MATHEMATICAL MODELLING ON THE SPREAD OF HAND, FOOT AND MOUTH DISEASE (HFMD) IN SARAWAK

A dissertation submitted

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By

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Abstrak

Negeri Sarawak telah mengalami wabak penyakit berjangkit tangan, kaki dan mulut (HFMD) sejak tahun 1997. Pada tahun 2006, wabak penyakit tersebut telah mengakibatkan 13 kematian dengan 14,423 kes direkodkan. Akibatnya arahan penutupan semua taska, tabika dan darjah satu hingga tiga sekolah rendah untuk two minggu telah dilaksanakan dalam proses menghentikan sebaran wabak tersebut. Setiap kali wabak penyakit berjangkit tangan, kaki dan mulut berlaku, perasaan takut dan risau dalam komuniti akan timbul. Wabak penyakit tangan, kaki dan mulut yang seterusnya dijanka akan berlaku pada tahun 2009. Model matematik telah digunakan secara meluas untuk meramal dan memahami dinamik penyakit berjangkit. Dalam projek ini, kami membina satu model matematik yang mudah untuk meramal sebaran wabak penyakit kaki, tangan dan mulut dari segi bilangan mangsanya. Seterusnya dengan menggunakan model tersebut, kami cuba menentukan parameter kritikal yang akan membantu dalam membantutkan sebaran wabak tersebut. Kami membina model matematik untuk penyakit tangan, kaki dan mulut berdasarkan kajian tentang ciri-ciri klinikalnya. Dengan menggunakan sistem persamaan pembezaan kami menghubungkan semua parameter dalam model berkenaan. Kami menyelesaikan sistem persamaan pembezaan tersebut berdasarkan analisis berangka dan seterusnya memaparkan hasil penyelesaian tersebut. Hasil dapatan tersebut juga dianalisiskan bersama dengan data penyakti tangan, kaki dan mulut untuk tahun 2006. Model matematik tersebut juga dianalisiskan berdasarkan penyelesaian titik pegun dan membandingkannya dengan hasil analisis berangka. Hasil kajian mendapati jumlah individual yang dijangkiti serta tempoh wabak penyakit dapat diperolehi melalui analisis berangka berdasarkan model matematik tersebut. Ia juga mendapati bahawa parameter yang dapat mengawal sebaran jangkitan wabak tersebut adalah bilangan yang belum dijangkiti.

Abstract

Since 1997, every three years Sarawak had been experiencing outbreak of hand, foot and mouth disease (HFMD). The outbreak of HFMD in year 2006 resulted in 13 deaths with 14,423 cases reported. It also resulted in closing of all nurseries, kindergartens and primary one to primary three classes for about two weeks. Each outbreak of HFMD caused fear and anxiety in the community. The next outbreak is predicted to be in year 2009. Mathematical models have been widely used to predict and understand the dynamics of infectious disease. In this project we build a simple mathematical model to predict the spread of HFMD in Sarawak in terms of number of infected individuals per unit of time and the duration of the outbreak. Then using the model we try to determine the critical parameter that can help in curbing the spread of HFMD. We studied the clinical characteristics of HFMD. Based on that study, we built the HFMD model. We formulated a system of differential equations that related all the parameters in HFMD model. Using numerical analysis, we solved the equations and presented the numerical results in graphical form. The results were analyzed with year 2006 outbreak and also through obtaining the steady state solutions analytically and compare them with the numerical results. Thus, the number of infected individuals and the duration of an outbreak can then be determined from the obtained numerical results. It was found that the parameter that would be able to control the spread of HFMD is the number of susceptible in the system.

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1. Mathematical Modelling on the Spread of Hand, Foot and Mouth (HFMD) in Sarawak, 2nd Postgraduate Colloquium 2007, Faculty of Computer Science and Information Technology, UNIMAS, 18 December 2007.

2. Mathematical Modelling on the Spread of Hand, Foot and Mouth (HFMD) in Sarawak, Seminar Kebangsaan Matematik dan Masyarakat, University Malaysia Terengganu, 13 – 14 February 2008, Kuala Terengganu.

3. A Simple Deterministic Model for the Spread of Hand, Foot and Mouth (HFMD) in Sarawak, Asia Modelling Symposium 2008, Second Asia International Conference on Modelling & Simulation, 13 – 15 May 2008, Kuala Lumpur.

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1 INTRODUCTION

1.1 Background

Hand, foot and mouth disease (HFMD) is caused by viruses from the group called enteroviruses of the family called Picornoviridae (Podin, et al., 2006). It is most commonly caused by Coxsackie virus (A16) and human enterovirus (HEV71) or other enteroviruses (Hand, Foot and Mouth Disease, 2007). Other viruses associated with HFMD are Coxsackie virus A (CAV) 4, 5, 9 and 10 and Coxsackie virus B (CBV) 2 and 5 (Ooi, et al., 2007) (Hand, Foot and Mouth Disease, 2006). The disease is believed to be a common illness of infant and children. Nevertheless, 2628 cases of HFMD with 31 deaths in Sarawak were recorded during an outbreak in 1997 (Soal Jawab Penyakit Tangan, Kaki dan Mulut (HFMD) Bersama Ketua Pengarah Kesihatan, 2006). The outbreak occurred again in 2000, 2003 and 2006. Table 1 shows the number of cases and deaths related to HFMD outbreaks in Sarawak since 1997 (Hand Foot Mouth Disease Outbreak in Sarawak, 2006, 2007; Hand, Foot and Mouth Disease, 2007).

Year	Number of cases	Number of deaths
1997	2628	31
2000	3560	0
2003	2113	0
2006	14,423	13

Table 1. Number of cases and deaths related to HFMD outbreak in Sarawak

In Table 1 it can be seen that the number of cases related to HFMD outbreak in Sarawak increased drastically to 14,423 cases as compared to those recorded in 1997, 2000 and 2003. The summation of the total cases for the three previous outbreaks cannot even match the single

total number of cases recorded in year 2006. Serious action should be taken to address this increase.

The outbreak in 2006 had prompted the Health Ministry of Malaysia to announce the closure of all child care centres and kindergartens in Sarawak for 2 weeks on 3 March 2006 (Arahan Penutupan Sementara ke atas Semua Tadika, Pra-Sekolah, Tabika dan Taska Seluruh Sarawak, 2006). As the spread of the disease did not subdued, all Primary one to Primary three classes in all primary schools in Sarawak were also ordered to be closed from 20 March to 26 March 2006 (Closure Directive -Director of Sarawak Health Department, 2006), Refer to Appendix A and B. These closures were ordered in the hope that it would break the transmission of the disease. The closure surely had caused problems for working parents who had to find other alternatives in caring for the children that were affected by the closure. Parents were requested to keep the children indoor and away from any crowded places such as supermarkets and playgrounds. It can be seen that HFMD not only caused health problems but also social and economical problems which are not easily quantifiable. As Barreto, Teixeira, and Carmo (2006) puts it, the explosive characteristics and unpredictability of epidemics are a cause of fear, insecurity, and panic for the community.

So, it is important especially in Sarawak to understand the spread of HFMD. The outbreak in 2006 was predicted by Podin, et al. (2006) which acknowledged a trend for the outbreak of HFMD every three years in Sarawak starting from the year 1997. The next outbreak is predicted to be in 2009 and this was acknowledged by the authorities in Hand Foot Mouth Disease Outbreak in Sarawak, 2006 (2007) and also in the article 'Outbreak of HFMD Expected Next Year (2008), Refer to Appendix C. It is only right that authorities concerned make

necessary preparation for the predicted outbreak in year 2009. We hope this project will be able to help authorities concerned.

It should be noted that HFMD not only strike Sarawak but also Taiwan, Western Australia and Singapore (McMinn, et al., 2001) and most recently China (Refer to Appendix D). As reported by Lim (2008) (Refer to Appendix E) 16,778 persons had been infected by HFMD in China since January 2008. In Taiwan it caused 78 deaths and 129,106 children infected during the outbreak from March to December 1998 (Ho, 2000). In Singapore it caused 4 deaths and 3526 infected during September to November 2000 outbreak. Study done by Chan, et al. (2003) revealed that most of the infected were children below the age of four years and HEV71 was the most frequently isolated cases in Singapore. Chong, et al. (2003) compared the fatality rate in Singapore with Taiwan and concluded that the difference could be due to genetic factors, viral virulence or underreporting of non-fatal cases. The study done by Chen, et al. (2007) in Taiwan also found that most of the cases were children below the age of four years. Furthermore, HFMD is a common disease in Taiwan with the incidence peak observed during the summer season. Chen, et al. (2007) attributed the outbreak of HFMD in Taiwan every two to three years to the accumulation of susceptible individuals during this interval.

Experts in the field of virology acknowledged that the virus that caused HFMD seemed to have evolved (Podin, et al., 2006). These together with the characteristics of HFMD such as no immunity and no available vaccine (Hand, Foot and Mouth Disease, 2006) should be of great concern to governments around the world and especially Sarawak where a trend for the outbreak HFMD is said to occur every three years (Podin, et al., 2006). That is where mathematical modelling of the spread of HFMD can be used.

A lot of modelling on the spread of diseases has been done for example on SARS epidemic (Choi & Pak, 2003; Gumel, et al., 2004), HIV (Nowak & May, 2000), malaria (Macdonald, 1957) to name a few. Wang and Sung (2004) did a mathematical modelling of the spread of HFMD. They used ***SIR*** (Susceptible-Infected-Recovered) model to model the spread of enteroviruses in Taiwan. The aim of their model is to see the association between the weather and the occurrence of enteroviruses complicated severe cases in Taiwan. Other than that, no mathematical modelling work has been done on HFMD cases in Sarawak.

With any mathematical model of infectious disease, the total number of infected persons can be predicted when an outbreak occurs, as well as the duration of the outbreak. This work is necessary as Podin, et al. (2006) stated that any extra knowledge on HFMD would be able to help the authorities concerned to predict the spread of the disease effectively and take pre-emptive measures in order to subdue the spread of HFM disease in time to come.

An outbreak is said to exist when there are more cases of a particular disease than expected in a given area, or among a specific group of people, over a particular period of time. Many epidemiologists use the terms "outbreak" and "epidemic" interchangeably; however, some restrict the use of "epidemic" to situations involving large numbers of people over a wide geographic area (Hand, Foot and Mouth Disease, 2006). Meanwhile, endemic is defined as a disease that is constantly present in a given geographic area or population group; may also refer to the usual prevalence of a disease.

1.2 Objectives

In order to model the dynamics of the spread of HFMD, we studied the model used in Wang & Sung (2004). We identify the similarity and did some modification to come out with a new model for the spread of HFMD in Sarawak. The project will focus on HFMD generally and not specifically on any viruses such as Human Enterovirus 71 (HEV71) or Coxsackie viruses. The objective of the research is to construct a simple mathematical model in order to:-

- predict the spread of HFMD in Sarawak in terms of number of infected persons;
- determine the duration of an outbreak when it happens; and
- determine factors that can help in preventing the outbreak.

1.3 Outlines

The dissertation is organized in the following way. Chapter 2 contains an overview of the history of mathematical modelling on infectious disease. In addition, Chapter 2 will discuss the classical ***SIR*** model. Chapter 3 will discuss on the steps taken to model HFMD which include the formulation of HFMD model and the differential equations involved in the model. Then we will discuss how the values for the parameters are determined and the initial values used for the model. Chapter 4 will discuss on the Runge-Kutta method used to solve the differential equations on the model. The numerical results are also included in the same chapter. In Chapter 5, the discussion is on the analysis of the model. First we will use the steady state to analyze and then we will use the actual data obtained from the Sarawak Health Department. We will state the conclusion and future works in Chapter 6.

2 LITERATURE REVIEW

2.1 A Brief History of Mathematical Modelling

Bailey (1975) gives a detailed description on the history of mathematical modelling for disease. It states that Daniel Bernoulli in 1760 initiated the application of mathematics to the study of infectious disease. Bernoulli used a simple mathematical model to evaluate the effectiveness of the improvement of variolation to protect against smallpox infection. However, their impact on public health policy and planning for the prevention of infection and associated disease has been rather limited at that time. According to Caldwell (2004) this is due to the lack of understanding of the mechanism of infectious spread. And so the development of mathematical models of infectious disease took a setback. Only after the increased understanding of contagious disease, did mathematical theories developed much faster.

According to Bailey (1975) the origins of modern theoretical epidemiology owe much to the work of Hamer (1906), Ross (1911) and Kermack & McKendrick (1927). Hamer introduced the concept of "*mass action*" for the transmission of directly transmitted viral and bacteria infections. It is one of the most important concepts in mathematical epidemiology. According to the concept, the course of an epidemic depends on the rate of contact between susceptible and infectious individuals and is proportional to the product of the densities of susceptible and infectious persons. The concept was originally formulated in a discrete-time model, but in 1908 Ronald Ross translated the problem into a continuous time framework. In 1927, Kermack and McKendrick explored in more detail the concept of Hamer and Ross and introduced the compartmental and deterministic model. Their model became a basic mathematical model for modelling infectious disease.

However the model was only fully explored later in the century. With the increased and availability of the processing power of computer various models have been introduced and developed for infectious disease (Keeling M. J., 2005; Keeling M. , 2006). Mathematical models have been developed for malaria disease, SARS, HIV and FMD (Brauer, 2005; Keeling & Rohani, 2007).

2.2 Mathematical Model of Infectious Disease

Generally mathematical modelling is defined as the process of creating a mathematical representation of some phenomenon in order to gain a better understanding of that phenomenon (Mathematical Modeling, 2006). The phenomenon could be population growth, heat flow or in this project the spread of disease. As summarized by Keeling & Rohani (2007) a mathematical model is a model that is able to describe and represent a system using the language of mathematics. Mathematical model of infectious disease is an attempt to use equation systems to represent elements of the dynamics of infectious processes involving agent, host, and environment (Barreto, Teixeira, & Carmo, 2006). To conclude, mathematical modelling of infectious disease is described as a process of representing the disease using the language of mathematics. In the process of modelling the disease, one has to find the relationship between all the elements in the dynamics of the disease and relate them in mathematics equations.

