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Compartmental Modeling of Hand, Foot and Mouth Infectious Disease (HFMD)

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Abstract: Hand, Foot and Mouth Disease (HFMD) is a contagious infectious disease which is very common in young children. Although, HFMD is considered as a mild to moderate contagious disease, recent outbreak of this disease not only caused health problems but also social and economical problems along with causalities in many countries. Therefore it takes the attention of public health researches in recent years. In this study a simple SEIR model was build to understand the dynamics of hand, foot and mouth disease among the young children. We theoretically analyze the disease model along with numerical simulation results. The results show that disease transmission depends more on the number of actively infected people in the population at the initial time and also on the disease transmission coefficient at a given time.

Key words: Compartmental modeling, SEIR model, differential equation, mathematical modeling of infectious disease, HFMD, Bangladesh

INTRODUCTION

Hand, foot and Mouth Disease (HFMD) is a contagious viral illness that commonly affects infants and children. HFMD occurs often in the countries with temperature climates especially in summer and early autumn. HFMD is caused by enteroviruses from the family called Picornoviridae. It is most commonly caused by coxsackie virus (A16), human enteroviruses (HEV71) or other enteroviruses including Coxsackie virus A (CAV) 4, 5, 9 and 10 or Coxsackievirus B (CBV) 2 and 5 (Tiing and Labadin, 2008; Podin *et al*., 2006; McMinn *et al*., 2001).

Symptoms usually begin with a fever, poor appetite, malaise (feeling vaguely unwell) and often a sore throat. A couple of days after the fever starts, painful sores can develop in the mouth. A skin rash with flat or raised red spots can also develop usually on the palms of the hands and soles of the feet and sometimes on the buttocks. This rash may blister but it will not itch. Some people with HFMD may only have a rash others may only have mouth sores. Other people with HFMD may show no symptoms at all.

Although, HFMD is moderately contagious and usually not a serious illness among the infected population, recent outbreak of HFMD in countries such as China, Taiwan, Singapore and Malaysia had brought the world attention to HFMD due to complications of death related cases (CDC website), (Wikipedia for HFMD). The recent outbreaks of HFMD are shown in Table 1.

Table 1: Outbreak of HFM disease

Years	Country	Reported number of infected cases and deaths (Wikipedia for HFMD)
1997	Sarawak in Malaysia	2626 infected children and 31 deaths.
1998	Taiwan	405 children with severe complication 78 died. Estimated cases were 1.5 million
2006	Sarawak in Malaysia	14,423 infected cases and13 deaths
2008	China	25000 infected cases and 42 deaths
2008	Singapore	2600 infected cases
2008	Vietnam	2300 infected cases and 11 deaths
2008	Mongolia	1600 infected cases
2008	Brunei	1053 infected cases
2009	China	115,000 reported cases, 773 were severe complication 50 were fatal
2009	Indonesia	Several severe cases with fatality
2010	China	Until march 70756 children were infected and 40 died from the disease

It is obvious that HFMD not only caused health problems but also it has great social and economical impacts which are not easily quantifiable. So it is important to understand the dynamics of HFMD spread among the susceptible populations and enable policy makers to take effective measure to curb the disease spread and reduce the adverse impact of the disease. It may be a general thought that statistical regression is the only modeling technique available for the health policy maker's toolkit to analyze the spread of infectious diseases but statistical models are only one of several types of analytical models that are valuable to understand and predict transmission of infectious diseases. In addition, mathematical modeling is a set of techniques, tools and equations that define interactions between individuals or populations and other individuals, populations and environments. By defining the rules of

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these interactions and translating those rules into equations, a complex set of processes can be broken down into components and quantified. The model can then be used to explore relationships in the modeled populations to examine the impact of changes of rules on the system and its components and the outcomes of various events that might have an effect on the population.

The foundations of mathematical modeling of human and mammalian disease epidemics were first established by Kermack and McKendrick (1927, 1932, 1933). Later, the extensive reviews (Anderson, 1982; Anderson and May, 1979; May and Anderson, 1979) and contributed to the subject of disease dynamics opening new discussions for concepts, critical threshold, basic reproductive ratio, transmission coefficient, etc. The importance of mathematical models in disease epidemics has been discussed extensively by many researchers (Bradley, 1982; Anderson and May, 1991; Heesterbeek and Roberts, 1995).

