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*Review Article*

# Spatio-temporal Analysis of Hand, Foot and Mouth Disease: A Systematic Review

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## ABSTRACT

**Background:** Hand, foot and mouth disease (HFMD) is a widespread pediatric disease caused primarily by human enterovirus 71 (EV-A71) and Coxsackievirus A16 (CV-A16). Over the past two decades, our understanding of HFMD has greatly improved and it has received significant attention. This study reports a systematic review of spatio-temporal analysis of HFMD.

**Materials and Methods:** Systematic and comprehensive searches were conducted in the PubMed, Scopus, Web of Science, and Google Scholar. Four different issues related this issue are presented under four sub-sections; including the analysis of spatial-temporal clustering, hotspot and coldspot, spatial-temporal heterogeneity and risk factors of HFMD.

**Results:** It was found from 64 articles that spatio-temporal analysis can effectively support the study of HFMD such as understanding of spatial patterns, hotspot, the spread and affecting factors.

**Conclusion:** The spatial-temporal analysis can provide important information and contribute to development of effective measurements to control and prevent its transmission. The study contributes to current research on the spread and affecting factor of HFMD.

***Keywords:*** Spatio-temporal analysis, Spatial autocorrelation, GIS, Spatial patterns, Hand, foot and mouth disease, Review.

## INTRODUCTION

Hand, foot and mouth disease (HFMD) has become an endemic childhood disease. Its main etiologic agents are human enterovirus 71 (EV-A71) and Coxsackievirus 16 (CV-A16) (1). As early as 1957, the characteristic symptoms of fever, vesicular rash on hands and feet caused by Coxsackievirus (CV), primarily CVA16, was first reported in Toronto (2,3). Later, in 1959, "hand-foot-and-mouth disease (HFMD)" was initially used to name a disease. HFMD is a viral illness commonly seen in young children under 5 years of age, characterized by typical manifestations such as oral herpes and rashes on the hands and feet (4). Over the past few decades, HFMD outbreaks caused by Enterovirus A71 (EV-A71), CVA16, CVA6 and Echoviruses (Echo) were reported frequently around the world (5). HFMD is caused by Human enteroviruses (EVs) that are members of the Enterovirus genus of the Picornaviridae family (6). EVs were initially classified into Poliovirus (PV), Echo, CV-A and B, and emerging EVs. Since 1999, EVs have been divided into four categories of Enterovirus A, B, C, and D, in the light of their molecular, biological, and genetic characteristics (4). HFMD is primarily transmitted via the fecal-oral route, respiratory droplets, contact with blister fluid of infected individuals, or general close contact with infected individuals (7–10). Most cases of HFMD are mild and patients are able to recover quickly; however, there are some severe cases and even some deaths (11). The HFMD disease was generally mild and lasted less than a week in most cases, characterized by fever, a blister-like rash on the hands and feet, and oral ulcers caused by ruptured blisters in the mouth (12). HFMD outbreaks have been reported worldwide, and Western Pacific countries have reported outbreaks of HFMD many times over the last decade (13–16). In Asia, HFMD is a threat to public health; in Singapore (17,18), Malaysia (18,19), Japan (20) and Vietnam (21–23). It has been reported many times, with large numbers of cases 20-25. Therefore, HFMD has become a significant concern for public health throughout the Asia-Pacific region and beyond (4).

HFMD-related data relates to geographical locations which have a spatial and geographic dimension and can be considered a type of spatial object. Such epidemiological data as HFMD can be studied using spatial statistics (24). Spatial statistic is an essential tool to examine the spatial pattern of spatial objects (25). Following this idea of Tobler's First Law of Geography, widely used statistics for spatial auto-correlation analysis such as global spatial statistics (Moran's I, Getis-Ord G* and Geary's C) and local indicators of spatial association (LISA) have been successfully employed in epidemiological studies (26–29) in general, and in the study of the spread of COVID-19 (30–32) and HFMD (10,33) in particular. For example, a study on spatiotemporal analysis and hotspots detection of COVID-19 in southern, northern and western Europe was carried out using spatial statistics (34). Local Moran's I autocorrelation coefficient, Getis-Ord General-G high/low clustering, and Getis-Ord Getis-Ord's $G_i^*$ statistic were emloyed to study spatio-temporal COVID-19 spread over Oman (35).

The objective of this paper is to provide a robust systematic review of spatio-temporal analysis of HFMD. The review covers four major areas: the analysis of spatial-temporal clustering, hotspot and coldspot, spatial-temporal heterogeneity and risk factors of HFMD.