Four steps to mathematical modelling (Mathematical Modeling, 2006) are:

1. Identifying the problem.
2. Stating the assumptions and start with a simple model.
3. Identifying variables and constants and their relationships.

4. Developing the equations that express the relationship between the variables and constants.

Trottier & Philippe (2001) conformed to the steps in mathematical modelling by rewording and rearranging the four steps to understanding the disease as the first step. Understanding the disease would mean recognizing the duration of the period of infectivity, the incubation period if any, and the immune status after infection. The second step is the collection of data on the demographic, epidemiologic and biologic characteristics of the infection (transmission rate) and the population birth and death rates. The third step is to choose a simple model that fits the descriptions from the previous step. Finally, the last step is the formation of the equations of the model. For building our HFMD model, we will use the four steps highlighted above. This will be discussed in the following chapter.

From the description of the steps in mathematical modelling, it can be seen that assumption is an important step in modelling the spread of disease. As Keeling & Rohani (2007) puts it, a model is a conceptual tool that explains how an object or system of objects will behave. In order to do that, the system has to be simplified in order to be modelled. In the process, only the important aspects of the system are retained. This ensures a better understanding of the way the system works. In modelling a disease we need to make assumptions about (Britton, 2005):-

- The population affected
- The way the disease is spread; and
- The mechanism of recovery from the disease.

However the simplifications also have their downsides. The model might be too simple to be able to mimic the real thing. It is difficult to determine how simple a model should be or

even how complex it should be. This is also agreed by Keeling & Rohani (2007) who in their writing stressed on the 'usefulness' of mathematical modelling based on three and yet conflicting elements: accuracy, transparency and flexibility. It also emphasized that by definition all models are "*wrong*" as they make some simplifying assumptions in even the most complex models. It summarized that it is difficult to determine which model is "*right*" because of the assumptions that were made. It stressed that what is important is that the model is able to capture the essential features of a system.

It is the same with infectious disease. There are many factors that can contribute to the spread of the infectious disease. Some assumptions have to be made in the process to model the spread of the disease. Although it might not seem real, the model will be able to help in understanding the disease better and in the end might help in preventing the spread of the disease.

2.3 What mathematical models can do

As mentioned earlier, mathematical models can be used to help predict the spread of infectious disease. They can be used to predict the development and spread of disease (Caldwell, 2004). In other words the model will be able to predict the number of infected persons during an outbreak and the duration of the outbreak when it occurs. Keeling & Rohani (2007) mentioned that models have two distinct roles namely prediction and understanding; with the previous being the most obvious. Keeling M. (2006) listed four mains area that models can contribute; i.e. planning, prediction, detection and understanding. In prediction, models would enable:

- The prediction of the large population-level epidemic from single individual-level knowledge of epidemiological factors;

- The prediction of the long term behaviour from the early invasion dynamics; or
- The prediction of the impact of vaccination on the spread of infection.

The prediction from the model can be used to decide how resources such as medication, vaccination, and others can be used during an outbreak. For example, models can be used to determine a certain group of people for vaccination rather than all or whether total inoculation is necessary to stop the spread of a disease.

Well-parameterised and carefully constructed models can be a powerful public health tool. The prediction obtained from the model can help policy makers and health administration in doing their work more effectively. The goal in modelling disease transmission is to understand how to control it (Allman & Rhodes, 2004).

Model can be used to understand how various complexities affect the dynamics of the spread of the disease in the real world. The models provide epidemiologists with an ideal world in which individual factors can be examined in isolation and where every aspect of the disease spread can be recorded in perfect detail. Examples given by Keeling & Rohani (2007) are the effects of variable numbers of partners on the spread of sexually transmitted diseases and the effects of increased transmission between children during school terms. Experimentation and testing theories can be done using mathematical models (Hethcote, 2000; Thieme, 2003). It can be used to plan, implement, evaluate and optimize various detection, prevention and control program for a particular disease. The model can be used to explore how a situation may develop in response to different interventions. These can be done by changing the parameters' values and estimating key parameters from data. Models can be used experimentally to test a wide range of

control strategies and outbreak scenarios without any risks associated with testing during a real epidemic (Keeling M. J., 2005).

Barreto, Teixeira, & Carmo (2006) agreed that mathematical models of infectious disease is a powerful tool for understanding, for predicting situations and even for evaluating the potential capacity of certain interventions to change the likelihood of new cases occurring. The ability of model in predicting and understanding the dynamics of the disease is also acknowledged by Murray (2002) and the models have the ability to pose possible means of control of the disease. However it stressed that the difficulty in transforming the complex situations involved in the process of transmission of many infectious agents into mathematical models is a limitation to their use in many situations. For this Keeling & Rohani (2007) stressed that only by building from simple to a more complex models that the rich complexities and dynamics that are observed in the real world can be understood. That is the approach that we are taking as this is an initial mathematical model on HFMD.

Besides predicting the spread of the disease and understanding the dynamics of the disease, the model can also be used as a guide to data collection. Trottier & Philippe (2001) explains that modelling can guide the collection of data towards further understanding and design programs for the control of the disease. Although one of the steps in building the model is collection of data, sometimes the initial data collected may not be suitable for the use of the model. Then the process of data collection has to be repeated. With the model, the process will be easier as now we will know precisely what type of data need to be collected.

It should be stated clearly that models have their limitations. Models will not be able to predict precisely the course of the epidemics nor who will be infected. To quote the following from Keeling M. (2006):

Models will never be able to accurately predict if, or when a particular person, farm or community will become infected. This is for two reasons:

- *The transmission of infection is a stochastic process, such that no two epidemics are identical;*
- *Models will always be an approximation, and rare or unforeseen behaviour events can have a significant impact on the disease dynamics.*

According to Keeling & Rohani (2007) a good model should be suited to its purpose; namely a model designed to help to understand the behaviour of an infectious disease should concentrate on the characteristics that are of importance while simplifying others. A model built for accurate prediction should provide a comprehensive picture of the full dynamics and include all the relevant features of the disease and host. The art of creating a good model is deciding which of the disease features are important to capture the right dynamics and which can be omitted to prevent the model from becoming too complicated to analyze (Allman & Rhodes, 2004). Caldwell (2004) stated that different models will be applied to different cases. So it can be said that a good model is context dependent.

2.4 Types of Mathematical Models

Deterministic model or compartmental model is the most basic or classical mathematical modelling. It is most useful when modelling for a large population and the total population is taken to be constant. In the deterministic model, the populations are grouped into different

compartments depending on their status with regard to the infection under study. The population can be divided into distinct classes using a string of letters that provides information about the model structure. For example, a model with the population divided into the susceptible (***S***), the infected (***I***), and the recovered (***R***) are known as ***SIR*** model. Later, classes such as exposed (***E***) are introduced which brings out the ***SEIR*** model. ***SIS*** (or an ***SIRS***) model are used when susceptibility can return after infection (or after loss of immunity). The susceptible (***S***) are the population who do have the disease and can catch the disease if they come into contact with infected person. The infected (***I***) are the population who have the disease and can transmit the disease. The recovered (***R***) are those who have recovered from the disease and are immune to the disease. The exposed (***E***) are those who have caught the disease but are not infective. They are in their latent period. Britton (2005) introduced Carrier (***C***) which refers to individuals who remain infectious for a long time but do not show any symptoms of the disease themselves.

It is important to identify the problem first as mentioned in the steps of mathematical modelling. By identifying the problem means understanding the disease. In order to understand the disease it is invaluable that the definition used in medical terms must be understood properly. For the definition of the terms used in mathematical modelling of infectious disease, refer to Barreto, Teixeira, & Carmo (2006) and Moghadas (2006).

The term incubation and latent period might overlap each other as shown in Figure 1.

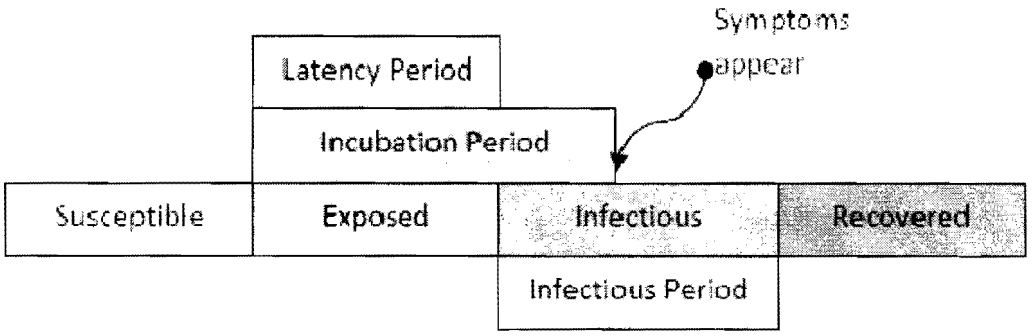


Figure 1: The relationship of latency, incubation and infectious periods to the dynamics of the disease. **(Epidemiology Simulations)**

Barreto, Teixeira, & Carmo (2006) also stressed on the importance of incubation period and latent period. Incubation period is the interval between the effective exposure of the susceptible host to an infectious agent and the appearance of signs and clinical symptoms of the disease in that host. However during the period of incubation, the host can be infectious as shown in figure 1. Most mathematical models ignore the incubation period when the duration is just a few days (Murray, 2002). Latent period is the time from infection to onset of the ability to infect. Some of the diseases such as HIV and tuberculosis have a very long latent period.

A combination of models can be derived from the classes based on the characteristics of the disease. Model such as ***SI***, ***SIS***, ***SIR***, ***SEIR***, etc can be used to model a disease. ***SI*** model only involve susceptible group and infected group whereas ***SIS*** model involves the infected going back to being susceptible after leaving the infected class. As for ***SIR***, the infected will recover and be removed. For ***SEIR***, it is used to model the diseases that have a latent period. The structure of the different types of deterministic models can be seen in Figure 2.

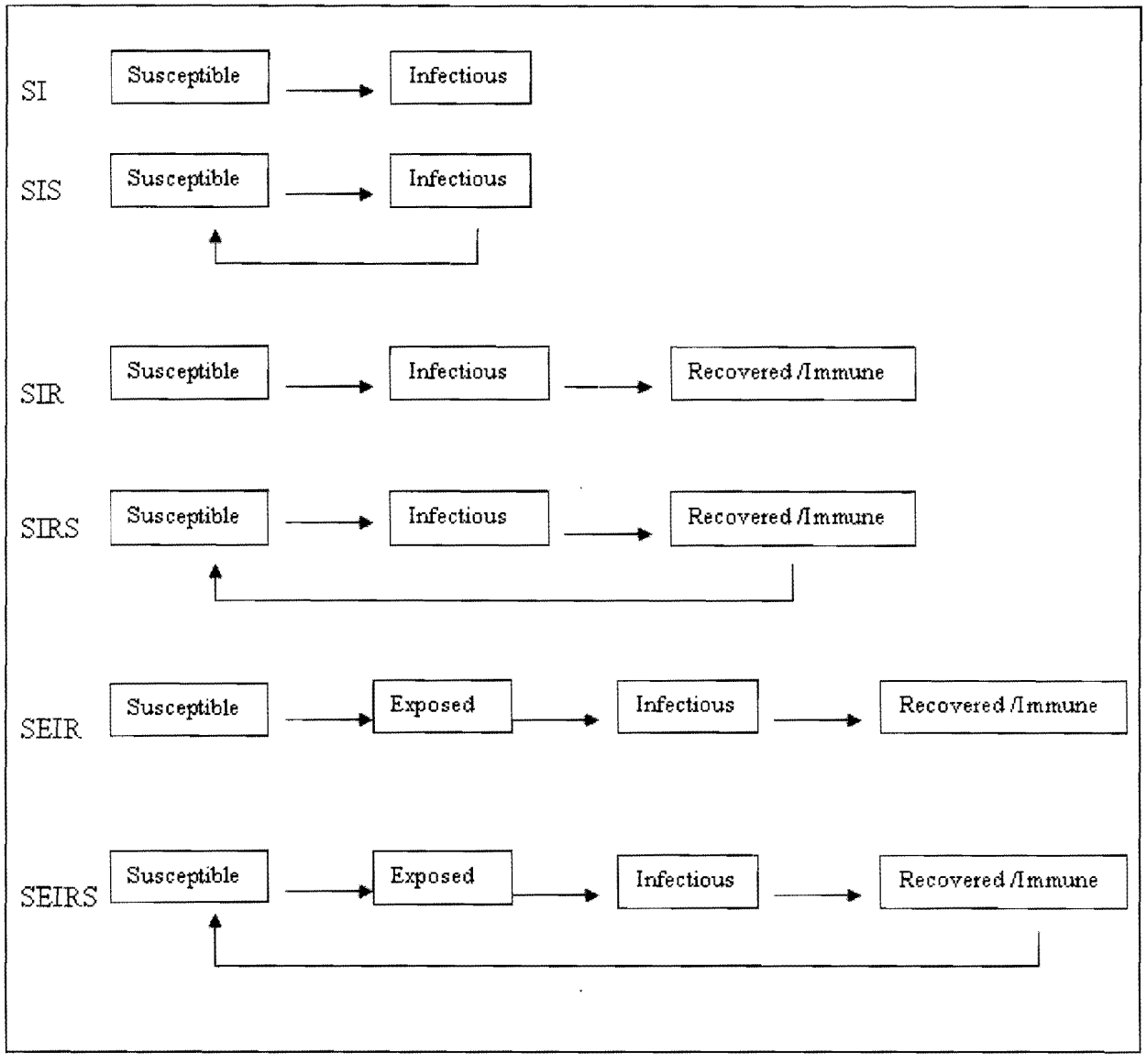


Figure 2: Some of the common models used in infectious disease modelling

(Trottier & Philippe, 2001)

2.5 *SIR* Model

SIR (***S***usceptible-***I***nfected-***R***ecovered) model is considered a classical model. The ***SIR*** model is a good starting model that can be refined as needed for particular diseases (Allman & Rhodes, 2004). The classical ***SIR*** model is a close model where the total population is kept

constant. There is no birth or death in the population. It is also known as compartmental as it divides the population into groups based on their current status with relative to the disease. The population is divided into three groups known as the susceptible (***S***), the infected (***I***) and the recovered (***R***) as shown in figure 3.

