A Dynamic SEIPR Model for The Spread of Hand, Foot and Mouth Disease in Sarawak

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***Abstract*—In Sarawak, a series of hand, foot and mouth disease (HFMD) outbreaks since 1997 started to catch the public attention. Feared and worried among society in the region had arisen followed by the unusual fatalities cases. Some clinical researches and mathematical models regarding HFMD were produced. Clinical researches revealed that there exist the incubation period and post-infection virus shedding period which are not captured together in any mathematical models so far. In this study, the SIR (Susceptible-Infected-Recovered) model is being improved by building a simple deterministic SEIPR (Susceptible-Incubation (Exposed)-Infected-Post infection virus shedding-Recovered) model. By adding the incubation and post-infection virus shedding as parts of the compartments into SEIPR model, the number of infected cases is predicted. The simulation result shows rapid spreading of HFMD viruses through cohort and the ability of the model to predict the outbreak behavior pattern in the first ten weeks. Comparison between the SEIPR model and SIR model verified SEIPR model. Validation of the model is done by comparing the simulation with the actual data in 2006. Basic reproduction number, R_0 computed was 2.15 which suggesting the highly contagious HFMD is likely to spread fast. The threshold value analysed can allow the possible interventions based on the minimum proportion of the population which create the liability of disease spreading. We hope that this model can help the public health personnel to reduce the burden of the disease by planning an effective manner of intervention during the outbreaks.**

***Index Terms*—Hand foot and mouth disease; Dynamic model; Incubation period; Post-infection virus shedding period**

I. INTRODUCTION

Hand, foot and mouth disease (HFMD) is an acute viral illness that primarily affects infants and children under the age of 10, but can also affect older children, teenagers and adults. HFMD is caused by several different viruses that belong to the enterovirus group, it is mostly caused by coxsackie virus (CV-A16), human enterovirus (EV71) or other enteroviruses including Coxsackie A viruses, CV-A2, CV-A4, CV-A5, CV-A6, CV-A7, CV-A10 and CV-A12 or Coxsackie B viruses, CV-B1, CV-B2, CV-B3 and CV-B5 [1].

HFMD is a worldwide concern disease as the outbreaks in the countries such as Taiwan, China, Singapore, Vietnam, Mongolia, Brunei and Australia brought the tense among the public due to the high number of infected cases and complicated death cases [2-4].

During the outbreaks, the patients are advised to be quarantined at home or hospitalised. This is to avoid the direct contact with the patients as the viruses can be easily transmitted through aerosol or ingestion and fomites [4]. Besides that, HFMD also caused the chaos of social welfare and economic problems. Due to the fear of the spreading disease, the closure of some schools had been implemented [4, 5]. The closure may bring the problems to the working parents as they need to find the alternative ways of taking care of their children. Parents were requested to keep their children away from crowded places during the outbreaks. Also, there are some other social and economic problems are taking place during the disease outbreaks which are not easily quantifiable [5].

In Sarawak, a state of Malaysia on the island of Borneo, encountered outbreaks of the HFMD since 1997. There were death cases reported. A cluster of unusual paediatric deaths due to encephalitis and cardiac failure were observed [6]. A seven years sentinel surveillance for EV71 in Sarawak was carried out to elucidate the epidemiology regarding the patterns of transmission of the viruses [1]. Also, some mathematical modellers have developed models for analysing the dynamic behaviour of the HFMD. SEIR model was analysed theoretically by using numerical simulation which showed that the number of actively infective people at initial time and the disease transmission coefficient play more role on the transmission [2]. In [7], the study showed that the disease transmission rate is affected by number of infected individuals and at which quarantined may help control the disease. Another study, in which a spatial-temporal ARMA model is presented where monthly average temperature, relative humidity and total sunshine are factors contributed to the incidence. In this study, the incidence peak season in Wenzhou, China was between May and July [8]. In another study, the effect of short-term changes in weather on the incidence of HFMD had been analysed in Singapore. The study showed that a maximum daily temperature above 32°C and rainfall up to 75 mm is expected to increase the HFMD incidence [9]. SEIQRS model was analysed theoretically by using numerical simulation, had suggested transmission rate and recovery-rate of non-hospitalised individuals are the most sensitive parameters. Thus, to curb HFMD, quarantine is the best method to be implemented [10]. Another model which was also analysed theoretically by using numerical simulation in Matlab is a delayed hand-foot-mouth disease epidemic model with pulse vaccination, the result showed that pulse vaccination is an effective strategy to eliminate HFMD [11]. Meanwhile, in Sarawak, SIR model had been studied to predict impending outbreaks in Sarawak and suggested that number of susceptible is the parameter that may be able to control the disease [5]. However, to date, no mathematical

models are taking the post-infection virus shedding into account. With this, the incorporated of incubation group and post-infection virus shedding group to SIR model as parts of the model compartments were thus found to be able to improve the prediction of the infected cases.