## MATERIALS & METHODS

### Materials

This study compares 64 scientific papers cited in PubMed, Scopus, Web of Science, and Google Scholar databases. This review focused primarily on highly cited articles and mainly published in recent years.

### Methods

Searches were executed in digital databases including PubMed, Scopus, Web of Science, and Google Scholar using a combination of search terms, including 'Hand foot and mouth disease' or 'Hand foot and mouth', 'HFMD', 'Enterovirus' or 'Enterovirus 71', 'EV-A71', 'Coxsackie A16', 'CV-A16' and 'CVA16' to find HFMD-related articles. In addition, different combinations of keywords including 'applications', 'spatial statistics', 'GIS' or 'Geographic Information System', 'spatial autocorrelation', 'spatial clustering', 'hotspot' or 'coldspot', 'spatial heterogeneity', 'affecting factors', 'risk factors', and 'review' or 'overview'. Four different sub-topics was then discussed and summarised based on the applications of analysis of spatial-temporal clustering, hotspot and coldspot, spatial-temporal heterogeneity and risk factors in HFMD studies.

## RESULTS AND DISCUSSIONS

A lot of attempts have been put into the use of spatial statistics in studies of HFMD. Main application of spatial statistics in HFMD studies include the analysis of spatial-temporal clustering, hotspot and coldspot, spatial-temporal heterogeneity and risk factors of HFMD.

### Analysis of spatial-temporal clustering

Spatio-temporal clustering indicates the composite of place and time i.e. where and when the incidence is abnormally high (36). Identification of spatio-temporal clusters allows public health officials to understand the disease nature and launch timely surveillance and intervention programs at the correct site (36). Therefore, analysis of spatial-temporal clustering has been widely applied in HFMD studies. Studies on analysis of spatial-temporal clustering of HFMD was summarised in Table 1. One of the first study on this issue was carried out in

China. In that study, SaTScan 9.4.2 was used to detect epidemiological characteristics and temporal and spatial clustering of hand, foot and mouth disease in Guangxi from 2008 to 2015 (37). The Local Indicator of Spatial Association (LISA) was successfully employed to investigate epidemiological features and spatial clusters of hand, foot, and mouth disease in Qinghai Province, China, 2009-2015 (as shown in Figure 1) (38). Exploratory spatial data analysis (ESDA) was used to conduct spatial statistical analyses on spatial clustering and changing trend of the HFMD using 2008 - 2011 data at both provincial and county/district levels in China (39). In 2014, with the help of Geographical Information System (GIS), a recent study has been conducted for a temporal and spatial mapping of HFMD that covered 13 all divisions of Sarawak. This study focused on reported cased of HFMD from the year 2006 until 2012. It was found that there was no significant clustering was detected (40). In Vietnam, a time-series analysis was used to examine the temporal patterns of HFMD in relation to climate factors while a retrospective space-time scan was used to detect the high-risk space-time clusters of this disease (33). General statistics and spatial-temporal analysis employing a GIS-based method have been successfully used to elucidate the phenomenon of HFMD outbreaks from 2003 to 2012 in Thai Land (41).

**Table 1. Summary of studies on analysis of spatial-temporal clustering of HFMD.**

| Methods | Objectives of study | Study area | Study |
|---|---|---|---|
| Time-series analysis | Analysis of temporal patterns of HFMD | Vietnam | (33) |
| SaTScan 9.4.2 | Epidemiological characteristics and temporal-spatial clustering of HFMD | Quang Xi, China | (37) |
| LISA | Epidemiological features and spatial clusters of HFMD | Qinghai, China | (38) |
| Exploratory spatial data analysis (ESDA) | Spatial clustering and changing trend of HFMD | China | (39) |
| Geographical Information System | Temporal and spatial mapping of HFMD | Sarawak Malaysia | (40) |
| General statistics and spatial-temporal analysis | Spatio-Temporal Distribution and Hotspots of HFMD | Thailand | (41) |