Several studies (Tiing and Labadin, 2008; Wang and Sung, 2007; Urashima *et al*., 2003) are investigated the spread of HFMD among the young children. In the study (Tiing and Labadin, 2008), the reseaechers established a simple deterministic SIR model of HFMD to predict disease outbreak. They estimated critical population density for the outbreak of HFMD in Sarawak, Malaysia in 2006. In Wang and Sung (2007), SIR model of HFMD has been used to analyze the occurrence of enterovirus complications among the severe ill cases in Taiwan.

In Urashima *et al*. (2003), the researchers attempted to established nonlinear mathematical models to simulate the impact of global warming on the incidences of HFMD in Tokyo. Numerical analysis has been shown to find the relationship between the outbreaks of HFMD with the weather patterns in the respective countries in those models. However in this study we formulated a compartmental SEIR model for HFMD using computer algebra providing the analytical results obtained from the model.

MARTERIALS AND METHODS

Clinical characteristics of Hand, Foot and Mouth Disease (HFMD): Clinical and pathological characteristics of hand foot and mouth disease are in many studies (Tiing and Labadin, 2008; Wang and Sung, 2007; Urashima *et al*., 2003) and also described on the website of (CDC website). The most susceptible populations to HFMD are the children aged below 10 years (Tiing and Labadin, 2008).

An individual who is exposed to HFMD viruses will exhibit the symptoms after 3-7 days. This is considered the incubation period of HFMD. Fever is usually the first symptoms of HFMD followed by poor appetite, malaise and sore throat. About 1 or 2 days after the fever begins, small red spots develop in the mouth that blister and often develop into ulcers. These are mostly found on the tongue, gums and inside of the cheeks. The skin rash develops over one or two days with flat or raised red spots, some with blisters on the palms of the hand and the soles of the feet. Thus, the name of the disease is hand, foot and mouth disease (HFMD). An individual with HFMD may some time have only the rash or the mouth ulcers.

HFMD is considered moderately contagious among children. An individual is most contagious during the 1st week of the illness. As the viruses are present in the throat and stools of an infected individual, infection generally occurs via the facial-oral or via contact with skin lesions and oral secretions. The virus may continue to be excreted in the stools of infected individuals up till 1 month. The spread of the virus does not involve any vectors.

At the moment there is no specific antiviral drug to cure HFMD. There is also no vaccine available for the treatment of HFMD. Infected person is usually given medication to provide relieve from the pain caused by fever, aches or mouth ulcers. Victims are asked to take plenty of liquid. An infected person will fully recover after 7-10 days.

There is no permanent immunity against HFMD as the disease is caused by a group of viruses much like the case of flu. A person who recovered from the HFMD caused by Coxsackie A is susceptible to HFMD caused by enteroviruses 71 or any other enteroviruses.

Hand Foot and Mouth Disease (HFMD) model: In order to study the compartmental SEIR model of spread of hand, foot and mouth diseases, we need to formulate four classes of human populations namely, susceptible class, asymptotic infected class, symptomatic infected class and recovered class. Each group or compartment is shown in Fig. 1.

S (t) represents the number of individuals who are not yet infected with the disease at time t or those who are susceptible to the disease. E (t) represents the number of asymptomatic infectious individuals (people who have been infected with the disease but don't show any signs of symptoms) at time t. I (t) is the number of symptomatic infectious individual (people who have been infected with disease and show the signs of symptoms) at time t.

R (t) is the number of recovered individuals (people in this class have been infected but then recovered from the disease they are also not able to be infected again or to transmit the infection to others) at time t. Therefore, the compartmental SEIR model for HFMD is shown in Fig. 1. Both symptomatic and asymptomatic infectious individuals are capable of

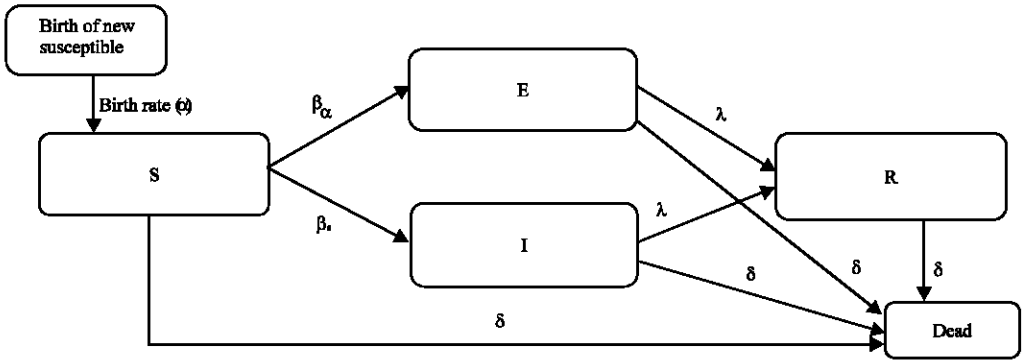

Fig. 1: Hand foot mouth disease (HFMD) model

spreading the disease to those in the susceptible category. The dynamics of the model for each compartment is then governed by the following set of differential equations:

$$\frac{d}{dt}S(t) = \alpha N - \frac{(\beta_\alpha + \beta_S)S(t)I(t)}{N} - \delta S(t) \quad (1)$$

$$\frac{d}{dt}E(t) = \frac{\beta_\alpha S(t)I(t)}{N} - (\lambda + \delta)E(t) \quad (2)$$

