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Trend Surface Analysis of Hand, Foot and Mouth Disease in Sarawak

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Abstract: In this study we aim to fit a trend surface model for Hand, Foot And Mouth Disease (HFMD) in Sarawak and also check the adequacy of the model obtained. For this, the epidemiological data of year 2012(outbreak year) and 2011 are used. Models were built up to second order polynomial based on the idea that number of HFMD cases can be described by regression residual analysis. With Moran *I* statistic, residuals from all the trend surface models were examined for spatial autocorrelation. All six trend surface models for 2011 data had residuals that were not spatially autocorrelated. However, one model for 2012 data showed spatial autocorrelation. The best model for each year of the two years that represent disease outbreak and non-outbreak situations was selected based on Mallows' Cp statistic. These models could be used to predict the number of cases for locations of interest.

Keywords: HFMD, Sarawak, spatial autocorrelation, trend surface model

INTRODUCTION

Hand, Food and Mouth Disease (HFMD) is defined as a common viral illness that usually affects infants and children younger than 5 years old (CDC, 2011). It is characterized by fever, blister-like sores in the mouth and a skin rash (CDC, 2011). These symptoms will show up after three to seven days of infection. At the beginning, a person will get mild fever, poor appetite, malaise (feeling vaguely unwell) and often a sore throat.

From (Sarawak Health Department, 2006), it is known that individual cases and outbreaks of HFMD occur worldwide. It becomes more frequent in summer and early autumn (in countries with a temperate climate). The incubation period is 4 to 6 days (Sarawak Health Department, 2003). In the recent past, major outbreaks of HFMD attributable to enterovirus 71 have been reported in Malaysia in 1997 and in Taiwan in 1998. Between 15 April to 30 June 1997 in Sarawak, 31 previously healthy infants and young children died after a short febrile illness against a background of an outbreak of HFMD in the state

Chinese Ministry of Health stated that HFMD is one of the diseases that are widely-spread infectious disease in China (Hu *et al*., 2012). A spatial autocorrelation that was first published by Cliff and Ord (1981) is considered since many studies in China focus on this topic, for example (Wang *et al*., 2011; Bie *et al*., 2010; Hu *et al*., 2012; Zhou, 2012). There is a significant association between the HFMD spatiotemporal type and the climate indicators that were identified in the maps (Wang *et al*., 2011). They also claimed that intervention and prevention measures should be focused predominantly on kindergartens and junior schools located in the HFMD risk areas during the risk periods.

A serious area of HFMD epidemic situation in 2008 concentrated in three regions which are three northern provinces/city (Hebei, Beijing and Shanxi), three southern provinces/autonomous region (Guangdong, Guangxi and Hainan) as well as the eastern provinces/city (Zhejiang, Shanghai and Anhui) (Bie *et al*., 2010). The number of reported cases, morbidity and mortality has remarkable differences between various provinces where the number of reported cases concentrated in eastern and southern of China and the Qinghai-Tibet Region. The Northwestern region is few.

Another study in China (Hu *et al*., 2012) found that child population density and climate factors are potential determinants of the HFMD incidence. The strength and direction of association between these factors and the incidence of HFDM is spatially heterogeneous at the local geographic level where child population density has a greater influence on the incidence of HFMD rather than the climate factors.

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According to Tiing and Labadin (2008), there is no permanent immunity against HFMD as the disease is caused by a group of viruses much like the case of flu. Sarawak Health Department also clarified that there is no specific antiviral drug to cure HFMD. Besides, there is no vaccine available for the treatment of HFMD. Therefore, many actions have been taken to prevent this disease from spreading such as practising good personal hygiene, covering the mouth and nose when coughing or sneezing and closing kindergartens and nurseries if there is a case of HFMD or suspected death due to enteroviral infection at the center.

Recently, Zhou (2012) reveals that in years of a high incidence of the disease, the spatial distribution of HFMD in Ningbo, China has a certain stability. That is, the direction of high incidence of disease (North-west 26 degrees) and the direction of low incidence of disease (North-east 64 degrees) basically remain stable.

Estimation and prediction of HFMD in space is important. In order to predict the number of cases for location of interest, we need a reliable model. The dataset used consist of observations considered over a given area and thus spatial component becomes necessary in the model. This imposes a question of whether HFMD in certain district is spatially correlated, then what is the trend of HFMD? Hence, trend surface analysis is needed. Since in the authors' knowledge there is no such study yet based on the Sarawak data, this study is carried out. In this study, all possible combination of models were obtained using Mallow's Cp statistic.

MATERIALS AND METHODS

Sarawak is one of two Malaysian states on the island of Borneo which is situated on the northwest of the island, bordering the Malaysian state of Sabah to the northeast, Indonesia to the south and surrounding Brunei. It is the largest state in Malaysia. There are 33 districts in Sarawak as shown in Fig. 1.

Study done by Podin *et al*. (2006) revealed that Sarawak has been experiencing outbreak of HFMD once every three years since 1997 and predicted that an outbreak would occur in 2006. The outbreak did occur in 2006 and health authorities in Sarawak confirmed this revelation as mentioned in Sarawak Health Department (2006).