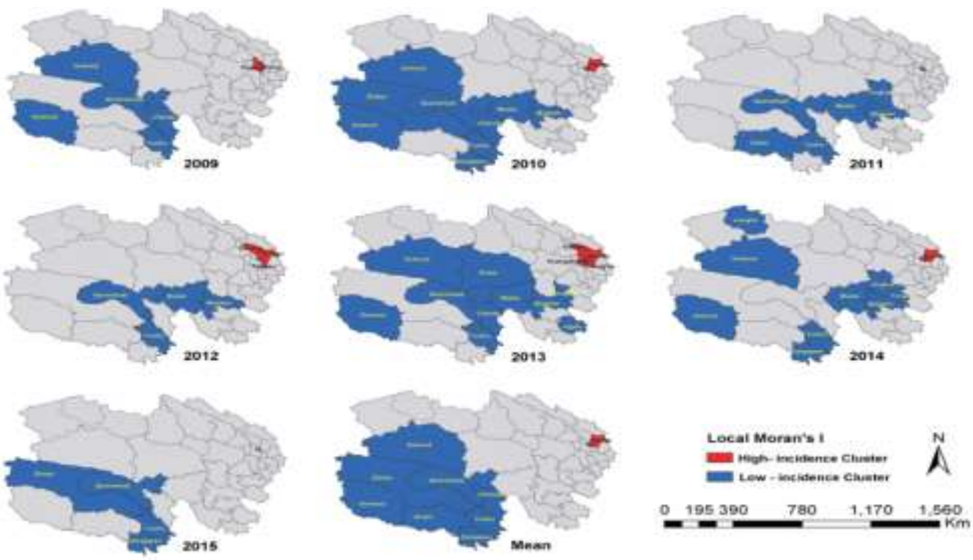


**Figure 1. Statistically significant county-level high incidence and low incidence spatial clusters of HFMD, for children 0 to 5 years of age, Qinghai Province, 2009–2015 (38).**

## Analysis of hotspot and coldspot

Table 2 summarises studies on analysis of hotspot and coldspot of HFMD. One of the first study on this issue was carried out in Thailand. In that study spatio-temporal distribution and hotspots of HFMD were successfully carried out using local Moran's statistic and GIS in northern Thailand (41). The potential HFMD hotspots in Sarawak, Malaysia were identified by determining the location nodes ranking with the help of Bipartite Network Approach (42). When investigating spatiotemporal cluster patterns of HFMD at the county level in mainland China, 2008-2012, based on the global and local spatial autocorrelation analysis, it was found that hotspots of the disease were mostly distributed in coastal provinces of China (43). Also in China, hotspots of norovirus outbreaks in Beijing were primarily found in contiguous areas between three central districts (Chaoyang, Haidian, Fengtai) and four suburban districts (Changping, Daxing, Fangshan, Tongzhou) using Global Moran's I statistics and Getis-Ord G statistics (44). When identifing spatial patterns for FMD virus exposure in northern Nigeria, Getis-Ord G statistic has been successfully employed to detect a hot-spot in Kaduna and a cold-spot in Plateau (45).

**Table 2. Summary of studies on analysis of hotspot and coldspot of HFMD.**

| Methods | Objectives of study | Study area | Study |
|---|---|---|---|
| GIS and local Moran's statistic | Hotspot analysis of HFMD | Thailand | (41) |
| Bipartite Network Approach | Identification the potential HFMD hotspots | Sarawak, Malaysia | (42) |
| Global and local spatial autocorrelation analysis | Hotspot and spatio-temporal cluster patterns of HFMD | Mainland, China | (43) |
| Global Moran's I and Getis-Ord G statistics | Hotspots of norovirus outbreaks | Beijing, China | (44) |
| Local Moran's I and Getis-Ord G statistics | Hotspot and spatial patterns for FMD virus exposure | Nigeria | (45) |

