 2.15 (regularly dispersed/uniform pattern).[18] NNI value interpretations are as follows, where NNI close to 1.0 indicates random pattern, while NNI value of less than 1.0 suggests clustering. In contrast, NNI value of larger than 1.0 suggests a dispersion pattern.[19]

We identified yearly cumulative NNI for HFMD infections from 2017-2022 with p-value less than 0.05 to be significant. Package spatialeco in R-software 4.2.3 was used for this analysis.[20]

RESULTS

There was a total of 15,586 cases of HFMD in Pulau Pinang notified to CDCIS between 2017 until 2022. Table 1 provides information on the characteristics of HFMD infections in Pulau Pinang according to age, age group, gender, ethnicity, and administrative districts. The mean age of infections was 3.5 years and the majority of the infections (83%) occurred among preschool-aged children (0-4 years), followed by children aged 5-10 years (14%) and those older

than 10 years (2.9%). Male children accounted for 54% of the overall cases, while the remaining 46% were female children. Among the ethnic groups, most of the infections occured among the Malay ethnicity (65%), followed by the Chinese ethnicity (29%), and other ethnicities (6%)

Table 1 Characteristic of Notified HFMD Infections in Pulau Pinang, 2017-2022 (N=15 586)

Characteristic	2017, n=1,378	2018, n=4,793	2019, n=2,752	2020, n=534	2021, n=205	2022, n=5,924	Overall, N=15,586
Age	3.11 (2.51)	3.42 (2.74)	3.15 (2.43)	2.93 (2.56)	2.24 (1.69)	4.00 (1.32)	3.53 (2.21)
Age Group							
0-4	1,202 (87%)	3,930 (82%)	2,379 (86%)	464 (87%)	197 (96%)	4,774 (81%)	12,946 (83%)
5-10	152 (11%)	726 (15%)	325 (12%)	60 (11%)	6 (2.9%)	918 (15%)	2,187 (14%)
>10	24 (1.7%)	137 (2.9%)	48 (1.7%)	10 (1.9%)	2 (1.0%)	232 (3.9%)	453 (2.9%)
GENDER							
Female	612 (44%)	2,184 (46%)	1,269 (46%)	243 (46%)	86 (42%)	2,699 (46%)	7,093 (46%)
Male	766 (56%)	2,609 (54%)	1,483 (54%)	291 (54%)	119 (58%)	3,225 (54%)	8,493 (54%)
ETHINICITY							
Chinese	726 (53%)	1,710 (36%)	1,223 (44%)	134 (25%)	17 (8.3%)	772 (13%)	4,582 (29%)
India	96 (7.0%)	228 (4.8%)	134 (4.9%)	22 (4.1%)	2 (1.0%)	182 (3.1%)	664 (4.3%)
Malay	542 (39%)	2,768 (58%)	1,365 (50%)	375 (70%)	186 (91%)	4,924 (83%)	10,160 (65%)
Non-Malaysian	9 (0.7%)	54 (1.1%)	11 (0.4%)	1 (0.2%)	0 (0%)	30 (0.5%)	105 (0.7%)
Others	5 (0.4%)	33 (0.7%)	19 (0.7%)	2 (0.4%)	0 (0%)	16 (0.3%)	75 (0.5%)
DISTRICT							
Barat Daya	177 (13%)	1,074 (22%)	621 (23%)	115 (22%)	63 (31%)	1,339 (23%)	3,389 (22%)
S.Perai Selatan	219 (16%)	780 (16%)	345 (13%)	49 (9.2%)	21 (10%)	784 (13%)	2,198 (14%)
S.Perai Tengah	214 (16%)	710 (15%)	374 (14%)	123 (23%)	63 (31%)	1,253 (21%)	2,737 (18%)
S.Perai Utara	58 (4.2%)	353 (7.4%)	368 (13%)	84 (16%)	14 (6.8%)	1,165 (20%)	2,042 (13%)
Timur Laut	710 (52%)	1,876 (39%)	1,044 (38%)	163 (31%)	44 (21%)	1,383 (23%)	5,220 (33%)

Mean (SD); n (%)

The trend of HFMD in Pulau Pinang follows an annual cyclical pattern, except for the years 2020 and 2021 as shown in Figure 2. The yearly cases exhibited a bimodal distribution with the first and taller peak usually starting in April and lasting until July or August, while the second and lower peak starting in November and lasting until December or January of the following year. The highest peak of HFMD cases was recorded in 2022, followed by 2018. However, the trend of HFMD cases dramatically reduced during the pandemic period of COVID-19 in 2020 and 2021.
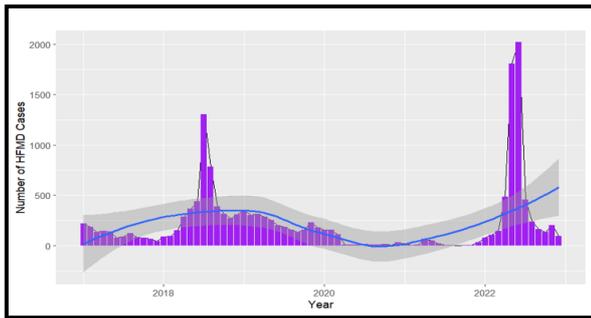
Mean (SD); n (%)