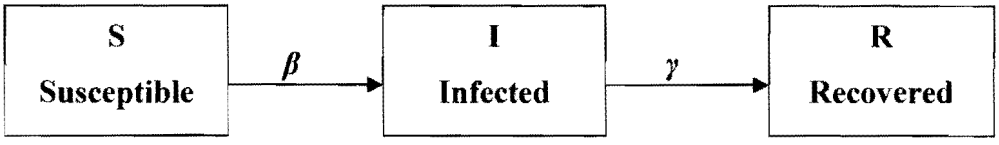


Figure 3: *SIR* model

A lot of literatures were written to explain the ***SIR*** model including Allman & Rhodes (2004), Bailey (1975) and Murray (2002) among others. They all give a very detailed definitions on terms used in the model. The susceptible (***S***) represents the population that can catch the disease. The infected (***I***) are those who currently have the disease and are contagious. The recovered (***R***) are those who have recovered from the disease and have immunity against the disease.

Looking at figure 3, the susceptible will move to the infected group when they contract the disease. The possibility of contracting the disease is represented by the parameter β (the parameter β will be discussed further in the section 2.6) which is known as the transmission coefficient or transmission rate. After a period of time of being infected, the person will move to the recovered group. This is known as the rate of recovery and is represented by γ (the parameter γ will be discussed further in the section 2.6). The original model was used to model contagious illness in a closed population over time.

The ***SIR*** model makes the following assumptions (Weisstein, 2004):

- the population size is fixed;
- there is no births and no deaths due to disease, or death by natural causes;
- there is no incubation period;
- the duration of infectivity is the same as length of the disease; and
- the population is completely homogeneous with no age difference, spatial, or social structure.

Clearly from Figure 3 and using the mass action principle, when the susceptible meets the infected, a certain number of susceptible will contract the disease after a certain time. As a result the number of susceptible will be reduced. Thus, the rate for the number of susceptible; $\frac{dS}{dt}$ is represented by $-\beta SI$ where the negative signify the movement away from the group, thus reducing the total number of susceptible. This is based on the *mass action* principle where the number of infected is proportional to the product of the densities of susceptible and infectious persons. The group of infected will then moved to the infective groups. So, the infective group will increase and the rate is represented by βSI at time t. Similarly, some of the infected will recover and move to the recovered group with the rate of recovery, γ. The rate for the number of infected who will recover is represented by $-\gamma I$ in which the negative sign means a reduction from the group. Thus, the rate for the number of infective; $\frac{dI}{dt}$ at time t is $\beta SI - \gamma I$. Whereas, the rate for the number of recovered; $\frac{dR}{dt}$ is represented by γI at time t.

Based on the brief descriptions above, the governing equations for each compartment can be established. A system of three coupled nonlinear ordinary differential equations is thus obtained:

$$\frac{dS}{dt} = -\beta S(t)I(t) \qquad \text{Equation (1)}$$

$$\frac{dI}{dt} = \beta S(t)I(t) - \gamma I(t) \qquad \text{Equation (2)}$$

$$\frac{dR}{dt} = \gamma I(t) \qquad \text{Equation (3)}$$

Where t is time, $S(t)$ is the number of susceptible people, $I(t)$ is the number of people infected, $R(t)$ is the number of people who have recovered and developed immunity to the infection, β is the transmission coefficient or transmission rate, and γ is the recovery rate. $\frac{dS}{dt}$, $\frac{dI}{dt}$ and $\frac{dR}{dt}$ are the rate of change for the number of each of the respective groups. In this model, the susceptible will become infected. From being infected, the infected will go to the recovered class.

SIR models have been used to model foot and mouth disease in the UK to determine the suitable measures to control the disease (Britton, 2005).

2.6 Critical Parameters and Threshold Values of SIR Model

In the ***SIR*** model, two parameters were introduced. The first is the β which is known as the transmission coefficient or the transmission rate. Callahan (1996) explains the meaning of transmission coefficient as the effective contact of the susceptible with the infective. Effective contact refers to the contact that resulted in contracting the disease. The transmission coefficient is determined by the product of the chances of the susceptible meeting the infective with the probability of contacting the disease when the susceptible meets the infective.

If we assume a = chances of the susceptible meeting an infected per day; and

$\boldsymbol{p}$ = the probability of the contacts leading to new infections

Then the transmission coefficient; $\beta = \boldsymbol{a} \times \boldsymbol{p}$.

As such the transmission coefficient depends on the general health of the population and the level of social interaction between its members.

Once infected, recovery is just a matter of time. If an infection has an infectiousness of three days, it means that an infected person will recover after three days. Looking at the whole infected population, there will be those who were just infected, some had been infected for two days and some for three days. Those that were infected for three days will recover today. As there is no definite information about all the groups, they are assumed to be of the same size. Based on that, $\frac{1}{3}$ of the infected population will recover everyday. So, for the parameter γ, if an infection has an infectiousness of k days, then every day there will always be some of the infective who will recover from the illness and thus not able to infect any other susceptible. Thus, the rate of recovery is represented by $\gamma = \frac{1}{k}$ persons per day.

In their model, Kermack and McKendrick introduced a so-called epidemiological threshold. The threshold is known as reproductive ratio; $\boldsymbol{R_0}$. Since then, $\boldsymbol{R_0}$ has become the single most important quantity in epidemiology (Bailey, 1975; Allman & Rhodes, 2004; Barreto, Teixeira, & Carmo, 2006). $\boldsymbol{R_0}$ is defined as the expected number of secondary cases that would arise from the introduction of a single primary case into a fully *susceptible* population. Allman & Rhodes (2004) explains clearly how $\boldsymbol{R_0}$ is derived and its meaning.

Looking at equation (2) page 18, it can be seen that the rate of number of infected; $\frac{dI}{dt}$ will determine the size of the infected. The size of the infective increases when $\frac{dI}{dt} > 0$ and an

outbreak of the disease look evident. On the other hand, the infections is considered to be subsiding when $\frac{dI}{dt} < 0$. Thus it is important to determine whether equation (2) is negative, zero or positive.

Rewriting equation (2):

$$\frac{dI}{dt} = \beta S(t)I(t) - \gamma I(t)$$

$$\boldsymbol{\frac{dI}{dt} = I(t)(\beta S(t) - \gamma)} \qquad \text{Equation (4)}$$

Clearly from equation (4), if $\boldsymbol{I(t)} = 0$ then $\frac{dI}{dt} = 0$. This is the natural course if the population is disease free. Then there will be no infections. Since for an infection to happen $\boldsymbol{I(t)} > 0$, this means that $\frac{dI}{dt}$ will be negative, zero or positive depending on what $(\beta S(t) - \gamma)$ is. As $\beta > 0$, then it can be rephrased that

$$If\ S(t) > \frac{\gamma}{\beta}, then\ \frac{dI}{dt} > 0.$$

$$If\ S(t) = \frac{\gamma}{\beta}, then\ \frac{dI}{dt} = 0.$$

$$If\ S(t) < \frac{\gamma}{\beta}, then\ \frac{dI}{dt} < 0$$

In order to establish the definition of the basic reproductive number; $\boldsymbol{R_0}$, it is convenient to rewrite equation (4) again:

$$\boldsymbol{\frac{dI}{dt} = \gamma\left(\frac{\beta}{\gamma}S(t) - 1\right)I(t)} \qquad \text{Equation (5)}$$

to compare the quantity of $\frac{\beta}{\gamma}S(t)$ with 1. Mathematical epidemiologists have called this quantity, $\frac{\beta}{\gamma}S(t)$ as the *basic reproductive ratio.*

$\boldsymbol{R_0}$ determines the numbers of people infected by a single infected person before his death or recovery. An infected person will infect less than one person before dying or recovering, when $\boldsymbol{R_0} < 1$. When this happens, the spread of the disease will phase out ($\frac{dI}{dt} < 0$). The infection will not continue as each successive generation will be smaller than its previous generation. When $\boldsymbol{R_0} > 1$, an infected person will infect more than one person, so the epidemic will spread and eventually becomes an outbreak ($\frac{dI}{dt} > 0$). The disease will spread initially as the successive generation will be larger than the previous generation. Luckily, this increase does not continue indefinitely. This is because the infection process reduces the number of susceptible, and thus reduces the probability that an infectious individual contacts a susceptible within its period of infectiousness. When $\boldsymbol{R_0} = 1$, the epidemic will become an endemic in the population as every infected person will infect one person before recovering.

So $\boldsymbol{R_0}$ is the key element in the infectious disease transmission dynamics. Some called it the threshold value. Based on the definition of $R_0 = \frac{\beta}{\gamma}S(t)$, it reveals that R_0 depends on the rate of contact between individuals, the probability of transmission during the contact and the time for which an infected person remains infective.

These are the components that can be used to control the disease from spreading. For example; isolation and quarantine reduces the rate of contact; hygiene measures and drug treatment reduce the probability of transmission. Drug treatment also reduces the length of

infectious period. Vaccination can help by reducing the number of susceptible by directly transferring the susceptible to the recovered class without going through the infected class.

2.7 Clinical Characteristics of HFMD

The following is a summary on the clinical characteristics of HFMD taken from multiple studies done on HFMD. Only the essential features of HFMD that are taken into account for modelling purpose are summarized here.

HFMD is caused by a group of viruses called enteroviruses or commonly known as gut-viruses as they multiply in the gut (Lim, 2008). This group of enteroviruses include Coxsackie virus (A16), human enterovirus (HEV71) (Hand, Foot and Mouth Disease, 2007) and Coxsackie virus A (CAV) 4, 5, 9 and 10 and Coxsackie virus B (CBV) 2 and 5 (Ooi, et al., 2007) (Hand, Foot and Mouth Disease, 2006). A person who is exposed to HFMD viruses will exhibit the symptoms after three to seven days (Hand, Foot and Mouth Disease, 2007).

Fever is usually the first symptoms of HFMD followed by poor appetite, malaise and sore throat. One or two 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 (Hand, Foot and Mouth Disease, 2007). The name of the disease - hand, foot and mouth disease (HFMD) – is descriptive of the organs that are commonly affected in the disease as described earlier (Lim, 2008).

HFMD is considered moderate to highly contagious with nearly 100% infection among children (Soal Jawab Penyakit Tangan, Kaki dan Mulut (HFMD) Bersama Ketua Pengarah Kesihatan, 2006). A person is most contagious during the first week of the illness. As the

viruses are present in the throat and stools of an infected person, infection generally occurs via the faecal-oral or via contact with skin lesions and oral secretions (Nerv, 2007). The virus may continue to be excreted in the stools of infected persons up till one month. The spread of the virus does not involve any vectors (Hand, Foot and Mouth Disease, 2007).

At the moment there is no specific antiviral drug to cure HFMD (Hand, Foot and Mouth Disease, 2007). 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 to 10 days (Hand, Foot and Mouth Disease, 2007; Soal Jawab Penyakit Tangan, Kaki dan Mulut (HFMD) Bersama Ketua Pengarah Kesihatan, 2006).

There is no permanent immunity against HFMD as the disease is caused by a group of viruses (Hand, Foot and Mouth Disease, 2007) 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. For a summary on the information of HFMD issued by the Health Ministry of Malaysia refer to Appendix F.

Based on the characteristics of HFMD we decided to use the ***SIR*** model. The reason for this is because HFMD does not exhibit latency in their course of infection. Additional to this is ***SIR*** model is a simple model but effective in modelling of infectious disease. However some necessary modifications are made to the classical ***SIR*** model to incorporate the characteristics of the disease better. The formulation of the HFMD model is further described in the next chapter.

2.8 Related Works

Recent outbreak of HFMD in countries such as China, Taiwan, Western Australia and Singapore had brought the world's attention to HFMD due to complications of death related cases. However, most of the researches done were specifically focused human enterovirus 71 (HEV71). Chang, et al., (2002) and Chen, (2007) researched on HEV71 in Taiwan while McMinn, et al., (2001) did a phylogenetic analysis in Western Australia, Singapore and Malaysia regarding HEV71. Chan, et al., (2003) studied HEV71 in Singapore while Chong, et al., (2003) studied HFMD in general in Singapore. Studies done by Ooi, et al., (2007) and Podin, et al., (2006) on HFMD in Sarawak were also focused on HEV71 except for Chan, et al., (2000). It can be said that most of the existing studies on HFMD were of clinical aspects based on HEV71 and not on HFMD in general. These studies did not reveal anything regarding the transmission coefficient and the immunity against HFMD which in our research revealed the importance of these two variables in understanding the dynamics of HFMD.

The study done by Ooi, et al. (2007) revealed that the victims of HFMD were between the ages of 0.5 to 5.9 years with the mean of 1.7 years while Podin, et al. (2006) revealed that the victims were between the ages of 18 days to 155 months with the mean of 32.2 months. These studies did not truly revealed the true age of the susceptible groups. Even though the results may mean that the susceptible group might only be children below the age of four or younger, we still maintain the susceptible group as children below the age of ten as all the studies are not conclusive regarding the age of the susceptible. In addition, Sarawak Health Department issued warning in which it is stated that the susceptible are those below the age of ten years old.

On the mathematical modelling side, Wang & Sung (2004) used the SIR model to analyze the association between the weather and the occurrence of enterovirus complicated

severe cases in Taiwan. The model was based on transformation function of seasonal factors in order to determine the transmission coefficient. Urashima, Shindo, & Okabe (2003) attempted to establish nonlinear mathematical models in order to simulate the incremental effects of global warming on HFMD incidences in Tokyo. The two models tried to find the relationship between the outbreaks of HFMD with the weather patterns in the respective countries.

3 FORMULATION OF HFMD MODEL

3.1 Understanding and Identifying the Problem

In section 2.7 we have described and identified the essential features of the characteristics of HFMD that we will use to model the disease. To summarize some of the essential features:-

- HFMD has an incubation period of three to six days;
- HFMD does not have a latent period;
- Recovered individuals are still susceptible to HFMD;
- At the moment there is no cure and an infected individual will fully recover in seven to ten days time; and
- No vector is involved in the spread of the disease.