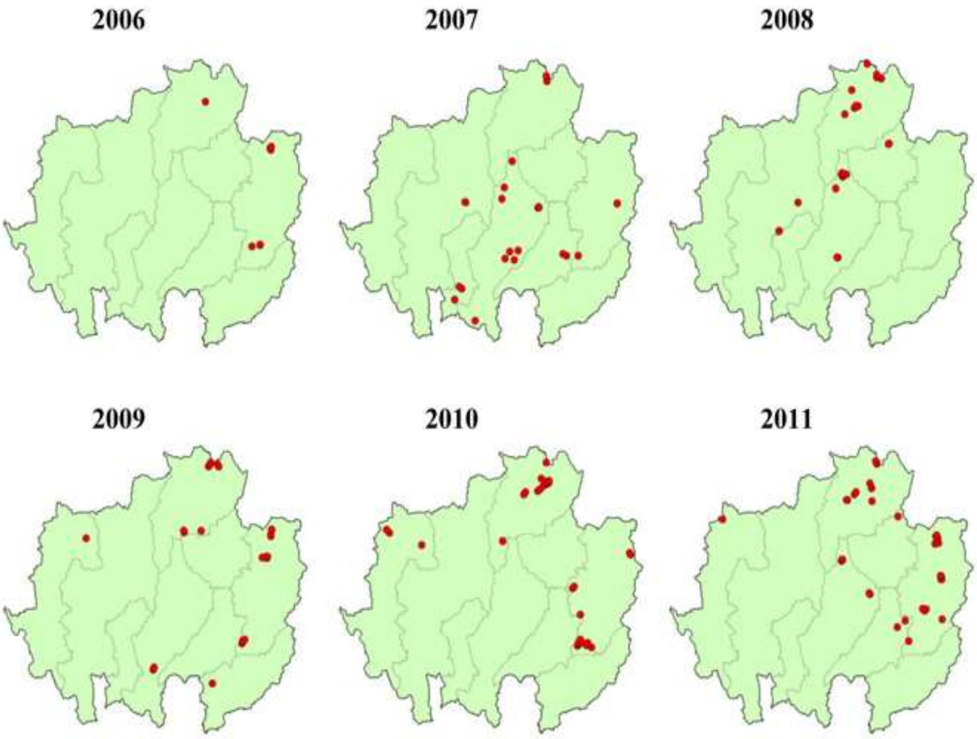


**Figure 2. HFMD hotspot development in Thailand from 2006 to 2011 (modified from (41)).**

## Analysis of spatial-temporal heterogeneity

Analysis of spatial-temporal heterogeneity play a vital role in the study the distribution of HFMD. Several studies have quantified spatiotemporal heterogeneity of HFMD and detected spatiotemporal interactive effect of potential driving factors on this disease These studies were summarised in Table 3. Data from Table 3 demonstrate that, GeoDetector and Bayesian space-time hierarchy model have been successfully applied to characterize the epidemiology of HFMD in Henan, one of the largest population provinces in China, from 2012 to

2013, and quantified the impacts of potential driving factors (46). Using the national surveillance data of HFMD in Xinjiang and meteorological parameters in the study area from 2008 to 2016, GeoDetector model was used to examine the effects of meteorological factors on the incidence of HFMD in Xinjiang, China, and test the spatial-temporal heterogeneity of HFMD risk, and explore the temporal-spatial patterns of HFMD through the spatial autocorrelation analysis (47). Another study on the spatial heterogeneity of the associations between relative humidity and pediatric HFMD was also carried out in mainland China distributed lag nonlinear multivariate and meta-regression models (48). Also in mainland China, short-term effects of rainfall on childhood HFMD and related spatial heterogeneity was successfully investigated from 143 cities in mainland China where the meta-regression model was adopted to pool the city-specific estimates and explore the sources of heterogeneity by incorporating city-specific characteristics (49). It was found that spatio and temporal heterogeneity is important for understanding HFMD transmission (50). Therefore, Spatial and temporal heterogeneities of HFMD transmission were successfully quantified by the contribution of the hazard components. In addition, the transmission heterogeneity by age–gender subgroups was determined by the transmission probabilities derived from the transmission rate matrix using the spatio-temporal Bayesian hierarchical model (50).

**Table 3. Summary of studies on analysis of spatial-temporal clustering of HFMD**

| Methods | Objectives of study | Study area | Study |
|---|---|---|---|
| GeoDetector and Bayesian space-time hierarchy model | Analysis of space-time heterogeneity of HFMD | Henan, China | (46) |
| GeoDetector model and spatial autocorrelation analysis | Identification of spatial-temporal heterogeneity of HFMD risk | Xinjiang, China | (47) |
| Distributed lag nonlinear multivariate and meta-regression models | Exploring the spatial heterogeneity between relative humidity and pediatric HFMD | Mainland China | (48) |
| Meta-regression model | Effects of rainfall on childhood HFMD and spatial heterogeneity | Mainland China | (49) |
| Spatio-temporal Bayesian hierarchical model | Spatial and temporal heterogeneities of HFMD transmission | China | (50) |

## Analysis of risk factors

Classic statistical analysis cannot quantitatively explore the epidemic regularity of HFMD, whereas spatial-temporal analysis can provide the necessary HFMD incidence estimates. The incidence of HFMD is influenced by many factors. To formulate reasonable preparations, it is crucial to know transmission trends and risk factors of HFMD. Studies on analysis of HFMD risk factors were summarised in Table 4. Previous studies in Singapore, Japan and Malaysia demonstrated that outbreaks of HFMD generally occurred in a 2–3 year cyclical pattern with strong seasonality (13,51) and the incidence was independently related to meteorological parameters such as temperature, humidity and rainfall (20,52–55). Several studies suggested that HFMD was associated with meteorological factors such as precipitation (52,56), humidity (20,33,57) and temperature (58–60), in many Asian countries, including Singapore (52), Japan (20), Vietnam (52), and China (33). Therefore, studies on factors affecting HFMD risk play an important role in the control of HFMD. For example, an autologistic regression model was also used to identify spatial risk factors and spatial risk patterns of HFMD in mainland China (15). Bayesian space-time hierarchy model was used to analyze the temporal and spatial variations of disease risk of HFMD (Figure 3) (46).With the objective to identify the spatial spreading pattern of HFMD for urban divisions and non-urban Inverse Distance Weighted was used to interpolate the reported HFMD cases for the whole of Sarawak to identify the high-risk pattern of HFDM (61). Statistical analysis was applied to identify risk factors for HFMD in the Sichuan province of China from twenty potential environmental variables accounting for both climate and socioeconomic aspects