Figure 2 Trend of Notified HFMD Infections in Pulau Pinang between 2017-2022 Spatial and Temporal Intensity of HFMD infections between 2017-2022 estimated by Kerned Density Estimates (KDE) approach

The spatial intensity of notified HFMD infections in Pulau Pinang was mapped using KDE functions with a bandwidth of 2 km (Figure 3).
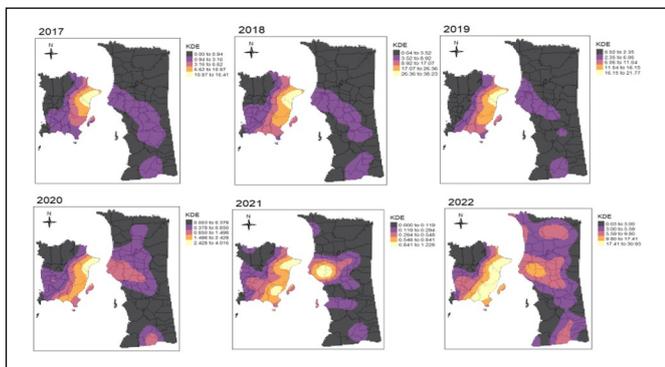

Figure 3 Spatial and Temporal Intensity of Notified HFMD Infections in Pulau Pinang between 2017-2022

The KDE values (cases per km²) exhibited fluctuations from 2017 to 2019, with the highest recorded value in 2018. However, the values were significantly reduced in 2020 and 2021, which could be attributed to the implementation of COVID-19 pandemic lockdown measures. The spatial intensity of infections mainly concentrated in the Penang Island area, specifically in Subdistrict Bandar Georgetown and Mukim 13 (Paya Terubong). The areas with high spatial intensity also extended to the industrial settlement areas of Subdistrict Mukim 12 (Bayan Lepas) between 2017 and 2019. In 2022, prominent spatial intensity was observed central areas of Seberang Perai Tengah, Seberang Perai Utara and Seberang Perai Selatan area, along with higher KDE values (cases per km²).

Nearest Neighboring Index (NNI)

The study observed a clustering pattern in the HFMD cases over the study period, with NNI values ranging from 0.20 to 0.51 (Table 2). A smaller value of NNI

Table 2 Nearest Neighboring Index (NNI) of Notified HFMD Infections in Pulau Pinang

Year	n	Mean Distance		NNI	z score	p-value*
		Observed	Expected			
2017	1378	163.48	503.67	0.32	-47.96	< 0.001
2018	4793	63.45	279.62	0.22	-102.39	< 0.001
2019	2752	99.2	637.85	0.26	-73.28	< 0.001
2020	534	342.68	794.17	0.43	-25.13	< 0.001
2021	205	635.01	1225.33	0.51	-13.19	< 0.001
2022	5924	50.63	252.08	0.20	-117.66	< 0.001

*p-value for Nearest Neighboring Index (NNI)

indicates a more significant clustering of cases. For instance, in 2022, the NNI value was 0.20 (p-value <0.001), which suggests that the cases were clustered, with an observed average distance of approximately 50.63 meters towards nearest neighboring case. Table 3 shows that the results were significant with a p-value <0.001 for every year, indicating a consistent significant cluster pattern in HFMD cases throughout the study period.

DISCUSSION

HFMD remains a significant public health concern in Pulau Pinang, particularly among young children aged 0-4 years old, who accounted for 83% of all reported cases. This finding is consistent with previous studies that have also identified young children as a high-risk group for HFMD.[10] Although infants under one year old are initially protected by maternal immunity, this protection may decrease over time, making them more susceptible to new HFMD infections.[21] In contrast, older children may have developed herd immunity through previous infections, which could explain the decrease in HFMD infections with increasing age.[22] These findings highlight the need for targeted prevention and control measures, especially for young children, to reduce the burden of HFMD in Pulau Pinang.