Where:

α = Birth rate
α = Death rate
β_α = Transmission co-efficient (asymptomatic)
β_s = Transmission co-efficient (symptomatic)
λ = Recovery or removal rate
S (t) = Susceptible
E (t) = Asymptomatic infectious class
I (t) = Symptomatic infectious class
R (t) = Recovered class
N (t) = S+E+I+R

$$\frac{d}{dt}I(t) = \frac{\beta_s s(t)I(t)}{N} - (\lambda + \delta)I(t) \quad (3)$$

$$\frac{d}{dt}R(t) = \lambda\big(E(t)+I(t)\big) - \delta R(t) \quad (4)$$

Now, knowing that S(t), E(t), I(t) and R(t) are fractions of the population, we can say that:

$$s(t)+ e(t)+i(t)+r(t)=1 \quad (5)$$

Where:

$$s(t) = \frac{s(t)}{N}, e(t) = \frac{E(t)}{N}, i(t) = \frac{I(t)}{N}, r(t) = \frac{R(t)}{N}$$

are the compartment densities. Using the equation of compartment densities we can resume the system Eq. 1-4 of HFMD as follows:

$$\left(\frac{d}{dt}s(t)\right) = \alpha - (\beta_a + \beta_s)s(t) - \delta s(t) \quad (6)$$

$$\left(\frac{d}{dt}e(t)\right) = \beta_a s(t)i(t) - (\lambda + \delta)e(t) \quad (7)$$

$$\left(\frac{d}{dt}i(t)\right) = \beta_\alpha s(t)i(t) - (\lambda + \delta)i(t) \quad (8)$$

$$\left(\frac{d}{dt}r(t)\right) = \lambda\big(e(t)+i(t)\big) - \delta r(t) \quad (9)$$

RESULTS AND DISCUSSION

Equilibrium analysis: At equilibrium the Left Hand Side (LHS) of the system equations of HFMD will be zeros, i.e.,

$$\left(\frac{d}{dx}s(t)\right) = 0, \left(\frac{d}{dx}i(t)\right) = 0, \left(\frac{d}{dx}e(t)\right) = 0$$

$$\text{and} \left(\frac{d}{dx}r(t)\right) = 0$$

For the HFMD model given by the systems of Eq. 10-13 the following properties hold when populations with constant size are assumed:

- The equilibrium point without infection called disease free equilibrium is given by:

$$s = S^0, e = 0, i = 0 \text{ and } r = 0$$

Thus we can take the disease free equilibrium as $(S^0, 0, 0, 0)$

- The equilibrium point with infection called endemic equilibrium is given by:

$$s = \frac{\alpha}{(\beta_a+\beta_s)i+\delta} = S$$
$$e = \frac{\beta_a si}{\lambda+\delta} = E^*$$
$$i = \frac{\beta_a si}{\lambda+\delta} = I^*$$
$$r = \frac{\lambda(e+i)}{\delta} = R^*$$

Thus we can take the endemic equilibrium as (S* ,E* ,I* R*).

Stability analysis: For stability analysis of each of the two equilibrium of the HFMD, we examine the behavior of the model population near the equilibrium solutions (the disease free and the endemic). By finding the eigenvalues of the associated Jacobian matrices of the system equations, we investigate the local stability of the steady state of the disease model. Therefore for the system of Eq. 7-9, the Jacobian matrix is:

$$J = \begin{bmatrix} -(\beta_a+\beta_s)i-\delta & 0 & -(\beta_a+\beta_s)S & 0 \\ \beta_a i & -(\lambda+\delta) & \beta_a S & 0 \\ \beta_s i & 0 & \beta_s S-(\lambda+\delta) & 0 \\ 0 & \lambda & \lambda & -\delta \end{bmatrix} \quad (10)$$

At disease free equilibrium, the Jacobian matrix becomes:

$$J^0 = \begin{bmatrix} -\delta & 0 & -(\beta_a+\beta_s)S^0 & 0 \\ 0 & -(\lambda+\delta) & \beta_a S^0 & 0 \\ 0 & 0 & \beta_s S^0-(\lambda+\delta) & 0 \\ 0 & \lambda & \lambda & -\delta \end{bmatrix} \quad (11)$$