In 2011, 2900 cases have been reported (Sarawak Health Department, 2012). During this year, the number of cases did not reach the outbreak level. The top five districts with the highest total number of reported cases were Kuching, Bintulu, Miri, Sarikei and Samarahan (Sarawak Health Department, 2012). Sarawak Health Department has announced an outbreak in 2012 from the week 10 but it started to decrease below the outbreak level since week 32. Kuching have been the highest number of cases followed by Samarahan, Miri, Sibu and Sarikei.

The number of cases given is by districts and epidemiology week in Sarawak. For this study, we look at two scenarios of HFMD where we used the number of notified cases for the year 2011 (no outbreak) and 2012 (during outbreak) as in Fig. 2.

The geographic data with the location coordinates for each district is denoted by x_1, the latitude (north-south direction) and x_2, the longitude (east-west direction). These coordinates were obtained from (Itouchmap.com, 2012).

Trend surface models: A general trend surface model is described as follow:

$$y = \sum_{i=0}^{p} \sum_{j=0}^{q} \beta_{ij} x_1^i x_2^j + \varepsilon$$

where,

Fig. 1: Area by districts in Sarawak (Sham, 2012)

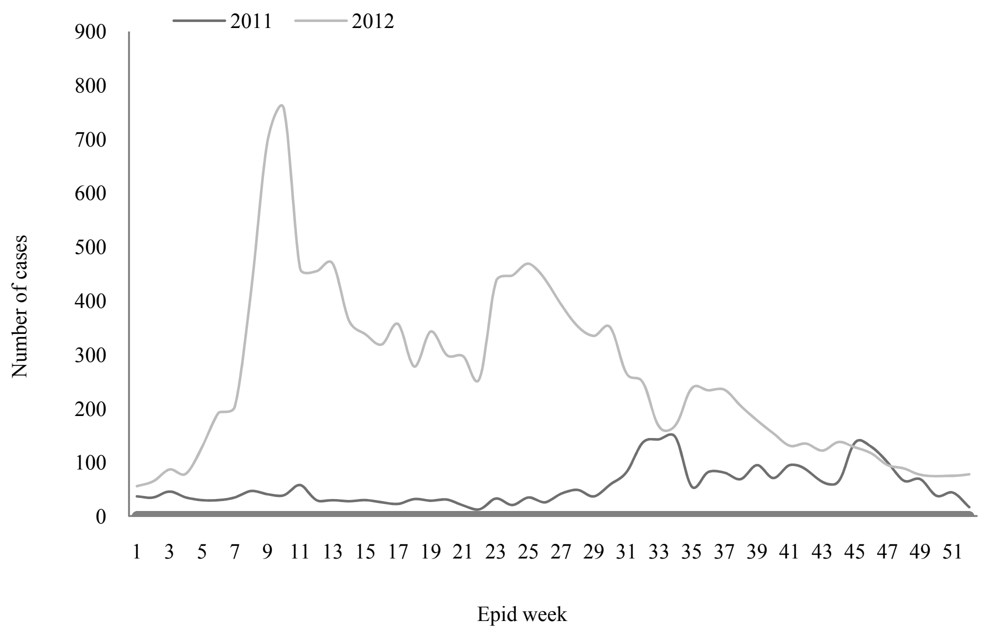

Fig. 2: Reported cases of HFMD for year 2011-2012 by epid week

y = The response variable
x_1 and x_2 = The predictors
β = The parameter and ε is the error term

In particular, a second order trend surface polynomial is given by:

$$y = \beta_{00}+\beta_{10}x_1+\beta_{01}x_2+\beta_{11}x_1x_2+\beta_{20}x^2_1+\beta_{02}x^2_2+\beta_{21}x^2_1x_2+\beta_{12}x_1x^2_2+\varepsilon$$

All possible combinations of second order trend surface models and the best subset were obtained using the Mallows' *Cp* statistic. In general procedure to find an adequate model by means of the *Cp* statistic is to calculate *Cp* for all possible combinations of variables and the *Cp* values against *p*.

The model with the lowest *Cp* value approximately equal to *p* is the most adequate model (Lohninger, 2012). Mallows' *Cp* statistic is given by:

$$C_p = \frac{SSE(p)}{\sigma^2} - n + 2_p$$

Hypothesis test for spatial autocorrelation: As given in Cliff and Ord (1981), the steps involved for testing the hypothesis are as follows:

Step 1: Formulation of hypothesis

H_0: No spatial autocorrelation
H_1: Spatial autocorrelation exist

Step 2: Choice of Test Statistics

The test statistics is:

$$Z^* = \frac{I-E(I)}{\sqrt{V(I)}} \sim N(0,1)$$

where,

$$I = \frac{n}{S_0}\frac{e^TWe}{e^Te}$$

(Neter *et al*., 2004)

e = The residual matri
W = The weight matrix
n = The number of observations and

$$S_0 = \sum_{i=1}^{n}\sum_{j=1}^{n} w_{i,j}; i \neq j$$

We used R programming language in order to calculate Moran *I* statistic. First of all, we need to create inverse matrix of distance weights. In the matrix, each entry for pairs of points that are close together is higher than for pairs of points that are far apart. To make it less complicated, we treat the latitude and longitude as values on a plane rather than on a sphere. However, when using latitude and longitude coordinates from more distant locations, it is advisable to calculate distances based on spherical coordinates.