Besides the essentials features listed above, there is still a lot of work that need to be done in order to fully understand the dynamics of HFMD. These can be achieved by building a mathematical model for HFMD. As reviewed in Chapter 2, mathematical model can be used to predict the spread of the disease and also to understand the dynamics of HFMD. It is crucial for the authorities to be able to predict the number of infected and the duration of the outbreak when it happens. By understanding the dynamics of the disease through mathematical model, we will be able to determine the essential parameters that can help in curbing the spread of the disease. These are problems that we hope to solve by building the HFMD model.

3.2 Characterization of the System

Based on the essential features of HFMD discussed in the previous section, the simplest model to model the HFMD is the ***SIR*** model with the possibility of the recovered going back to become susceptible. The model takes into account the natural birth and death of the population

as compared to the classical ***SIR*** in which the population is considered to be closed. Thus the model that is employed is ***SIRS*** in which the recovered experience the loss of immunity and return to the susceptible class. The model is modified from Hudson (2002) and Keeling & Rohani (2007). The model is shown in Figure 4.

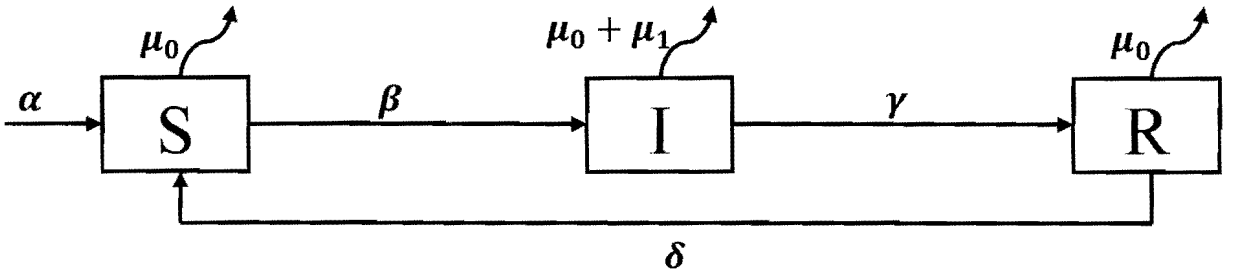


Figure 4: The HFMD model

The number of the susceptible in the ***S*** class increases through natural birth and also through recovered individuals who have lost their immunity against the disease. The rate of natural birth is the product of the per capita natural birth rate (α) with the total number of susceptible per unit time. In the model we assume that only the susceptible class experience natural birth. The rate of recovered individuals who have lost their immunity is the product of the rate for the lost of immunity (δ) with the number of recovered in class ***R***. At the same time, individuals in ***S*** class also experienced natural death. The number of individual that die due to natural death is the product of the natural death rate (μ_0) with the number of susceptible per unit time.

A susceptible person will move to the infected class (***I***) when he or she is infected with the disease even though the symptoms have not appeared. Using the "mass action" principle (Allman & Rhodes, 2004), a person will be infected through contact with an infective person.

The number of infected is the product of transmission coefficient (β) with the number of susceptible and the number of infected per unit of time. The infective class not only experienced natural death but also death due to HFMD. The number of infected individuals that will die is the product of the total of natural death rate with the rate of death due to HFMD ($\mu_0 + \mu_1$) with the number of infected. As HFMD has an incubation period of three to six days which is considered short, this duration is ignored (Murray, 2002). In the model, we assume that a person infected with the virus will automatically become infective and capable of transmitting the disease to a susceptible.

After a period of time, the infective will either be removed from the infective class due to death caused by HFMD or recovered. The number of infected who will recover from the disease is the product of the rate of recovery (γ) with the number of infected. For HFMD, an infected person will fully recover in seven to ten days.

An individual will have a short immunity or what is called as 'waning immunity' against HFMD after recovery. Once the immunity is loss, the individual returns to the susceptible class once more and is capable of being infected again. The rate is called the lost of immunity rate (δ). Some of the individuals in the recovered class will also die because of natural death. The number of death is the product of natural death rate (μ_0) with the number of infected in class $\boldsymbol{R}$.

To summarize for the HFMD model, the parameters involved in the model are:

- α; the natural birth rate;
- β; the transmission coefficient;
- γ; the rate at which an infectious individual recovers per unit time;
- δ; the rate at which a recovered individual loses its immunity;

- μ_0; the rate of natural death; and
- μ_1; the rate of death caused by the disease.

The following assumptions were made in order to model the HFMD disease.

- That individuals are uninfected at birth (Hand, Foot and Mouth Disease, 2007);
- That newly infected hosts can transmit the disease immediately (Murray, 2002);
- There is no intervention to prevent the disease from spreading;
- The susceptible group is only made up of children below the age of ten years old (Hand, Foot and Mouth Disease, 2007);
- Individuals mix at random within the population (homogeneous) (Allman & Rhodes, 2004);
- Age and sex of the individuals are not crucial variables (Allman & Rhodes, 2004);
- That infections occur randomly in proportion to the density of susceptible and infected individuals and the transmission coefficient; β.
- The model is deterministic where all the parameters take on constant values (Trottier & Philippe, 2001).

3.3 Formulation of the equations

From Figure 4, we can see that the number of susceptible in the S class increased per unit of time through natural birth and also through the recovered individuals who have lost their immunity. At the same unit of time, the number of susceptible in S class also decreased through natural death and through being infected. So the rate of change for the number of susceptible in S class per unit of time can be represented by

$$\frac{dS}{dt} = \alpha S(t) - \beta I(t)S(t) - \mu_0 S(t) + \delta R(t)$$

The number of infective in ***I*** class per unit of time increased through the conversion of the susceptible into the infective when they are infected. That number will decrease due to recovery from the disease or through natural death and death due to HFMD. The equation that relate all the parameters together for the rate of change for the number of infected in ***I*** class is

$$\frac{dI}{dt} = \beta I(t)S(t) - \gamma I(t) - (\mu_0 + \mu_1)I(t)$$

When the infective recovered from the disease, they will move to the recovered class. That is why the number of recovered in ***R*** class will increase per unit of time. However as there is no lasting immunity for HFMD, the recovered will loss their immunity and move on to become susceptible. This will decrease the number of recovered in ***R*** class. Not forgetting also that the number of recovered will be decreased by natural death. The differential equation that governs ***R*** class is

$$\frac{dR}{dt} = \gamma I(t) - \delta R(t) - \mu_0 R(t)$$

To summarize, the differential equations that model the HFMD are as follows:

$$\frac{dS}{dt} = \alpha S(t) - \beta I(t)S(t) - \mu_0 S(t) + \delta R(t) \qquad \text{Equation (6)}$$

$$\frac{dI}{dt} = \beta I(t)S(t) - \gamma I(t) - (\mu_0 + \mu_1)I(t) \qquad \text{Equation (7)}$$

$$\frac{dR}{dt} = \gamma I(t) - \delta R(t) - \mu_0 R(t) \qquad \text{Equation (8)}$$

The system of equations (6) – (8) governs the dynamics of the spread of HFMD. As anticipated, the system is coupled nonlinear ordinary differential equations.

3.4 Parameters and Initial Values

The fastest way to study the behaviour of the model is through numerical solution. In order to run such simulation, the parameters involve in the governing equations need to have values. Due to the fact that the data that is available from the Sarawak Health Department regarding the number of HFMD cases reported is collected on a weekly basis in the year 2006, the unit time in our model will be weekly as well. This needs to be consistent for analyses purposes.

As the data for the crude birth rate and crude death rate for the year 2006 is still not available at the time of this project, we use the crude birth and crude death rate from the year 2005 as estimates for the year 2006. According to Jabatan Perangkaan Malaysia (2006) the crude birth rate for year 2005 = 15.2 per 1000 and the crude death rate = 5.6 per 1000. The formula used to calculate the crude birth rate and crude death rate is as follow:

$$Crude\ birth\ rate = \frac{No.\ of\ live\ birth\ in\ year - t}{Mid - year\ population\ in\ year - t} \times 1000$$

$$Crude\ death\ rate = \frac{No.\ of\ death\ in\ year - t}{Mid - year\ population\ in\ year - t} \times 1000$$

As we are interested in a week as per unit of time and percentage as the indicator, the natural birth rate and death rate per week is obtained using the following steps.

$$\alpha = \frac{Crude\ birth\ rate/_{1000}}{52} \times 100\%\ per\ week$$

$$\alpha = \frac{15.2/_{1000}}{52} \times 100\%\ per\ week$$

$$\alpha = 0.02923\% \ per\ week$$

$$\mu_0 = \frac{Crude\ death\ rate/_{1000}}{52} \times 100\% \ per\ week$$

$$\mu_0 = \frac{5.6/_{1000}}{52} \times 100\% \ per\ week$$

$$\mu_0 = 0.01077\% \ per\ week$$

The fatality rate for HFMD = 0.9 per 1000 cases for the year 2006 (Hand Foot Mouth Disease Outbreak in Sarawak, 2006, 2007). The formula used to calculate the fatality rate is given below:

$$The\ fatality\ rate = \frac{No.of\ death\ recorded\ due\ to\ the\ disease\ in\ year - t}{Total\ population\ for\ the\ year - t} \times 1000$$

Thus to obtain the rate of death per week due to HFMD is

$$\mu_1 = \frac{The\ fatality\ rate/_{1000}}{52} \times 100\% \ per\ week$$

$$\mu_1 = \frac{0.9/_{1000}}{52} \times 100\% \ per\ week$$

$$\mu_1 = 0.001731\% \ per\ week$$

For the purpose of discussion, Sarawak Health Department did calculate the incidence rate for HFMD for the year 2006. Yet it should be stressed here that the incidence rate given is considered to be the probability of getting HFMD and not the transmission coefficient. This is due to the formula that is being used to calculate the incidence rate.

$$Incidence\ rate = \frac{The\ total\ number\ of\ cases\ reported\ for\ the\ year - t}{The\ total\ population\ in\ year - t} \times 100000$$

In this project we were not able to find any sources which have defined the value for the parameter of transmission coefficient for HFMD. The transmission coefficient used by Wang & Sung (2004) was estimated based on exponential transformation involving seasonal and ambient temperature. As our mathematical model is deterministic based, this method for obtaining the transmission coefficient is relevant. Therefore, we look for other diseases transmission coefficient value and try to see the similarity so as to make a better assumption on the value. Callahan (1996) wrote in his article that the transmission coefficient that he has provided for measles; namely 0.00001 is within the range of used in epidemic studies. As for other diseases, he equated the value with 0.00002. Allman & Rhodes (2004) provided some values ranging from 0.001 to 0.000035 for transmission coefficient of diseases without specifically mentioning the type of diseases. The range of values for the transmission coefficient existed as they depended on the number of susceptible that was involved. As HFMD is considered moderate to highly contagious with nearly 100% infection among children in Sarawak context (Soal Jawab Penyakit Tangan, Kaki dan Mulut (HFMD) Bersama Ketua Pengarah Kesihatan, 2006), and taking into account the perspective of the reproductive ratio, $\boldsymbol{R_0}$ for HFMD (Refer to section 5.2), we decided to estimate the transmission coefficient as 0.00015. We reached this estimated value after we had run a few scenarios for transmission coefficient with value less than 0.00015 and more than 0.00015. Thus;

$\beta = 0.00015$

As mentioned earlier, a victim of HFMD usually recovers in seven to ten days. Thus the average number of days required for a person to recover is 8.5 days. Taking the average of the duration of recovery period (Trottier & Philippe, 2002) and referring to the explanation in section 2.6, then

$$\gamma = \frac{1}{the\ period\ of\ infectiousness}\ per\ day$$

$$\gamma = \frac{1}{the\ period\ of\ infectiousness} \times 7\ per\ week$$

$$\gamma = \frac{7}{8.5}\ per\ week$$

$$\gamma = 0.8235\ per\ week$$

As HFMD is caused by a group of enteroviruses, a person who recovers from HFMD does not incur permanent immunity. The infection will result in immunity to the specific virus, but a second episode may occur following infection with a different virus belonging to the enterovirus group (Nerv, 2007). In the research done by Ooi, et al., (2007), they did acknowledge that there were cases where the victims had been hospitalized before due to HFMD.

Due to the fact that the rate for the loss of immunity, δ against HFMD is not known it is thus appropriate to vary the value δ. Using the same procedure for obtaining the rate of recovery to get the rate of loss of immunity against HFMD, then

$$\delta = \frac{1}{the\ period\ of\ immunity} \times 7\ per\ week$$

Thus;

$\delta = 0\ per\ week$; (Permanent immunity against HFMD)

$\delta = 7\ per\ week$; (Acquired immunity is 1 day (Wang & Sung, 2004).)

$\delta = 1\ per\ week$; (Acquired immunity is 7 days.)

$\delta = 0.07\ per\ week$; (Acquired immunity is 100 days.)

It will become apparent in the next chapter that, in order to model the spread of HFMD using the model, the classes S, I and R must have initial values. As children below the age of ten are more prone to be infected by the disease we assume the S class is made up of these children. However the data collected regarding the total population of Sarawak only have the total population for children below the age of nine years old. The next total population is for children below the age of 12 years old (Jabatan Perangkaan Malaysia, 2006). So, we decide to use the total number of population below the age of nine as the initial value for S. Therefore, the initial value of S is taken to be $S(0) = 550,700$.

As for the class I, we used the data taken from the Sarawak Health Department. At the beginning of 2006 outbreak, there were four cases reported initially. Thus, $I(0) = 4$.

Since at the beginning of an outbreak, it is assumed that nobody has recovered from the disease, thus, $R(0) = 0$.

Using all these parameters and initial values and substituting them into the system of equation (6) - (8), we run simulation test to obtain results on the HFMD model. The results and discussions are presented in Chapter 4.