Now from Eq. 11 we get the eigenvalues:

$$\alpha_1 = -\delta,\ \alpha_2 = -\delta,\ \alpha_3 = -(\lambda+\delta) \text{ and } \alpha_4 = -(\lambda+\delta)+\beta_s S^0$$

Obviously, $\alpha_1 <0$, $\alpha_2<0$, $\alpha_3<0$ and $\alpha_4<0$ if and only if $\beta_s S^0<(\lambda+\delta)$ since all model parameters are positive. Therefore, the implication of the negativity of all the eigenvalues of J^0 is that disease free equilibrium is stable and this so as long as $\beta_s S^0 <(\lambda+\delta)$ holds. The basic reproductive number, R_0 can be estimated using the following formula:

$$R_0 = \frac{\beta_s S^0}{\lambda+\delta}$$

In the case of disease free equilibrium the R_0 would be <1 i.e., $R_0<1$. At endemic of equilibrium, the Jacobian matrix becomes:

$$J^* = \begin{bmatrix} -(\beta_a+\beta_s)I^*-\delta & 0 & -(\beta_a+\beta_s)S^* & 0 \\ \beta_a I^* & -(\lambda+\delta) & \beta_s S^* & 0 \\ \beta_s I^* & 0 & \beta_s S^*-(\lambda+\delta) & 0 \\ 0 & \lambda & \lambda & -\delta \end{bmatrix}$$

$$J^* = \begin{bmatrix} -(\beta_a+\beta_s)\frac{\beta_s si}{(\lambda+\delta)}-\delta & 0 & -(\beta_a+\beta_s)\frac{\alpha}{(\beta_a+\beta_s)i+\delta} & 0 \\ \beta_a\frac{\beta_s si}{(\lambda+\delta)} & -(\lambda+\delta) & \frac{\beta_a\alpha}{(\beta_a+\beta_s)i+\delta} & 0 \\ \beta_s\frac{\beta_s si}{(\lambda+\delta)} & 0 & \frac{\beta_s\alpha}{(\beta_a+\beta_s)i+\delta}-(\lambda+\delta) & 0 \\ 0 & \lambda & \lambda & -\delta \end{bmatrix} \quad (12)$$

Depending on the various combinations of model parameters, the eigenvalues of J* could all be negative, positive, zero or any combinations of the three alternatives. Thus, the endemic equilibrium could be stable, unstable or saddle depending on the values of the various model parameters combined at a given time.

Numerical simulations: The systems of equations of HFMD could be numerically solved by using Berkeley Madonna v8.13 package. Using the hypothetical values for each of the model parameters, we described the dynamics of the model. Initially we assumed that disease might be occurred in a closed population with no birth and death rate.

Figure 2 shows the dynamics of the disease in a closed population. The values of model parameters for the HFMD model in closed population are given inTable 2. The dynamics of the disease with birth and death rate are shown in Fig. 3.

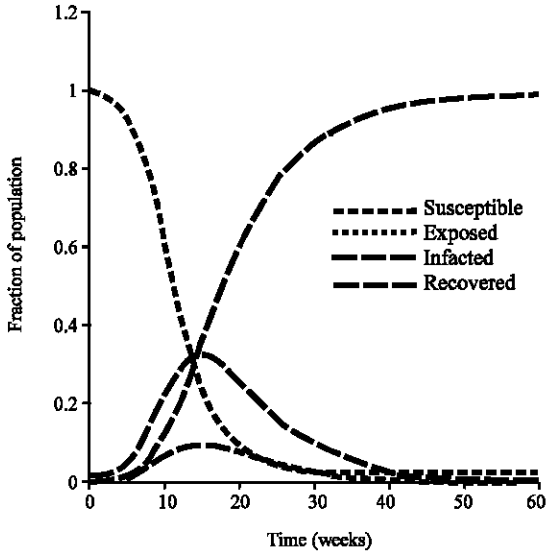

Fig. 2: Dynamics of HFM Disease in a closed population

Table 2: Values of hand, foot and mouth disease model parameters

Parameters	Initial values
S	1.000
E	0.000
I	0.010
R	0.000
α	0.000
δ	0.000
β_S	0.500
β_a	0.140
λ	0.125