We can first generate a distance matrix, then take inverse of the matrix values and replace the diagonal entries with zero.

We have created a matrix where each off-diagonal entry [i, j] in the matrix is equal to:

Table 1: Results of the hypothesis test

Year	Model	p-value	Conclusion
2011	TS 1	0.8483	No spatial autocorrelation
	TS 2	0.8152	No spatial autocorrelation
	TS 3	0.8151	No spatial autocorrelation
	TS 4	0.8702	No spatial autocorrelation
	TS 5	0.8550	No spatial autocorrelation
	TS 6	0.7139	No spatial autocorrelation
2012	TS 1	0.9965	No spatial autocorrelation
	TS 2	0.9965	No spatial autocorrelation
	TS 3	0.9965	No spatial autocorrelation
	TS 4	0.0038	Spatial autocorrelation exist

$$w_{ij} = \frac{1}{distance\ between\ i\ and\ j}\ ; i \neq j$$

$$w_{ij} = 0\ when\ i = j$$

$$i = 1,2, \dots \dots \dots \dots \dots \dots \dots ,11$$

$$j = 1,2, \dots \dots \dots \dots \dots \dots \dots ,11$$

Step 3: Critical Region

At 95% significance level (α=0.05), reject H_0 if *p*-value <α

RESULTS AND DISCUSSION

Trend surface models could adequately explain the variation in the number of HFMD cases. All models (Appendix 1 and 2) were listed as the residuals that are not spatially autocorrelated except for TS 4 for 2012. Therefore, we can choose the best model among all to represent the number of HFMD cases in Sarawak for preferred locations.

Based on Table 1, TS 1 is suggested as the best for year 2011 and TS 3 for year 2012 since it has the smallest variance of the residuals. Thus, we believe that these models could fit the number of HFMD cases data with a higher degree of reliability. Location coordinates were the only explanatory variables used in this study. More regressor variables should be used to make a better model.

CONCLUSION

From the beginning, we have considered a few models based on the idea that number of HFMD cases can be described by a fairly simple mechanism such as regression residual analysis. The residuals from all the trend surface models were examined for spatial autocorrelation using the coefficient, *I*. We tested *I* for significance by using Moran *I* command.

For 2011, all models had residuals that were not spatially autocorrelated. One of them was selected as the best model that could explain the trend surface of the HFMD cases in Sarawak. Since the model mentioned is a first order polynomial, this means that the number of HFMD cases in Sarawak has a linear surface. Hence from this model we could say that as in any direction the change in the disease pattern could be similar since HFMD has linear trend in both north-south and east-west directions in a non-outbreak situation.

However, in 2012, one out of the four models is spatially autocorrelated. Among the three models, the best model selected is a second order polynomial. This means that the HFMD cased in Sarawak for year 2012 has a quadratic surface. The disease has a quadratic trend in the east-west direction and a linear trend in the north-south direction. Meaning that the disease pattern changes faster as we move along the east-west direction compared to north-south direction in an outbreak situation.

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Appendix 1:

The fitted trend surface models and the results of the hypothesis test for 2011 are as follows.

$$y = 18404.15+196.26x_1-165.696x_2 \quad \text{(TS 1)}$$

$$y = 9068.00+4602.81x_1-83.24x_2-38.77x_1x_2 \quad \text{(TS 2)}$$

$$y = 14078.64+2217.35x_1-129.6x_2-15.98\ x_1x_2 -36.53x_1^2 \quad \text{(TS 3)}$$

$$y = 1394132.78+30776.8x_1-25223.27x^2-275.82\ x_1x_2 +119\ x_1^2+114.06x_2^2 \quad \text{(TS 4)}$$

$$y = 1322972.26-124881.68x_1-22217.65x_2+1114.71\ x_1x_2 +24979.6\ x_1^2+ 92.88\ x_2^2-222.12x_1^2x_2 \quad \text{(TS 5)}$$

$$y = -5682994.50+103365.53x_1-100933.85x_2+ 103614.37\ x_1x_2\ -469.48\ x_1^2 -910.3\ x_2^2+461.67x_1 \quad \text{(TS 6)}$$

Appendix 2:

The fitted trend surface models and the results of the hypothesis test for 2012 are as follows.

$$y = 86855.56-17698.78x_1+1.501x_1x_2^2-170.27\ x_1^2-6.96x_2^2 \quad \text{(TS 1)}$$

$$y = 75717.97-12615.73x_1+1.03x_1x_2^2 -6.01x_2^2 \quad \text{(TS 2)}$$

$$y = 49456.36+0.06x_1x_2^2-3.96x_2^2 \quad \text{(TS 3)}$$

$$y = 23414.42-1.76x_2^2 \quad \text{(TS 4)}$$

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