4 NUMERICAL RESULTS AND SIMULATIONS

4.1 Numerical Method

As stated in section 1.2, the objective of the research is to construct a simple mathematical model which would be able to predict the number of infected persons during an outbreak of HFMD and to determine the duration of the outbreak. The mathematical model for HFMD that we had constructed in the previous chapter consisted of system of coupled nonlinear differential equations. In order to achieve the objectives of the research we need to solve the equations. We had also identified all the parameters that were required in order to solve the equations. As the equations consist of nonlinear differential equations, we use numerical method to solve the equations for the HFMD model.

The 4^{th} order Runge-Kutta method is chosen for the task. The main advantages of Runge-Kutta methods are that they are easy to implement, they are very stable, and they are "self-starting" (i.e., unlike multi-step methods, we do not have to treat the first few steps taken by a single-step integration method as special cases) (Fitzpatrick, 2006). 4^{th} order Runge-Kutta method is a numerical technique to solve ordinary differential equation (ODE) of the form

$y' = f(t,x), \quad y(a) = y_0$ (Otto & Denier, 2005)

by using weighted averages of slopes near a point instead of the single slope involved by following the tangent line at a point.

Let *[a: b]* be the interval over which an approximation to the solution is desired. (Thus $t = a$ and $t = b$ are the initial and final values of the independent variable, respectively.) Partition

this interval into N subintervals each of length $h = \frac{(b-a)}{N}$, called the step size. Let $t_0 = a$ and define

$$t_{k+1} = t_k + h, \quad for \ \ k = 0, 1, \dots, N-1.$$

Notice that $t_N = b$ and the other t_k so-defined are the interior endpoints of the subintervals. These collectively are the discrete values of the independent variable.

The initial value of the dependent variable is given by the initial condition, $y(a) = y(t_0) = y_0$. The others discrete dependent variable values are computed iteratively as follows.

$for\ k = 0\ to\ N-1$

$$s_1 = f(t_k, y_k)$$

$$s_2 = f\left(t_k + \frac{h}{2}, y_k + \frac{h}{2}s_1\right)$$

$$s_3 = f\left(t_k + \frac{h}{2}, y_k + \frac{h}{2}s_2\right)$$

$$s_4 = f(t_k + h, y_k + hs_3)$$

$$t_{k+1} = t_k + h$$

$$y_{k+1} = y_k + h\frac{s_1 + 2s_2 + 2s_3 + s_4}{6}$$

This method is also a single-step numerical solver since it depends only on data obtained from the preceding step. It is a fixed-step solver since the lengths of the subintervals of *[a; b]* are all equal.

The model consisted of systems of coupled nonlinear differential equations as described in section 3.3. The parameters values are constant value and the functions on the right ($\frac{dS}{dt}, \frac{dI}{dt}$ and $\frac{dR}{dt}$) are determined by the variables t and $(S(t), I(t), R(t))$. To use the Runge-Kutta method to solve the systems of coupled nonlinear differential equations, ($\frac{dS}{dt}, \frac{dI}{dt}$ and $\frac{dR}{dt}$)are put in a vector function. The function must return a column vector with three components as the right hand side has three parts. The transformation is shown in Appendix G.

MATLAB has ordinary differential equations (ODE) solver called *ode45* (fourth/fifth order), which implement Runge-Kutta methods (Hahn & Valentine, 2007). The function is chosen due to the fact that it is simple to use and the result are very accurate (Palm, 2005). The following numerical results are obtained by using the MATLAB function built in *ode45*. The examples of programming code used in *ode45* are shown in Appendix G.

4.2 Numerical Results

The following are the parameters and initial values that were discussed in section 3.4.

$\alpha = 0.02923\%$

$\mu_0 = 0.01077\%$

$\mu_1 = 0.001731\%$

$\beta = 0.00015$

$\gamma = 0.8235$

As discussed earlier the rate for the loss of immunity δ is unknown so for this project we will keep the other parameters at the values above and vary δ with the following values:

$\delta = 0\ per\ week$ (Permanent immunity)

$\delta = 7\ per\ week$ (Acquired immunity of one day)

$\delta = 1\ per\ week$ (Acquired immunity of seven days)

$\delta = 0.07\ per\ week$ (Acquired immunity of 100 days)

The numerical results for each of the cases above will be discussed.

4.2.1 Permanent Immunity ($\delta = 0\ per\ week$)

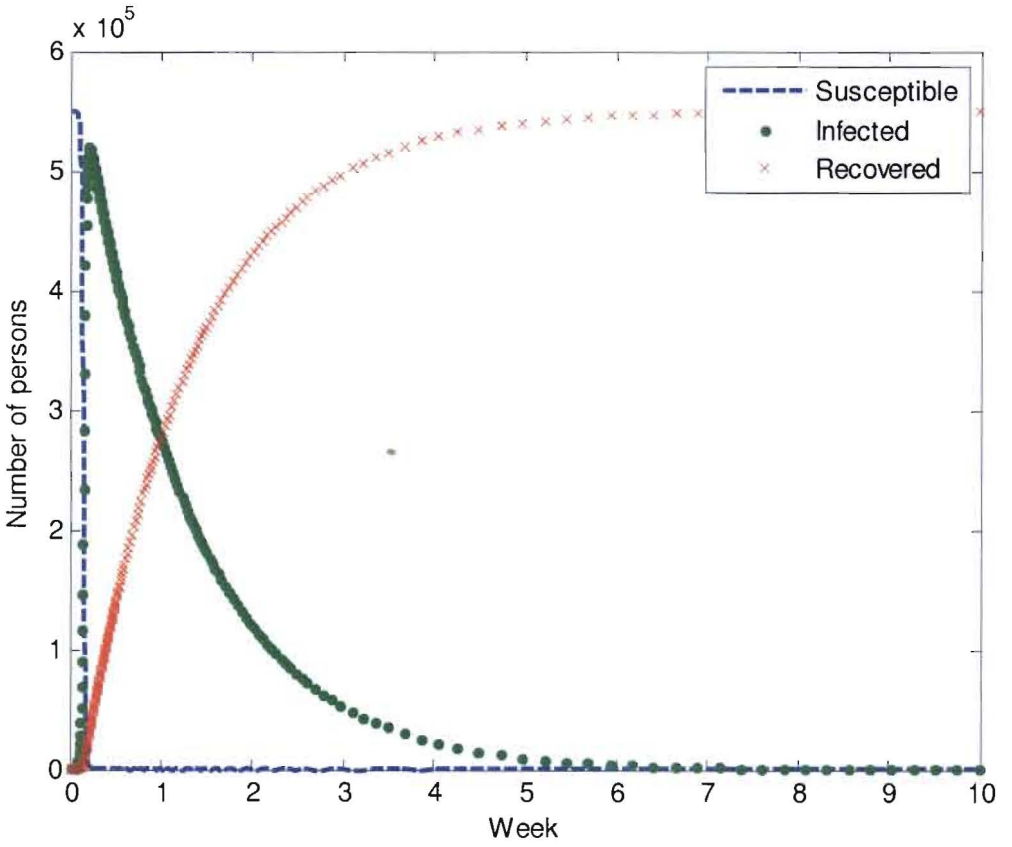


Figure 5: The result for HFMD model with $\boldsymbol{\delta = 0}$ or permanent immunity

The purpose of running the test with $\delta = 0$ is to show that recovered individuals do not have permanent immunity against HFMD. The result shows that in the long run the number of infected will decrease until 0.

This result is in accordance with the results for all the ***SIR*** models in which the models do not take into account the status of immunity (assuming permanent immunity). All the susceptible will be infected and moved to become recovered. However, this is not the case for HFMD. In Sarawak context, HFMD is endemic, meaning there is always cases of HFMD reported. The authorities and the public are occasionally reminded to take precaution against HFMD as reported in the newspaper in Appendix H.

As this result contradicted the actual situation; we can conclude that HFMD has no permanent immunity and that the case of HFMD with $\delta = 0$ (permanent immunity) is not possible. This is also due to the fact that HFMD is caused by a group of enteroviruses at mentioned in section 2.7. An individual who is infected and recovered from HFMD will acquire immunity against the specific virus but not against all the entroviruses. The individual is still susceptible to HFMD caused by other enteroviruses (Hand, Foot and Mouth Disease, 2006). Thus, it can be said that a recovered individual only acquired immunity for a certain period of time and is capable of being infected by HFMD again. The duration of the immunity however is not known and need further research. Following are the results for $\delta = 7\ per\ week$, $\delta = 1\ per\ week$ and $\delta = 0.07\ per\ week$. The reason for having δ as a variable is to try to find the most reasonable rate for the loss of immunity against HFMD from the mathematical modelling perspective.

4.2.2 Acquire Immunity for 1 day ($\delta = 7$ *per week*)

From the previous simulation, the mathematical model shows that HFMD do not have permanent immunity when comparing it to the real situation in Sarawak. As the exact value for the loss of immunity is unknown, we need to estimate the value for the loss of immunity. First, we will used the value proposed by Wang & Sung (2004), in which they estimated that the loss of immunity against HFMD is 1 days. Therefore, we simulate the mathematical model with $\delta = 7$ *per week* and the following results are obtained.

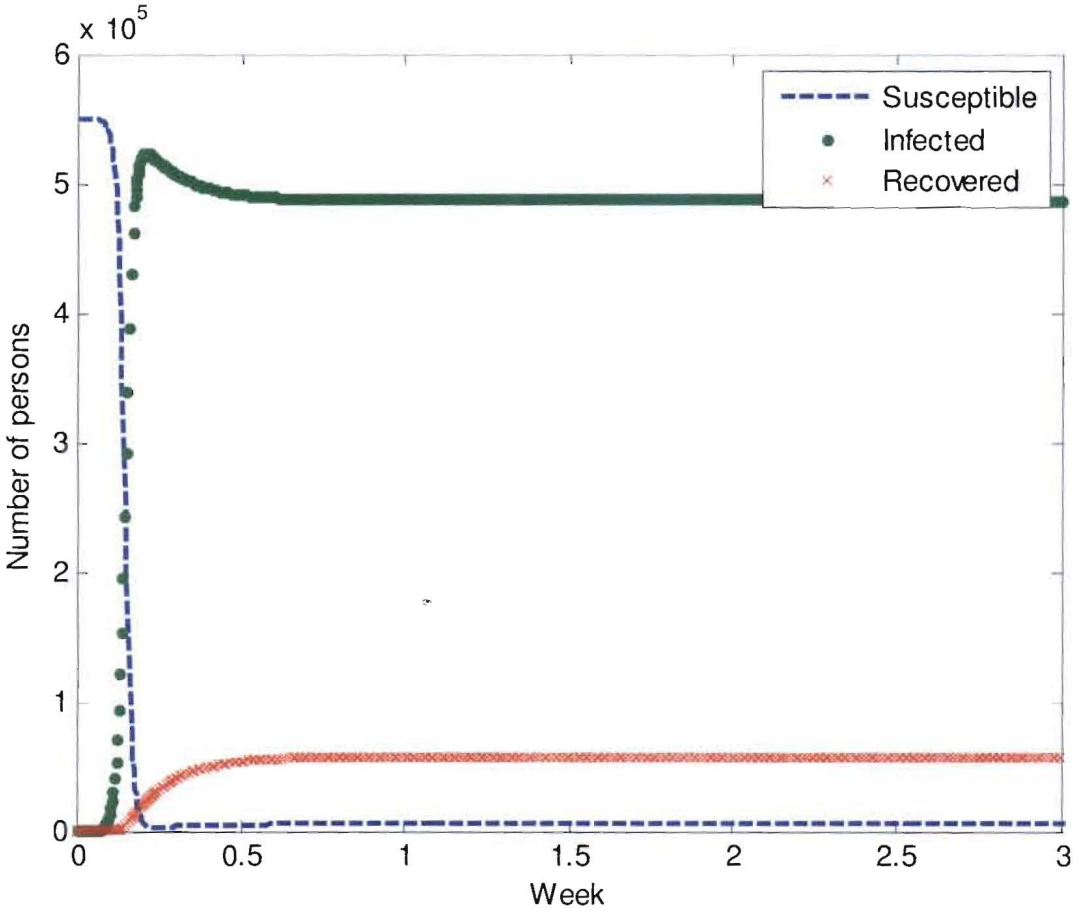


Figure 6: The results for HFMD model with $\delta = 7$ per week.

Figure 6 shows that HFMD is very contagious. In a period of less than half a week, the disease had infected almost everyone in the population. This is shown by the susceptible line which had gone down from 550,700 to almost zero during the period. This may seem unrealistic but the result is a mathematical projection where there are no preventive steps taken against the spread of the disease. Moreover during this same period, the infected population has reached its maximum as shown in the Figure 6 (Legend ●). Based on the graph, the susceptible, infected and recovered population will reach a steady state. By visual inspection, these states were achieved at approximately in less that a week time. The value obtained by numerical analysis for the infected population was at 487,500 after 3 weeks. In addition, there is no sign that the value will go down soon. These signified that the disease is still at an outbreak as the initial population taken into account is 550,700. Based on the simulation result, the disease is still in an outbreak stage for number of weeks to come as the infected line is still at a very big number and seemed to reach a steady state.

This may be due to the fact that every recovered person experienced lost of immunity in just 1 day. A faster replenishment of the susceptible pool existed and this provided the resources for the disease to spread. Therefore in this case, the outbreak of HFMD will not subside. We suspect that there exists an endemic eqüilibrium solution at limiting time.

4.2.3 Acquire Immunity for 7 days (δ = 1 per week)

In the previous simulation, we estimated the loss of immunity is 1 day. The result that was obtained did not portray the actual scenario as the disease continued to be on an outbreak with the number of infected at 487,500 even after three weeks. Therefore, we suspected that the period for the loss of immunity is more than 1 day. Next, we simulated the model with the loss of immunity of seven days, namely δ is one per week. The result is shown in figure 7.