(62). With the aim of spatial-temporal mapping and risk factors for hand foot and mouth disease in northwestern inland China, panel negative binomial model was successfully used to identify climate, geographical and demographic determinants for HFMD incidence (63). Global and local Moran's I statistics were applied to examine the spatial pattern of HFMD and series analysis to explore the temporal pattern. The effects of meteorological factors and socioeconomic factors on HFMD incidence in Guangxi, China were analyzed using GeoDetector Model (64).

**Table 4. Summary of studies on analysis of spatial-temporal clustering of HFMD.**

| Methods | Purposes of study | Study area | Study |
|---|---|---|---|
| An autologistic regression model | Identification of spatial risk factors and spatial risk patterns of HFMD | Mainland China | (15) |
| Bayesian space-time hierarchy model | Identification of spatial relative risks of HFMD | Henan, China | (46) |
| Inverse Distance Weighted interpolation | Identification of the high-risk pattern of HFDM | Sarawak, Malaysia | (61) |
| Statistical analysis | Identification of risk factors of HFMD | Sichuan, China | (62) |
| Panel negative binomial model | Spatial-temporal mapping and risk factors for HFMD | China | (63) |
| Global and local Moran's I statistics | Spatial-temporal variation and risk factor analysis of HFMD | Guangxi, China | (64) |

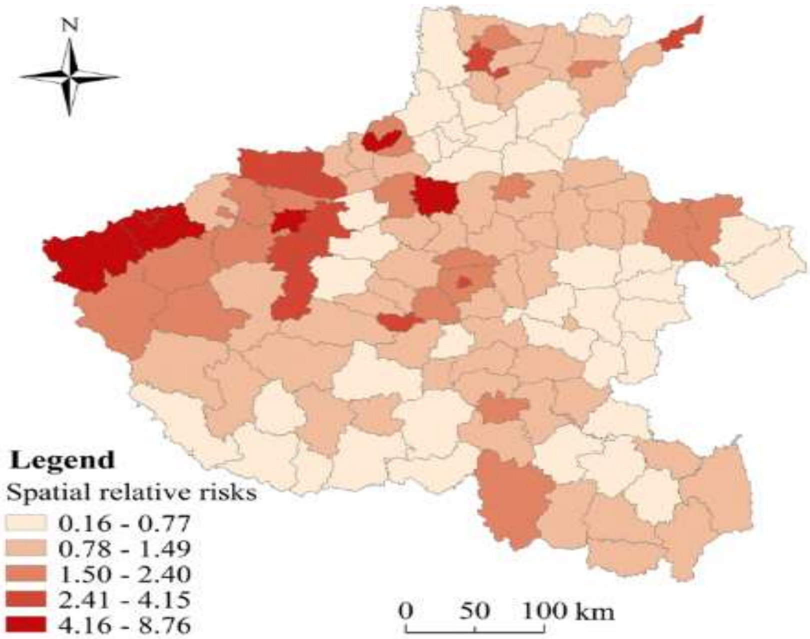


**Figure 3. Spatial relative risks of HFMD in children for each county, Henan province (46).**

## CONCLUSION

Hand foot and mouth disease is becoming one of the common human infectious diseases. This study systematically reviewed 64 articles on the spatio-temporal analysis of HFMD. Databases including PubMed, Web of Science and Google Scholar were searched up to September 2023 for most relevant articles. Four different issues related this issue were summarised and discussed under four sub-sections; namely the analysis of spatial-temporal clustering, hotspot and coldspot, spatial-temporal heterogeneity and risk factors of HFMD. The study results show that spatio-temporal analysis can effectively support the study of HFMD such as understanding of spatial patterns, hotspot, the spread and affecting factors. It can be concluded that the spatial-temporal analysis can provide important information and contribute to development of effective measurements to control and prevent HFMD transmission. Findings in this study greatly contributes to current research on studies of the spread and affecting factor of HFMD. However, more research to assess risk factors and spatio-temporal analysis of HFMD is needed.

***Declaration by Authors***

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