In the following section, we will discuss our mathematical SEIPR model which can be used to predict the spread of HFMD by using numerical method. We will then present our threshold value and basic reproductive number R_0. Threshold value found suggested minimum proportion of the population which can contribute to the spreading of the disease [12]. The outbreak occurs when $R_0 > 1$ [13]. The partial basic reproductive numbers caused by incubation period, infectious period and during post-infection virus shedding period were analysed as well. With the R_0, incubation period, infectious period and post-infection virus shedding period are suggested to be the factors which are contributed to the outbreaks.

II. Materials And Methods

A. Clinical characteristic

HFMD outbreaks occur when a cohort of children who have not been exposed to the disease encounter the viruses. These susceptible children mostly below the age of 10, providing the conditions for the virus transmission where a major outbreak may occur. HFMD is highly contagious in the first week after symptoms appear. Once the enteroviruses spread via aerosol or ingestion, the infected individual is presented with rapid onset of fever, poor appetite, malaise and sore throat and soon will be accompanied by vesicles and ulcers developed in the mouth, skin lesions on palms, soles on the buttocks, knees, feet and other areas [1, 2]. The fever and rash may subside within a week and the patient is said to be clinically recovered. However, the viruses may continue to shed for several weeks examined by throat swaps and fecal sample and the post-infection virus shedding may serve as reservoirs which may extend the contagious period and raise the likelihood of secondary infection [1, 14-16].

B. Mathematical modelling

i. Introduction

In Sarawak, SIR model had been studied to curb the HFMD [5]. However, the model used only showed a better goodness of fit when the real data being pushed one week in advance. Adjusting the real timing in order to fit the predicted data cannot show the SIR model able to predict the real dynamic infectious behavior convincingly. With this, we hypothesize that by the inclusion of the incubation period and post-infection virus shedding period, we can provide a better prediction. Hence, we formulated a mathematical model SEIPR to improve the previous SIR model [5] to enhance the better understanding of the dynamics of the disease by adding the compartments of the incubation group and post-infection virus shedding group.

In order to verify the result, we compare the simulations ran by SIR model [5] and our SEIPR model by using Matlab. For the next session, we will introduce our model in which incubation period and post-infection virus shedding period are being included in the compartments model.

ii. Formulation of the model

We formulated a simple deterministic SEIPR model by improving SIR model [5] to deal with the periodic infected cases. Comparison results were made by using the same clinical data. The study is with the intention to describe the behaviour of the disease mathematically. The compartmental model is shown below.

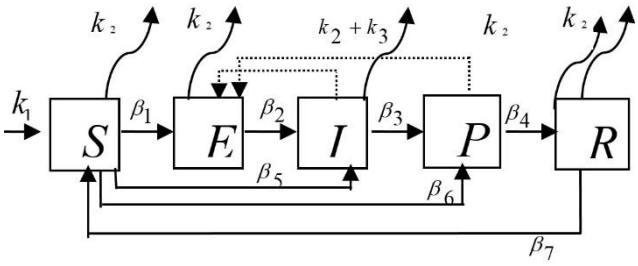

Figure. 1: HFMD model

where: S = the number of susceptible
E = the number of exposed individual (incubation period with asymptomatic group)
I = the number of infectious individuals (symptomatic group)
P = the number of clinically recovered Individual (symptoms subside but carrying the post-infection virus shedding)
R = the number of fully recovered individual
k_1 = natural birth rate
k_2 = natural death rate
k_3 = death rate caused by the disease
β_1 = the transmission coefficient of susceptible individuals (S) getting infected by exposed individuals (E)
β_5 = the transmission coefficient of susceptible individuals (S) getting infected by infectious individuals (I)
β_6 = the transmission coefficient of susceptible individuals (S) getting infected by clinically recovered individuals (P)
β_2 = the rate at which an asymptomatic patient developing symptoms per unit time
β_3 = the rate at which an infectious individual clinically recovered per unit time
β_4 = is the rate at which a clinically recovered individual fully recovered per unit time
β_7 = the rate at which a recovered individual loses its immunity