Although the proportion of Chinese and Malay populations in Pulau Pinang was almost similar, the proportion of notified HFMD infections was higher among the Malay ethnicity (65%) compared to the Chinese ethnicity (29%). This disparity in infection rates could be due to differences in knowledge and awareness about the transmission of HFMD infections among parents from the Malay ethnic group. Recent report suggests that some parents from this group may have a lack of knowledge about the disease, including failure to

recognize clinical symptoms of HFMD at an early stage.[23]

The trend of HFMD infection in Pulau Pinang shows larger peaks in 2018 and 2022. The peak in 2018 was also reported in other states in Malaysia where in cumulative more than 76 000 cases were reported nationwide during that year.[1] According to molecular analysis, the emergence of CV-A6 as co-circulating agent along with known to be aggressive EV-71 and CV-A16 were among the contributing factors towards large outbreak in 2018 including Pulau Pinang.[1] The number of notified HFMD infections dropped incredibly for 2 years in 2020 and 2021 owing to the impact of non-pharmaceutical intervention (NPI) such as school and kindergarten closure during COVID-19 pandemic which reduced risk of transmission HFMD, as well as of other infectious diseases.[9]

The gradual easing of non-pharmaceutical interventions (NPIs) that followed during the COVID-19 pandemic may have contributed to the larger number of HFMD infections observed in Pulau Pinang in 2022. Similar increases in infections after the loosening of NPIs have also been observed in other countries.[9,24] NPIs implemented during the pandemic may have reduced exposure to the circulating agents responsible for HFMD infections. However, this may have created an immunity gap among children, leaving them more vulnerable to HFMD infections.[25]

According to a spatial point pattern analysis using KDE analysis, the District of Timur Laut has consistently recorded higher numbers of notified HFMD infections compared to other districts in the state, with the highest density of infections observed in the urban centers of Subdistrict Bandar Georgetown and Mukim 13 (Paya Terubong). These areas are primarily urban centers with higher population densities.[13] Similar studies conducted in Sarawak and Terengganu, Malaysia have also linked higher population density to higher numbers of HFMD infections.[26, 27] This may be due to the higher rate of transmission among children in overcrowded schools or childcare centers in urban areas. [28]

The study also found that the clustering of HFMD infections had begun to spread to the district of Barat Daya, particularly in Subdistrict Mukim 12. Subdistrict Mukim 12 is home to major industrial areas, highly dense settlements, and major international and domestic points of entry into the state through Penang International Airport. Additionally, it has emerged as a popular place for many Penangites to stay and is easily accessible to tourists and visitors. Collectively, this has increased the population density in the area, including the number of children, and has contributed to the higher intensity of HFMD infections. A study conducted in China reported that increasing population density had 52% influence on the reported number of HFMD infections compared to other parameters.[28]

The pattern of HFMD intensity observed in 2022 began to resemble the map of Development Priority Areas (DPA) outlined in the Penang State Structure Plan 2030.[29] As the urban sprawl continues and more new settlement areas emerge, the number of child care centers will also increase to cater the children of working parents within the urbanized region. However, the lack of training among staff in newly operated child care centers can reduce the effectiveness of gatekeeping strategies, leading to mingling between sick, and healthy but susceptible children, and resulting in major outbreaks. [23] Comprehensive health education including basic knowledge of prevention of infectious disease should be emphasized to every child-care center especially in new settlement areas. Local district Health Office (DHO) should have accurate information on urbanization plan within the state to anticipate potential area with higher HFMD infections and prioritization of prevention strategies.

LIMITATIONS

The current findings highlight the importance of using spatial analysis in understanding spread of HFMD infections in Pulau Pinang. However, it should be noted that our study did not include environmental parameters that may influence the spatial risk of HFMD infections across the state. Therefore, further research is needed to validate our findings on spatial intensity using additional

spatial parameters such as climate variables, to enable a more detailed spatial profiling of the disease. Incorporating such parameters could improve the accuracy and completeness of our findings and enhance our understanding of the underlying factors driving the spatial distribution of HFMD infections.

CONCLUSION

The spatial analysis revealed that the highest intensity of HFMD infections was concentrated in urban areas, specifically in Subdistrict Mukim 13 and Bandar Georgetown in the district of Timur Laut. However, temporal clustering of HFMD intensity was also observed in other areas, such as Subdistrict Mukim 12 in the district of Barat Daya, as well as urban centers in each district within the Seberang Perai area. These findings suggest that HFMD infections are spreading to new locations and settlements, raising concerns of future outbreaks if appropriate measures are not promptly implemented. It is crucial to take prompt and targeted actions to mitigate the spread of HFMD and prevent further escalation of the disease in these areas.

CONFLICT OF INTEREST

The authors disclose that they have no conflicting interests.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

Ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM), USM JEPeM Code: USM/JEPeM/22110717 (Appendix A) and the National Medical Research Registry (NMMR) Ethics Initial Approval: NMRR ID-22-02848-USX (IIR) (Appendix B), Ministry of Health Malaysia. Data confidentiality was maintained at the highest possible level. Only the researchers had access to the data. Individuals' names and identification numbers were not extracted from the data.

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