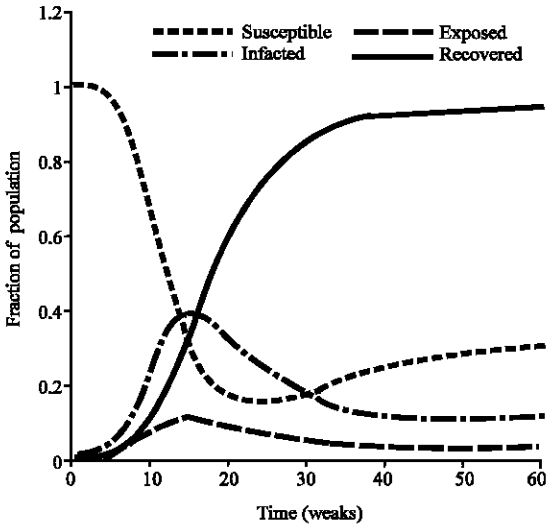

Fig. 3: SEIR curves for the disease model considering birth rate = 0.03 and death rate = 0.018

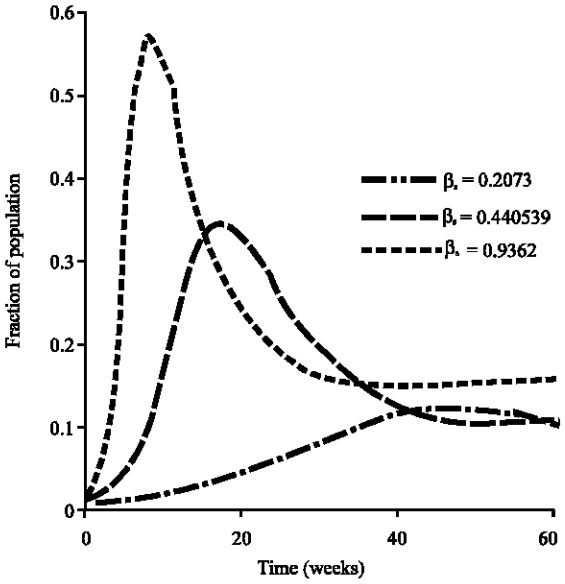

Fig. 4: Changes in fraction of infected population due to varying disease transmission coefficient

The number of infected population is largely depended on the transmission co-efficient of the disease.

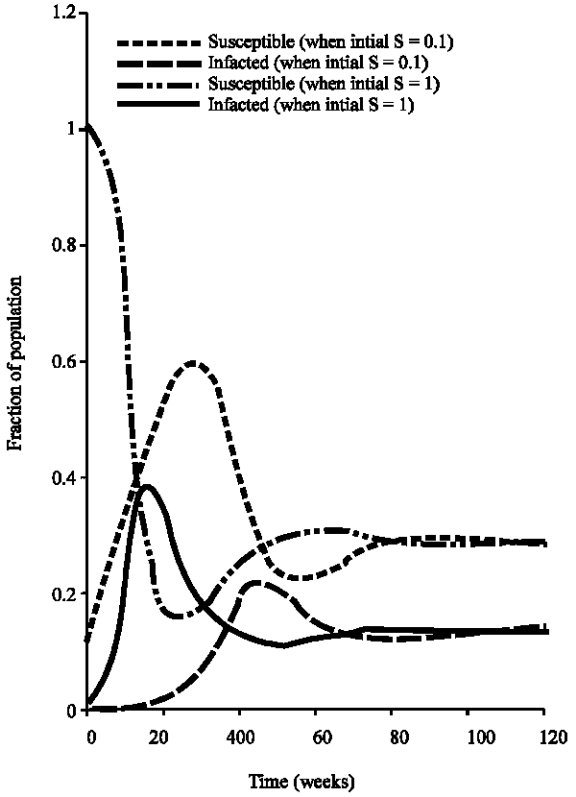

Fig. 5: Dynamics of critical population density to persist an epidemic

In Fig. 4 the impact of different transmission coefficients are shown. The critical density of susceptible population is an important factor to carry on a disease. The critical density is equivalent to $\lambda/\beta_a + \beta_s$. If susceptible is less than $\lambda/\beta_a + \beta_s$ then the disease will not persist until there would be sufficient susceptible. The phenomenon is shown in Fig. 5.

CONCLUSION

In this research, we considered the dynamics of the hand, foot and mouth disease (HFMD) using SEIR model. The resulting model equations were solved numerically and results were presented graphically based on the simulations.

The results show that disease transmission depends more on the number of actively infected people in the population at the initial time and also on the disease incidence transmission rate at a given time. Most importantly, we also showed that the disease free equilibrium is stable while the endemic equilibrium may or may not be stable depending on the various values of the model parameters.

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