By using the balance law, the compartmental model in Figure 1 is formulated by the following differential equations:

$$\frac{dS}{dt} = k_1 + \beta_7 R - \beta_1 SE - \beta_5 SI - \beta_6 SP - k_2 S \quad (1)$$

$$\frac{dE}{dt} = \beta_1 SE + \beta_5 SI + \beta_6 SP - \beta_2 E - k_2 E \quad (2)$$

$$\frac{dI}{dt} = \beta_2 E - \beta_3 I - (k_2 + k_3) I \quad (3)$$

$$\frac{dP}{dt} = \beta_3 I - \beta_4 P - k_2 P \quad (4)$$

$$\frac{dR}{dt} = \beta_4 P - k_2 R - \beta_7 R \quad (5)$$

The population is split into five compartments namely the susceptible (S), the incubation group (E), the infectious group (I), the post-infection virus shedding group (P) and the fully recovered group (R). The susceptible class increases through the natural birth and fully recovered individuals who have lost their immunity. Meanwhile, the susceptible class also decreases through the natural death, the moving to incubation group, infectious group and post-infection virus shedding group. The susceptible (S) gains the HFMD infection through the contact with the asymptomatic patients (E), symptomatic patients (I) or with those carrying post-infection virus individuals (P) [1, 14-16]. Once infected, the asymptomatic patients will move to incubation group (E). During this incubation period, HFMD patients have no symptom shown. Symptoms can be developed within few days [1, 5], however after many simulations ran, we assume that symptoms are developed in about one day and the patients are moved to the

infected group (I). Another one week, when the symptoms subside then they will move to the post-infection virus shedding group (P) where the patients are said to be clinically recovered and do not exhibit any symptom. Here, we say that the virus may continue to shed. One more week later, the patients are fully recovered and will move to fully recovered group (R) [14-16].

An individual will attain an immunity from HFMD after recovery, however the patient can be infected again through different HFMD viruses. Thus, the recovered patient returns to susceptible class and capable to be infected again [5].

iii. Derivation of basic reproductive number (R_0)

The derivation of R_0 follows the next generation model [13] and we obtained the following expression for R_0:

$$R_0 = R_1 + R_2 + R_3$$
$$R_0 = \frac{\beta_1 S_0}{k_2 + \beta_2} + \frac{\beta_2 \beta_5 S_0}{(k_2 + \beta_2)(\beta_3 + k_2 + k_3)} + \frac{\beta_2 \beta_3 \beta_6 S_0}{(k_2 + \beta_2)(\beta_3 + k_2 + k_3)(k_2 + \beta_4)} \quad (6)$$

The numerators of the formula consist of three parts which are shown by three terms as above. The first term R_1 is the number of secondary infectious during the asymptomatic stage, the second term R_2 is the number of secondary infectious during the fully infectious stage and the third term R_3 is the number of secondary infectious during the clinically recovered stage. The denominator of the first term is the inverse of the natural death rate plus the transition rate from asymptomatic to symptomatic cases $k_2 + \beta_2$, while in second term, in addition to $k_2 + \beta_2$, the denominator is incorporated with the inverse of the natural death rate plus death rate caused by disease plus the transition rate from symptomatic to clinically recovered cases ($\beta_3 + k_2 + k_3$), and for the third term, in addition to $(k_2 + \beta_2)(\beta_3 + k_2 + k_3)$, the denominator is incorporated with the inverse of the death rate plus the transition rate from clinically recovered to fully recovered cases ($k_2 + \beta_4$).

iv. Numerical solution

The mathematical model is formulated by the nonlinear ordinary differential equations from (1) to (5). The numerical method is chosen to run the simulation in order to predict the infected cases and the duration of the outbreak for the year 2006. It was being solved by the built-in function in Matlab based on the fourth-order Runge-Kutta method. The numerical results were compared with the observed cases. With this, the chi-square, X^2 were obtained to calculate the P-value. The observed cases were assessed whether were closed enough compared to the predicted cases. Any P-value that is more than 0.1, we have no good reason to reject the predicted results. The method is called goodness of fit method [17], Parameters used for k_1, k_2, k_3, β_5 and β_7 are obtained from previous SIR study [5].

Meanwhile, the parameter for β_1, β_2, β_3, β_4 and β_6 are the best results used after running the simulations for many times.

Table 1
The parameters of and values of SEIPR model for HFMD outbreak in Sarawak

Parameters		Initial	Values
k_1	2.923×10^{-4}	S	10000
k_2	1.077×10^{-4}	E	4
k_3	1.731×10^{-5}	I	4
β_1	3.000×10^{-5}	P	4
β_2	5.500	R	0
β_3	1.000		
β_4	1.000		
β_5	1.500×10^{-4}		
β_6	6.000×10^{-5}		
β_7	7.000×10^{-2}		

As we are improving the previous work, the initial values used for susceptible, infected individual and recovered individual are same. However, the initial values for added compartments which are incubation group and post-infection virus shedding group are newly suggested (see Table 1).

III. RESULTS

In Figure 2, the comparison result showed the predicted cases and the real infected cases in the year 2006 by using SEIPR model. The simulated cases indicated a good fit in the first ten weeks with visual inspection. The predicted results were then analysed by using the goodness of fit test resulted in Pearson, $X^2 = 9.48$ with 13 degrees of freedom for first 13 weeks. P-value obtained was 0.74. The tested result showed no absence of goodness of fit.