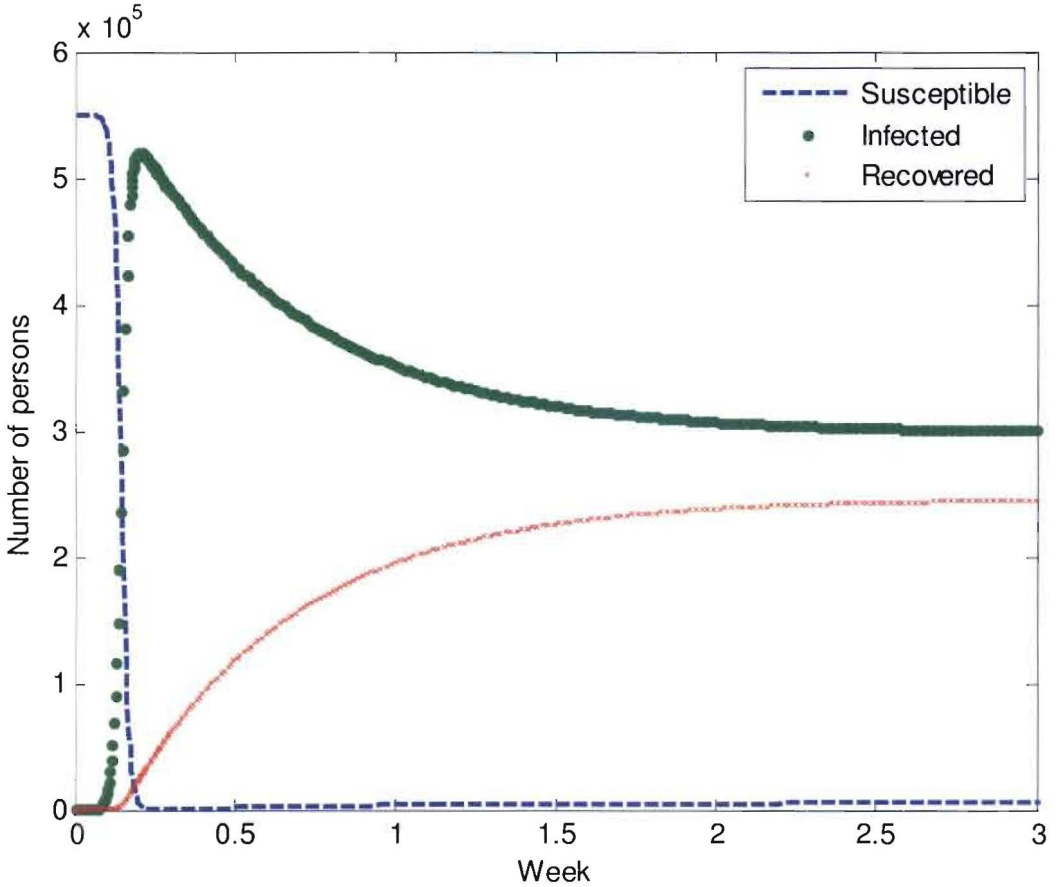


Figure 7: The result for HFMD model with $\delta = 1$ *per week*

Figure 7 also shows that HFMD is very contagious in Sarawak. According to the graph, the disease will infect almost everyone in less than half a week time. However, figure 7 shows that the outbreak lasted for about two weeks where the number of infected were reduced to about 300,000. However, the number of infected is still very high after three weeks in which the infected line seemed to reach a steady state. This may be contributed by the reason that the recovered returns to the susceptible class in seven days time which is still quite short. This again replenished the susceptible pool for the disease to spread. The significant thing is that by visual

inspection on the graphs, the steady state for the number of susceptible is the same for both Figure 6 and 7.

4.2.4 Acquire Immunity for 100 days ($\delta = 0.07$ *per week*)

From Figure 6 and 7, we learnt that as the period for loss of immunity increases, the number of infected decreases at limiting time. Thus, we suspected that the period for the loss of immunity might be longer and decided to simulate the result for the loss of immunity against HFMD as 100 days. (*The simulation result for acquired immunity of 50 days is shown in Appendix I*) So, with $\delta = 0.07$ per week, the following result was obtained and shown in figure 8.

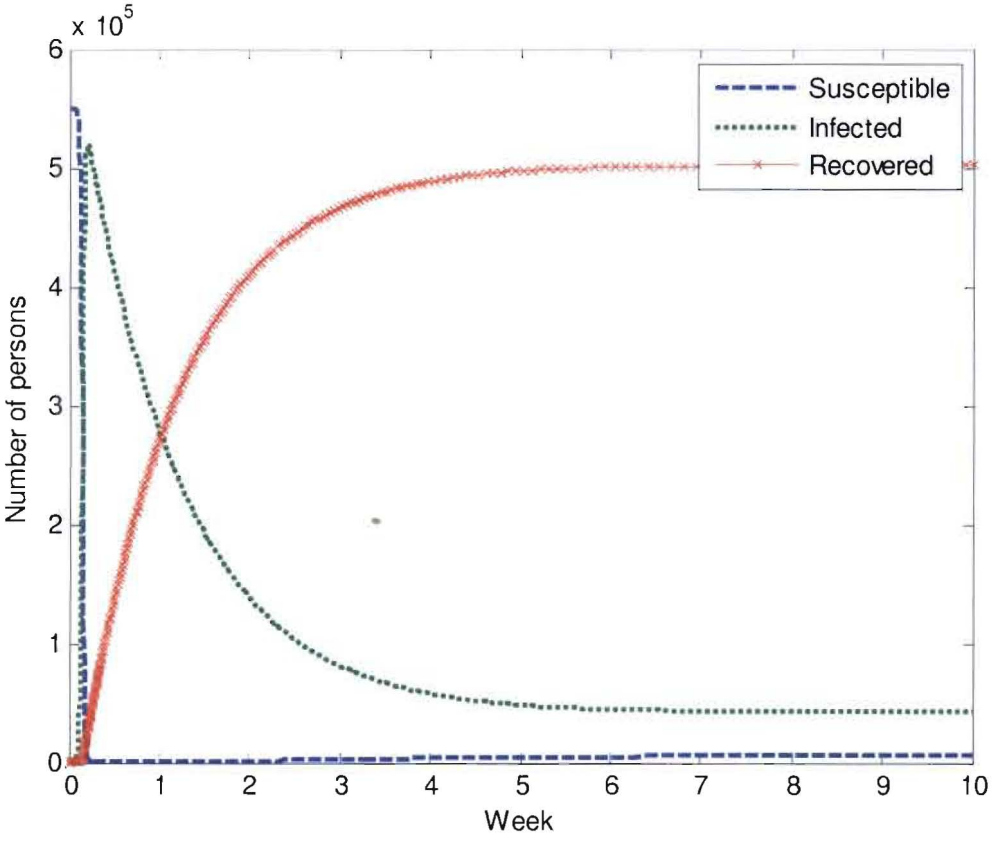


Figure 8: The result for HFMD model with $\delta = 0.07$ per week

Figure 8 also shows that HFMD is contagious. The number of infected also reached its maximum in less that a week time. Comparing figure 8 with figure 6 and 7, it can be seen that by the end of three weeks, the number of infected is smaller for $\delta = 0.07$ (loss of immunity = 100 days). The outbreak of the disease seemed to subside as the number of weeks increased. In figure 8, it shows that the disease has become endemic as compared to figure 6 and 7 in which the disease is still at an outbreak stage even after 3 weeks. Thus, we felt that the simulation in figure 8 is nearer to the dynamics of HFMD that is experienced in Sarawak in which there are constantly cases of HFMD disease reported even when the outbreak is over (Refer Appendix H). The spread of the disease is slowing down after about 7 weeks of outbreak. This can be seen in the number of susceptible, the infected and the recovered. The slope for all the three classes seems to be reaching 0.

The increase in duration for the lost of immunity to 100 days may have contributed to this effect. Based on the simulations results and comparing it to the general results of epidemic simulations (Allman & Rhodes, 2004) and the situation of HFMD in Sarawak, we believe that the duration for the immunity against HFMD after recovery is 100 days.

From all these results, we are able to conclude that the model can determine the number of infected at certain period of time. The duration of outbreak can also be determined using the HFMD model. The model also supported the clinical view that there is no permanent immunity against HFMD. The model provides a better understanding of HFMD in which the duration of the immunity affects the dynamics of the disease. It shows that HFMD is contagious if there is no step taken to curb the spread of the disease.

4.3 Critical Values

In order to determine the factors that can be used to curb the spread of the HFMD disease we need to recall back the concept of reproductive ratio, $\boldsymbol{R_o}$. $\boldsymbol{R_o}$ is defined as the number of secondary cases which will arise with the introduction of an infective individual into the population. We have look at how the concept is being used in section 2.6. Thus looking at equation (7) from section 3.3 and using the same idea in obtaining the basic reproductive ratio for the classical ***SIR*** model we obtain the following:-

$$\frac{dI}{dt} = \beta I(t)S(t) - \gamma I(t) - (\mu_0 + \mu_1)I(t)$$

$$\frac{dI}{dt} = I(t)[\beta S(t) - \gamma - (\mu_0 + \mu_1)]$$

$$\frac{dI}{dt} = I(t)[\beta S(t) - (\gamma + \mu_0 + \mu_1)]$$

$$\frac{dI}{dt} = \boldsymbol{I(t)(\gamma + \mu_0 + \mu_1)\left[\frac{\beta S(t)}{(\gamma+\mu_0+\mu_1)} - 1\right]} \qquad \text{Equation (9)}$$

Since $I(t) > 0$ and $(\gamma + \mu_0 + \mu_1) > 0$ then the behavior of $\frac{dI}{dt}$ is determined by how $\frac{\beta S(t)}{(\gamma+\mu_0+\mu_1)}$ behaves with respect to the value 1. Therefore, the mathematical model for HFMD in which natural birth, death and death caused by HFMD are taken into account, the reproductive ratio;

$$\boldsymbol{R_0 = \frac{\beta S(t)}{(\gamma+\mu_0+\mu_1)}} \text{ (Hudson, 2002)} \qquad \text{Equation (10)}$$

Analyzing R_0, we get three cases which will determine the direction of $\frac{dI}{dt}$:-

- If $\frac{\beta S(t)}{(\gamma+\mu_0+\mu_1)} < 1$ then $\frac{dI}{dt} < 0$. As the rate for the number of infected is less that zero, this means that the number of infected is decreasing and no new infections will occur. Thus the disease will eventually subside.
- If $\frac{\beta S(t)}{(\gamma+\mu_0+\mu_1)} = 1$, then $\frac{dI}{dt} = 0$. In this case, as the rate for the number of infected is zero, it means that the number of infected is at a constant value. Thus the disease will not spread further as the number of infected will not increase.
- If $\frac{\beta S(t)}{(\gamma+\mu_0+\mu_1)} > 1$, then $\frac{dI}{dt} > 0$. Since the rate for the number of infected is greater that zero this means that the number of infected is increasing. Thus the disease will spread and eventually become an outbreak.

Then by letting $\boldsymbol{R_0} = 1$ and rearranging the expression for Equation (10) we obtain

$\boldsymbol{S(t)} = \frac{(\gamma+\mu_0+\mu_1)}{\beta}$ (Hudson, 2002) Equation (11)

Equation (11) is known as the threshold value for the model (Hudson, 2002), we can rewrite the three cases above as:-

- $S(t) = \frac{(\gamma+\mu_0+\mu_1)}{\beta}$ then $\frac{dI}{dt} = 0$
- $S(t) < \frac{(\gamma+\mu_0+\mu_1)}{\beta}$ then $\frac{dI}{dt} < 0$;
- $S(t) > \frac{(\gamma+\mu_0+\mu_1)}{\beta}$ then $\frac{dI}{dt} > 0$

From the three cases above it can be said that the spread of HFMD is governed by ***S(t)*** in Equation (11) which specifies the susceptible host density necessary to sustain the spread of HFMD disease. The implication is that HFMD will not spread successfully if the number of susceptible is less than this threshold value.

By analyzing equation (11), it can be seen that the threshold is independent of the parameter δ, which is the rate for the loss of immunity and α, which is the natural birth rate. Somehow the threshold value is only governed by the rate of recovery; γ, natural death rate; μ_0, death due to HFMD; μ_1 and also the transmission coefficient; β. The value for the parameter of γ and μ_1 were based on the information obtained from the Health Ministry Department of Sarawak (Hand Foot Mouth Disease Outbreak in Sarawak, 2006, 2007) regarding HFMD while μ_0 was obtained from Jabatan Perangkaan Malaysia (2006).

Solving equation (11), for all the simulations that we tested, the susceptible host density value is 5,490. The meaning of this value is that if the number of susceptible is greater than 5,490 then the disease will spread and eventually become an outbreak. If the number of susceptible is less than 5,490 then the disease will not spread. Therefore, if the number of susceptible, namely those that are prone to be in contact with infective persons can be brought to down to this value, we will be able to control the outbreak for the year 2006. This can be done through quarantine of susceptible in order to minimize the chances of the susceptible coming into contact with infective persons. This is a challenging task as the initial number of susceptible is 550,700 (Jabatan Perangkaan Malaysia, 2006). This might be the reason why the outbreak in year 2006 was more severe as compared to other HFMD outbreaks in this country.

Analyzing equation (11) shows that the threshold value will increase when the value of the transmission coefficient decrease. As the transmission coefficient decrease, this would mean that the disease will be more difficult to spread. In order for the outbreak to happen the number of susceptible need to be very big. If the value of the transmission coefficient is big, which means that it is easier for an individual to contract the disease, then the number of susceptible

required for the outbreak to happen will decrease. From this threshold value we can see that there are two ways to reduce the outbreak of HFMD.

First is to reduce the transmission coefficient. In section 2.6 we mentioned that the transmission coefficient; $\beta = \boldsymbol{a} \times \boldsymbol{p}$, where

$\boldsymbol{a}$ = chances of the susceptible meeting an infected per day; and

$\boldsymbol{p}$ = the probability of the contacts leading to new infections

Thus in order to reduce the value of β, we should reduce the value of $\boldsymbol{a}$ and $\boldsymbol{p}$. To reduce $\boldsymbol{a}$, we can use quarantine or isolation so that the chances of meeting per day can be reduced. The steps taken by the authorities in announcing the closure of nurseries, kindergarten and primary classes in year 2006 outbreak helped bring the value of $\boldsymbol{a}$ down. To reduce the value of $\boldsymbol{p}$, individuals have to be taught about personal hygiene regarding the disease. Many flyers regarding HFMD were distributed to schools and public in order to create awareness on HFMD.

