The Epidemics of Hand, Foot, and Mouth Disease in Island-Type Territory, East Asia

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Abstract: Hand, foot, and mouth disease (HFMD) has threatened East Asia for more than three decades and has become an important public health issue owing to its severe sequelae and mortality among children. Severe epidemics of enterovirus have occurred frequently in Malaysia, Singapore, Taiwan, Cambodia, Japan, and China. The lack of effective treatment and vaccine for HFMD highlights the urgent need for efficiently integrated early warning surveillance systems in the region. In this study, we try to integrate the available surveillance and weather data in East Asia to elucidate possible spatiotemporal correlations and weather conditions among different areas from low to high latitude. We used geographical information system (GIS) and statistical model to understand the association between HFMD and latitude, as well as meteorological factors for islands in East Asia, namely, Japan, Taiwan, Hong Kong, and Singapore, from 2012 to 2014. Furthermore, we narrow down our focus to explore the spatio-temporal transmission pattern of HFMD in Taiwan and Japan. In summary, weather conditions and geographic location could play some role in affecting HFMD epidemics. The spreading direction of HFMD epidemic is from south to north. Based on this unique characteristic of the HFMD epidemic, the early warning surveillance method can be developed.

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1. Introduction

Hand, foot, and mouth disease (HFMD) is a syndrome which usually affects children below the age of five (Ho, Chen et al. 1999, Chen, Chang et al. 2007, Tseng, Huang et al. 2007). The causal agents are various enteroviruses, especially human enterovirus 71 (EV71) and coxsackie virus A16 (CVA16), responsible for 50% to 90% of HFMD in many episodes (Ho, Chen et al. 1999, De, Changwen et al. 2011, Ni, Yi et al. 2012). In the 1960s, both the Netherlands and U.S. recorded cases of EV71 (Schmidt, Lennette et al. 1974, van der Sanden, Koopmans et al. 2009). Afterward, severe cases with about a 10% case fatality rate occurred in Bulgaria and Hungary in 1975 and 1978, respectively (Chumakov, Voroshilova et al. 1979, Nagy, Takatsy et al. 1982). Meanwhile, cases with HFMD, CNS manifestations, and death were associated with EV71 in Japan in 1973 and 1978 (Ishimaru, Nakano et al. 1980, Tagaya, Takayama et al. 1981). In the late 20th century, a vast death toll related to HFMD occurred in Southeast Asia. In 1997, 29 fatal cases were attributed to EV71 infection in Malaysia (Chan, Parashar et al. 2000). One year later, an outbreak of around 1.5 million estimated HFMD cases occurred in Taiwan, and led to 405 severe cases and 78 children dead (Ho, Chen et al. 1999). Since then, HFMD has become endemic in Southeast and East Asia. In particular, approximately 7.2 million probable cases of HFMD were reported in China during 2008 to 2012 (Xing, Liao et al. 2014). To date, HFMD and enterovirus-derived severe syndromes have resulted in a heavy disease burden, especially to children, in this area.

Thus, this aims of this study are : (1) to determine whether the known meteorological factors associated with HFMD are appropriate to island type countries (Lee, Tang et al.) (2) to examine whether different geographical zones and latitudinal ranges are associated with the incidence of HFMD within or between those island countries (Lee, Tang et al.) (3) to explore the spatio-temporal transmission pattern of HFMD in Taiwan and Japan (Chan, Hwang et al. 2014).

2. Data and Methods

2.1 Data

Hand, foot, and mouth disease (HFMD) surveillance data were mostly collected online from the National Institute of Infectious Diseases (NIID) in Japan (http://www.nih.go.jp/niid/en/survaillance-data-table-english.html), Taiwan CDC (http://nidss.cdc.gov.tw/RODS_5.aspx), Department of Health in Hong Kong (http://www.chp.gov.hk/en/sentinel/26/44/292.html) and Ministry of Health in Singapore (http://www.moh.gov.sg/content/moh_web/home/statistics/infectiousDiseasesStatistics/weekly_infectiousdiseasesbulletin.html). The length of the data is different in this study. For addressing the first two aims, the data in those four territories started from week 31 of 2012 to week 27 of 2014. The length of the studied period was 101 weeks. For addressing the third aims, we need more data in Taiwan and Japan. Thus, we also applied and bought data from the Taiwan Centers for Diseases Control (Tw-CDC) including national notifiable diseases surveillance, sentinel physician surveillance and laboratory surveillance from July 1, 1999 to December 31, 2008. In addition, prefecture-level data from HFMD cases in Japan were collected online during the period from the 1st week of 2008 to the 52th week of 2014 (a total of 365 weeks), from the National Institute of Infectious Diseases (NIID) (http://idsc.nih.go.jp).