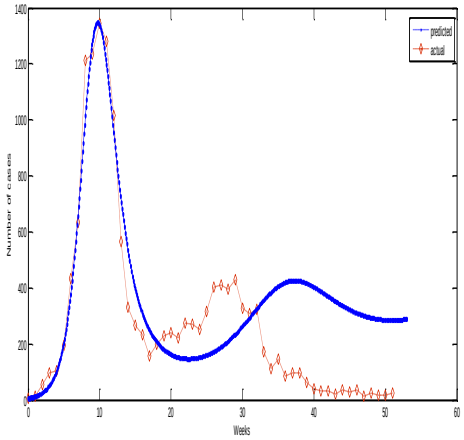

Figure 2: The predicted infected population vs the actual cases reported by using SEIPR model

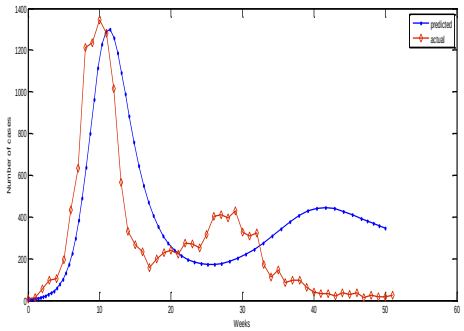

Figure 3: The predicted infected population vs the actual cases reported by using SIR model

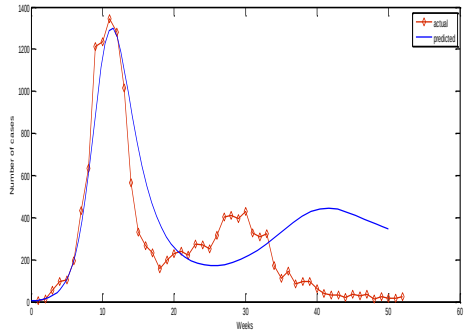

Figure 4: The predicted infected population vs the actual cases reported by using SIR model after the actual data being push one week in advance

However, the goodness of fit tested by using SIR model (see Figure 3) was not in good agreement as the P-value ≈ 0. The results showed by using SIR model from previous research is found only able to make a good fit when the real data had been push one week in advance (see Figure 4). With this, there is a consensus that the SIR model was unstable for the prediction. By using the parameter values for numerical simulation, the basic reproduction number for SEIPR model was obtained as 2.15. As mentioned earlier, the estimation of R_0 is observed to be from three parts (see equation 6). R_0 = 0.05 + 1.5 + 0.6. The R_0 suggested the acute viral illness is highly contagious and the rapid onset of the symptoms which last for a week contributed the most transmission for the infected cases in 2006 as the R_2 for this part is 1.5. However, after the symptoms subside, the HFMD virus continue to shed and cause the transmission and contributed to the number of infected, and R_3 for this part is 0.6. The incubation group, on the other hand, was being able to transmit the virus even without symptoms shown, R_1 = 0.05. This was a blind spot for disease prevention. Meanwhile, the threshold value based on SEIPR model estimated was approximately equal to 4642. In this case, any cluster with number of cohorts goes beyond 4642 is likely to cause second outbreaks (see Figure 5).

However, in Figure 2, we can see that the second round of the outbreak was not a good fit. This is probably because of the transmission rate had changed after the first outbreaks [17].

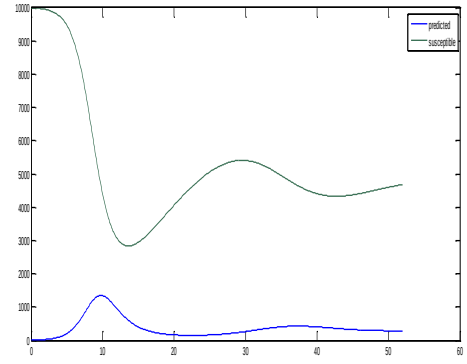

Figure 5: The predicted infected population and the number of susceptible shown by using SEIPR model

IV. Discussion

The SEIPR model is the improvement model from SIR model. Incorporating the factors of viruses spreading during the incubation period, infected period and post-infection virus shedding period would make a more reliable predicting to the real scenario of the disease outbreaks in 2006. Based on the simulation of HFMD occurrence, R_0 was calculated and the highest secondary number of infectious in 2006 was predicted to be contributed by the infected period. In addition, estimation of R_0 indicated the incorporating factors discussed above were the major causes of the quick spreading of the HFMD. On the other hand, threshold value found may help to allow the possible interventions based on the minimum proportion of the population which create the liability of disease outbreaks.

The quarantine method used to prevent the HFMD transmission is suggested to extend the quarantine time to at least another one week after symptoms subside as the clinically recovered patients are still being capable to transmit the disease.

In this work, the SEIPR model can help to predict the outbreaks base on the reliable parameters inputs and hence, more effective control interventions can be planned to reduce the effect of the future outbreaks.

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