Secondly is to control the threshold value of the susceptible host density. By estimating the transmission coefficient during an outbreak, the threshold value can be calculated. Using this value, authorities can plan effective measures to reduce the population to below the value. When this is achieved the outbreak of the disease can be controlled.

5 MODEL ANALYSIS

The test results obtained in Chapter 4 shows that the model is able to achieve the objectives of the research outlined in section 1.2, namely, to:-

- predict the spread of HFMD in Sarawak in terms of number of infected persons;
- determine the duration of an outbreak when it happens; and
- determine factors that can help in preventing the outbreak.

We analyse the mathematical model from two perspectives. The first one is to find the steady state and the second approach is to compare the output of the HFMD model with the actual data obtained from the Sarawak Health Department for the year 2006.

5.1 Steady State

The differential equations that model the HFMD as formulated in section 3.3 are: -

$$\frac{dS}{dt} = \alpha S(t) - \beta I(t)S(t) - \mu_0 S(t) + \delta R(t) \qquad \text{Equation (6)}$$

$$\frac{dI}{dt} = \beta I(t)S(t) - \gamma I(t) - (\mu_0 + \mu_1)I(t) \qquad \text{Equation (7)}$$

$$\frac{dR}{dt} = \gamma I(t) - \delta R(t) - \mu_0 R(t) \qquad \text{Equation (8)}$$

At steady state we must have $\frac{dS}{dt} = 0, \frac{dI}{dt} = 0$ and $\frac{dR}{dt} = 0$. Letting the steady state solutions be $(\boldsymbol{S(t), I(t), R(t)}) = (\boldsymbol{S, I, R})$ and with $\frac{dS}{dt} = 0$; equation (6) becomes

$$\alpha S - \beta IS - \mu_0 S + \delta R = 0$$

$$\boldsymbol{S(\alpha - \beta I - \mu_0) + \delta R = 0} \qquad \text{Equation (12)}$$

When $\frac{dR}{dt} = 0$; equation (8) becomes

$$\gamma I - \delta R - \mu_0 R = 0$$

$$\gamma I = R\,(\delta + \mu_0)$$

$$\boldsymbol{I = \frac{R\,(\delta + \mu_0)}{\gamma}} \qquad \text{Equation (13)}$$

or $\boldsymbol{R = \frac{\gamma I}{(\delta + \mu_0)}}$ Equation (14)

From equation (13), it is clearly seen that $\boldsymbol{I}$ is proportional to $\boldsymbol{R}$ and δ while in equation (14) $\boldsymbol{R}$ is proportional to $\boldsymbol{I}$ but at the same time has an inverse effect with δ. As, the value for the parameter μ_0 and γ are constant and only δ is not known, this means that δ plays an important role in the dynamics of HFMD.

When $\frac{dI}{dt} = 0$; equation (7) becomes

$$\beta IS - \gamma I - (\mu_0 + \mu_1)I = 0$$

$$I(\beta S - \gamma - (\mu_0 + \mu_1)) = 0$$

$$\boldsymbol{I(\beta S - \gamma - \mu_0 - \mu_1) = 0} \qquad \text{Equation (15)}$$

From the factorization in equation (15), there exist two cases:-

Case 1

If $I \neq 0$ (which means there exist infected individuals) then definitely $(\beta S - \gamma - \mu_0 - \mu_1) = 0$. Thus,

$$\beta S = (\gamma + \mu_0 + \mu_1)$$

$$S = \frac{\gamma+\mu_0+\mu_1}{\beta}$$ Equation (16)

Equation (16) that is obtained using the steady state process is the same as the threshold value of the susceptible host density discussed in section 4.3 (Equation (11)) .

Substituting equation (14) and (16) into equation (12) to obtain the value for I at steady state.

$$\frac{\gamma + \mu_0 + \mu_1}{\beta}(\alpha - \beta I - \mu_0) + \delta\frac{\gamma I}{(\delta + \mu_0)} = 0$$

$$\frac{(\gamma + \mu_0 + \mu_1)(\alpha - \mu_0)}{\beta} - \frac{\beta I(\gamma + \mu_0 + \mu_1)}{\beta} + \delta\frac{\gamma I}{(\delta + \mu_0)} = 0$$

$$\frac{\beta I(\gamma + \mu_0 + \mu_1)}{\beta} - \delta\frac{\gamma I}{(\delta + \mu_0)} = \frac{(\gamma + \mu_0 + \mu_1)(\alpha - \mu_0)}{\beta}$$

$$\frac{\beta I(\gamma + \mu_0 + \mu_1)(\delta + \mu_0) - \beta\delta\gamma I}{\beta(\delta + \mu_0)} = \frac{(\gamma + \mu_0 + \mu_1)(\alpha - \mu_0)}{\beta}$$

$$I(\gamma + \mu_0 + \mu_1)(\delta + \mu_0) - \delta\gamma I = \frac{(\gamma + \mu_0 + \mu_1)(\alpha - \mu_0)(\delta + \mu_0)}{\beta}$$

$$I[(\gamma + \mu_0 + \mu_1)(\delta + \mu_0) - \delta\gamma] = \frac{(\gamma + \mu_0 + \mu_1)(\alpha - \mu_0)(\delta + \mu_0)}{\beta}$$

$$I = \frac{(\gamma+\mu_0+\mu_1)(\alpha-\mu_0)(\delta+\mu_0)}{\beta[(\gamma+\mu_0+\mu_1)(\delta+\mu_0)-\delta\gamma]}$$ Equation (17)

Substitute equation (17) into equation (14) in order to get the value for R at steady state.

$$R = \frac{\gamma I}{(\delta + \mu_0)}$$

$$R = \frac{\gamma(\gamma + \mu_0 + \mu_1)(\alpha - \mu_0)(\delta + \mu_0)}{(\delta + \mu_0)\beta[(\gamma + \mu_0 + \mu_1)(\delta + \mu_0) - \delta\gamma]}$$

$$R = \frac{\gamma(\gamma+\mu_0+\mu_1)(\alpha-\mu_0)}{\beta[(\gamma+\mu_0+\mu_1)(\delta+\mu_0)-\delta\gamma]}$$ Equation (18)

Substituting the parameter values discussed in section 4.2 with the various values of δ (i.e., $\delta = 7$, $\delta = 1$ and $\delta = 0.07$) into equation (16), (17) and (18) the following results shown in table 6 was obtained.

δ (per week)		7	1	0.07
The Steady State Value	**S**	**5,490**	**5,490**	**5,490**
	I	**7,362**	**4,743**	**729**
	R	**866**	**3,905**	**8,565**

Table 2: The steady state for ***S***, ***I*** and ***R*** with respect to δ

The value for the steady state of ***S(t)*** is consistent with the results obtained from the numerical analyses. The steady state for ***S(t)*** can be seen clearly in Figure 6, 7 and 8 for all the cases above. However the value for the steady state of ***I(t)*** and ***R(t)*** are not visible from these figures. We believe that it will take a longer duration (more than 52 weeks) for the disease to reach the steady state. In order to validate the model, we run the test again for a longer period of time of 100,000 weeks and the following results were obtained.

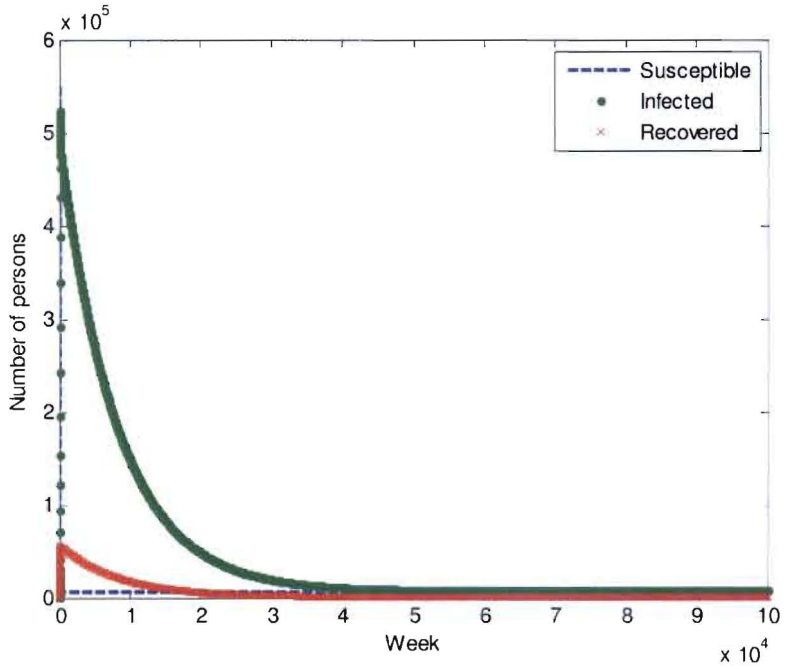


Figure 9: Result for HFMD model at limiting time for $\delta = 7$ per week

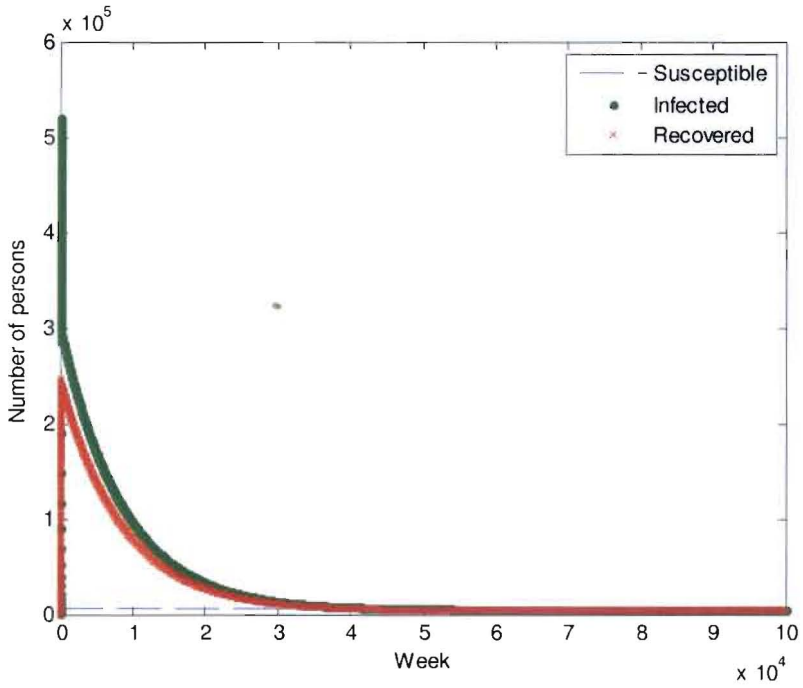


Figure 10: Result for HFMD model at limiting time for $\delta = 1$ per week

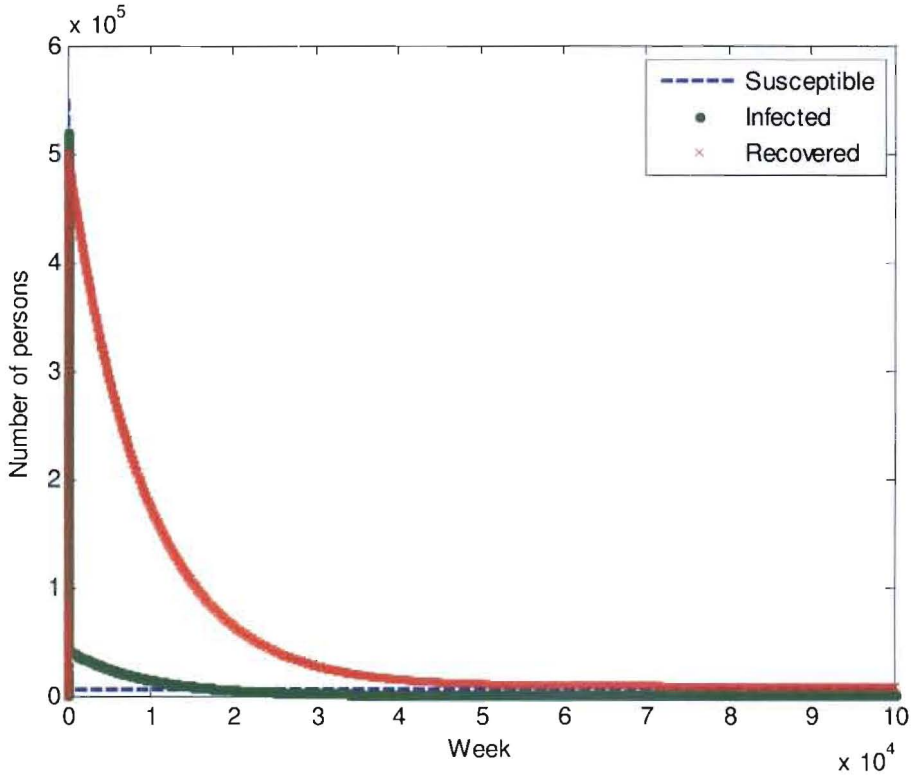


Figure 11: Result for HFMD model at limiting time for $\delta = 0.07$ per week

δ (per week)		7	1	0.07
Values at 100,000 weeks	*S*	5490	5490	5493
	I	7369	4752	730
	R	867	3912	8590
CPU Time in seconds		580.51	116.27	6.50

Table 3: The value obtained through the numerical analyses based on figure 9, 10 and 11 and the CPU time taken to obtain the results

The results in figure 9, 10 and 11 supported by table 3 also show that the steady state for ***I(t)*** and ***R(t)*** were as calculated above. In table 3 is also shown the processing time taken for the simulations to achieve the steady state for each of values for δ at 100,000 weeks. The processing time is the longest for $\delta = 7$ as compare to $\delta = 1$ and $\delta = 0.07$. This maybe because $\delta = 7$ involve processing of larger number as compared to the other twos. The comparison on the values obtained through steady state calculation and numerical analyses are shown in the table 4.