2.2 Methods

We firstly included 55 spatial areas to explore the spatio-temporal HFMD epidemic pattern in East Asia including 47 prefectures in Japan, six surveillance areas in Taiwan which belonged to six control centers of Taiwan's CDC, one area in

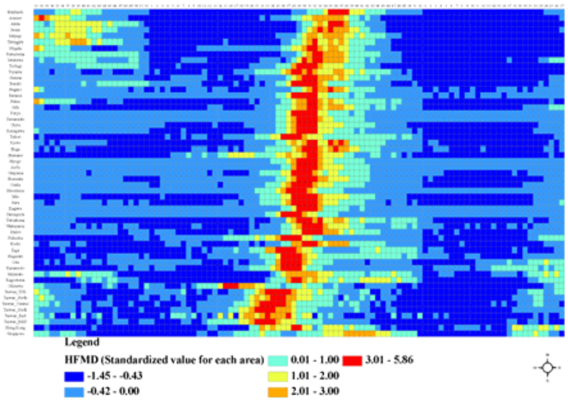
Hong Kong and one area in Singapore. The spatial extent ranged from 1.35°N to 43.38°N in latitude and from 103.81°E to 142.57°E in longitude. The analysis used a semi-parametric Generalized Additive Model (GAM) to examine the association between weekly standardized HFMD cases and the meteorological factors. All GAM parameters were estimated by SAS software (SAS Institute, Cary, NC). The spatio-temporal distribution of HFMD standardized values (Zrate) were analyzed by the fishnet toolbox in ArcGIS (ArcMap, version10.2; ESRI Inc., Redlands, CA, USA).

In order to detect the disease clusters, we applied spatial statistic, temporal statistic, space-time scan statistic to identify most likely clusters with high incidence of severe EV in SaTScan v.9.1.1.(Kulldorff, Athas et al. 1998). After identifying the space-time clusters of the severe EV cases, the corresponding data of the mild EV cases came from sentinel physician surveillance was further analyzed for the consistent temporally increasing trends or even earlier increasing trends. Space-Time permutation was applied for detecting the mild EV clusters due to the lack of the population at risk (Kulldorff, Heffernan et al. 2005). The directional distribution method with 2 standard deviations of the ellipse size weighted by either the mild EV cases per doctor or the number of severe EV cases (Shobugawa, Wiafe et al. 2012). Then, we used ArcGIS for visualizing the clusters and diffusion pattern.

3. Results and Conclusions

All areas with HFMD Zrates among 101 weeks were shown in the spatio-temporal map (Figure 1). HFMD was endemic in all four areas, especially in 2013. In Japan, severe HFMD outbreaks occurred from week 25 to 38 in 2013 in almost all prefectures. Okinawa was the exception and reached the peak earlier from week 15 to 17 in 2013. Most of those prefectures demonstrated high Zrates of HFMD around 4 to 5 weeks long. In Taiwan, early outbreaks of HFMD showed up in southern Taiwan compared to the rest of Taiwan in 2013. The HFMD continued for at least four weeks in the three metropolitan areas (Taipei, Central Taiwan, and Kaohsiung-Pingtung (KKP)), and the highest Zrate level stopped at week 27. Compared to Japan and Taiwan, only two weeks of highest Zrate of HFMD occurred in Hong Kong in 2013. Overall, the timing of the HFMD peak delayed with the increase on latitude.

Figure 1 Spatio-temporal map of HFMD Zrate from week 31 of 2012 to week 27 of 2014



Based on the linear estimation of each explanatory variable from GAM (Table 1), latitude and weekly dew point were significantly associated with increasing HFMD Zrate. Visibility and wind speed were inversely associated with increasing HFMD Zrate. However, mean temperature and total precipitation were not significantly correlated with the Zrate.

Table 1**The parameter estimates of the linear terms in general additive model (GAM)**

Variable	Estimate	Standard Error	p-value
Latitude	0.0465	0.0020	<.0001*
Mean temperature	0.0031	0.0063	0.5917
Dew point	0.0566	0.0060	<.0001*
Visibility	-0.0066	0.0023	0.0037*
Wind speed	-0.0514	0.0118	<.0001*
Total precipitation	0.0018	0.0021	0.4100

* p-value < 0.05

When we used more data to validate the south-north diffusion pattern of HFMD epidemics in Taiwan and Japan, we also found this pattern indeed existed. Thus, we developed the surveillance method for detecting the aberrations of HFMD based on the latitude difference. The preliminary results showed that we can detect the aberrations of HFMD timely and accurately.

In conclusion, we found out that latitude is a major risk factor for increasing the Zrate of HFMD in islands in East Asia. In addition, only some meteorological factors (dew point, low visibility and low wind speed) from previous mainland China studies are associated with the outbreaks. This indicates that island-type geographical areas have intrinsic differences from continental areas, both in climate impact and in causes of HFMD. Since HFMD strikes East Asia every year, and there are no effective pharmaceutical treatments for this disease, integrated surveillance with timely multiple surveillance sources and meteorological information in different countries can assist in the control and mitigation of the impacts of HFMD in East Asia. Also, these results can be applied to islands in other oceans for predicting HFMD or other infectious diseases.

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