δ (per week)	**Classes**	**Values obtained through**		**Difference in percentage (%)**
		Numerical Analyses	**Steady State Calculations**	
7	***S***	5490	5490	0
	I	7369	7362	0.095
	R	867	866	0.115
1	***S***	5490	5490	0
	I	4752	4743	0.190
	R	730	729	0.137
0.07	***S***	5493	5490	0.055
	I	730	729	0.137
	R	8590	8565	0.292

Table 4: The analyses on the difference of the values obtained through numerical analyses and steady state calculation.

From table 4, it can be seen that the difference in the value obtained through numerical analyses and steady state calculations do not differ very much. The highest difference in percentage is only 0.3%.

Case 2

If $I(t) = 0$ it would mean that a disease free equilibrium is achieved. This indirectly means that there are no infective. Then, in equation (13); if $\boldsymbol{I(t)} = 0$ then $\boldsymbol{R(t)} = 0$. This will fit the disease free equilibrium state where if there are no infective or infected individuals then there will be no individual who needs to recover from the disease.

For equation (11), if $\boldsymbol{I(t)} = 0$ and $\boldsymbol{R(t)} = 0$, then

$$S(\alpha - \mu_0) = 0$$

So either $\boldsymbol{S(t)} = 0$ or $\alpha = \mu_0$.

In order to achieve disease free equilibrium for HFMD where $\boldsymbol{I(t)} = 0$, then there should not be any susceptible or the rate for natural birth must equal to the rate for natural death from the perspective of mathematical modelling. As there must be some infected or infective individuals, thus $\boldsymbol{I} \neq 0$.

The two cases of disease free equilibrium existed due to the nature of the model which takes into account the natural birth rate for the increase in the susceptible class; namely $\beta S(t)$. Thus to make the analysis more tractable we propose that for future work the recruitment rate into the susceptible class should better be approximated with a constant rate.

5.2 Actual Data Validation

With the courtesy of Pengarah Kesihatan Negeri, Jabatan Kesihatan Negeri Sarawak, the data for the HFMD outbreak of year 2006 were obtained. The data were in weekly format as shown Figure 12.

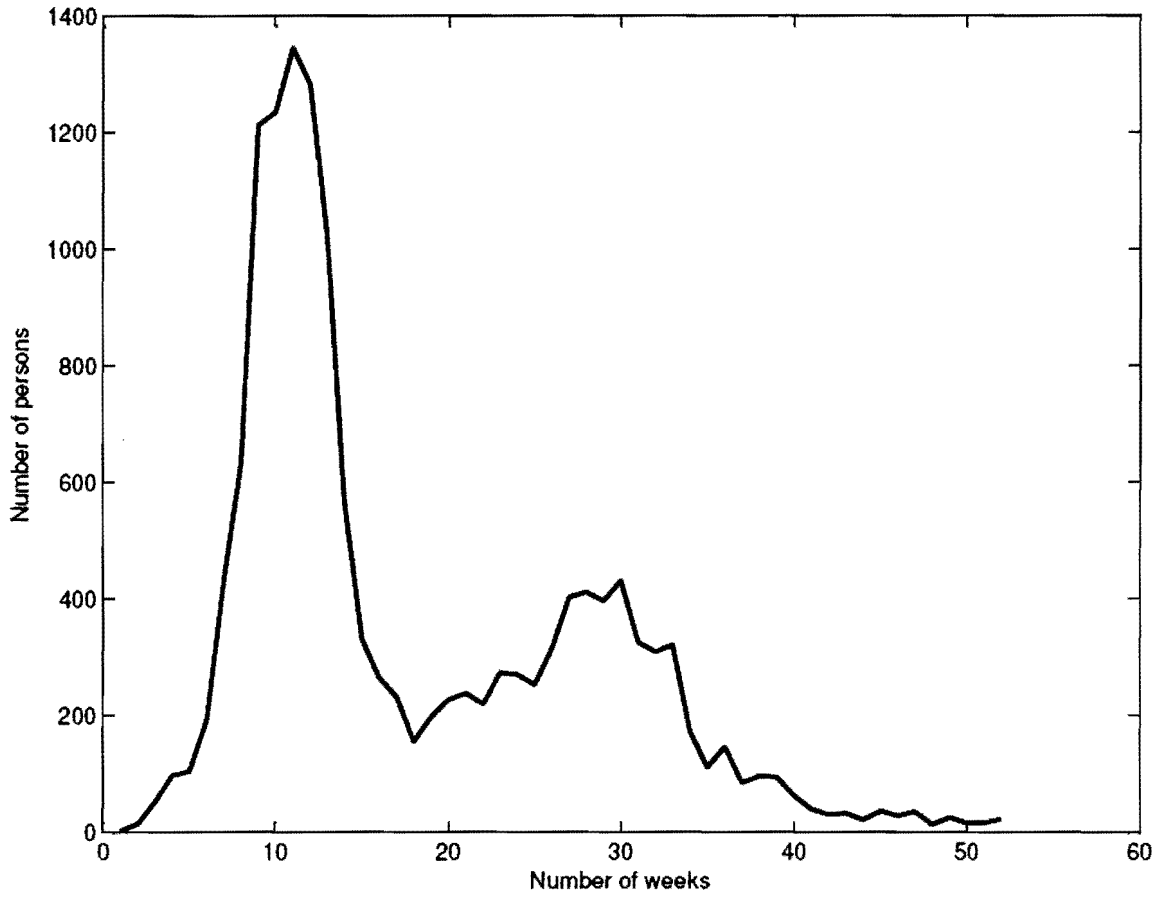


Figure 12: The number of infected during the outbreak of HFMD for year 2006

We used the data to validate the HFMD model. However, we have to change the initial value of S; the total number of susceptible. Even though the total population of age nine and below is 550700, this figure is not suitable to verify the model in the case of modelling the spread of HFMD in Sarawak. The exact initial figure for the susceptible could be lower than this because of several reasons. First, the age of the susceptible group could be lower than nine years of age with some studies revealing that most of the infected are below six years of age with the mean and median between 27 to 36 months of age (Podin, et al., 2006). Second, Sarawak is a big state with an area of 124,449 square kilometres (Jabatan Perangkaan Malaysia, 2006). The

population is dispersed throughout the country. Quite a majority of the population are still staying in the rural areas such as interior of Kapit District and Baram District just to name a few. Moreover the model made the assumption of using the mass action principle to determine the transmission coefficient. The mass action principle takes into account the chances of the susceptible meeting the infected. In interior area, the chances are lower as compared to town or cities area. Therefore, the susceptible would refer to the population who are prone to be in constant contact with infective. The disease seemed to spread among school going children either in nurseries, kindergartens and primary schools. Furthermore, the reported cases of HFMD are mainly from urban area such as Kuching, Sibu, Bintulu and Miri. Taking into account all these factors, we decide to lower down the number of susceptible to 10,000.

Thus, the new initial values are $S(0)$ = 10,000, $I(0)$ = 4 and $R(0)$ = 0. The other parameters values are kept the same as listed in section 4.2 except for δ. Based on the test results in section 4.2.3, we decided to use the parameter value for the loss of immunity; δ = 0.07 *per week* where the loss of immunity is 100 days since it gave the best simulated results for the case of HFMD. We run the simulation with the new initial value for the susceptible and the following result is shown in figure 13.

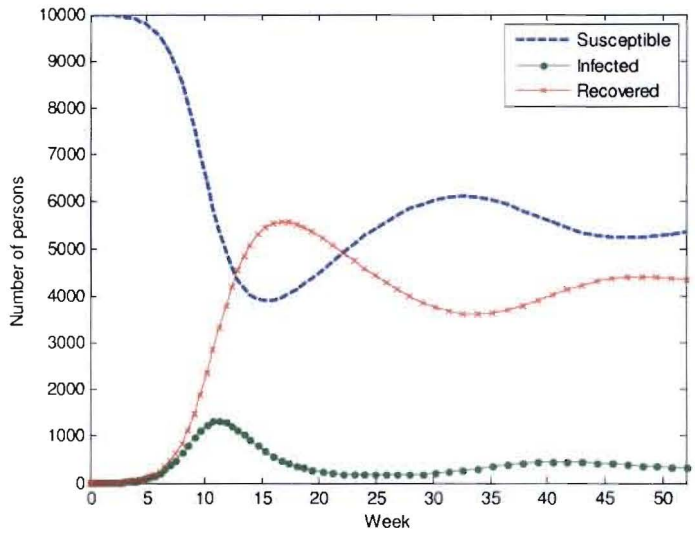


Figure 13: The numerical result for $S(0)$ = 10,000

Isolating the result for the number of infected from the number of susceptible and the recovered, figure 14 is obtained.

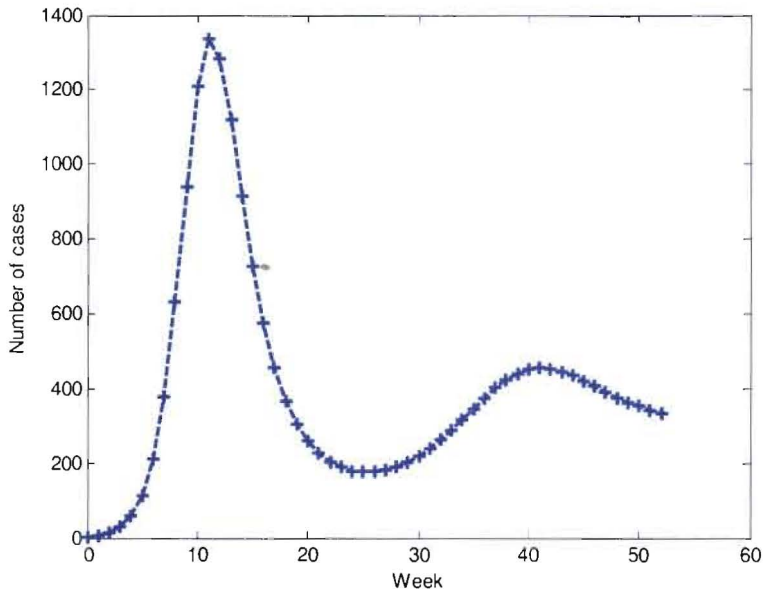


Figure 14: The number of infected with $S(0)$ = 10,000

For comparison purposes we superimpose Figure 12 and Figure 14 to get Figure 15.

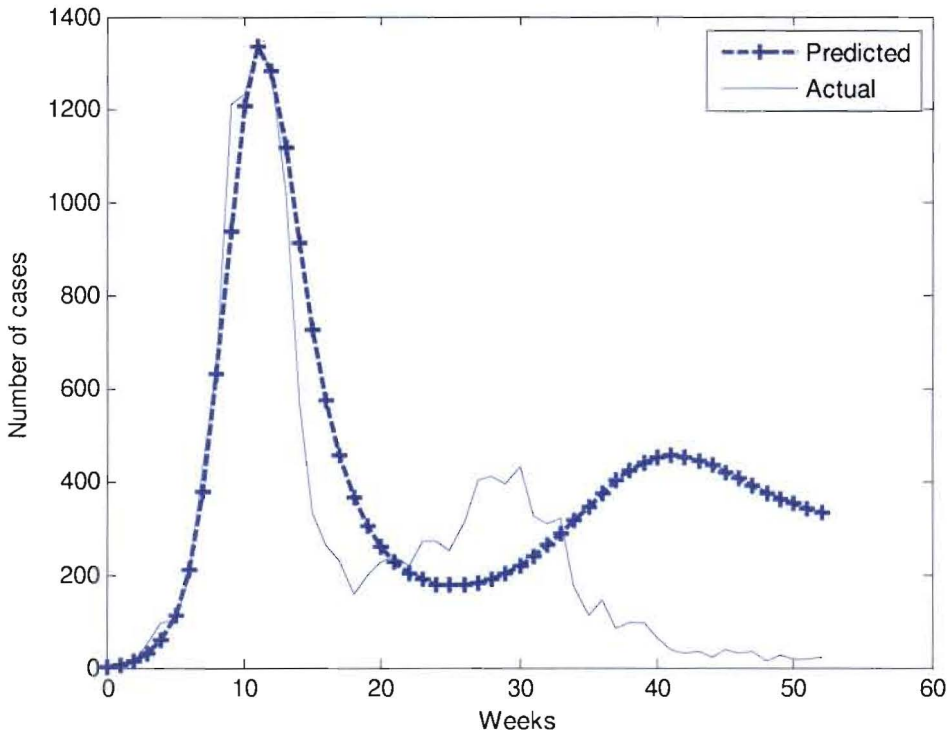


Figure 15: Results for the number infected based on actual data and the data simulated from the model

The results from the mathematical model seem to overlap the graph for the actual data around week 5 to week 8. This shows that the model is able to predict how the disease will spread in terms of number of infected given the relevant parameters and initial values.

There is a drastic drop in the number of cases after week 12 for the actual data and this is because steps were taken to curb the outbreak of the disease. According to the mathematical model if the disease takes it own courses it will take a bit longer before the outbreak ease. The model did predict that there will be a second wave at about 40 weeks but it will be milder. The

actual data did record the second wave of the outbreak but at a shorter period of time which is 10 weeks ahead. Both the actual and the predicted data show that the disease is endemic even after the outbreak is over. The value for the one predicted by the model is higher as the disease is taking its own course while for the actual one, measures and action are taken to reduce the spread of the disease. Moreover, the actual data used were only for those cases that are reported to the health authority. We believe there were cases that were not reported due to distant such as interior area and also that were not referred to any clinic or hospital. These may contributed to the reason that the number of infected predicted by the model is higher as compared to the actual data.

5.3 Basic Reproductive Ratio

Using the initial value for the susceptible and the parameters values mentioned in section 5.2, we calculate the value for HFMD reproductive ratio; R_0 based on Equation (10).

$$\boldsymbol{R_0} = \frac{\beta S(t)}{(\gamma+\mu_0+\mu_1)} \qquad \text{Equation (10)}$$

$$R_0 = \frac{0.00015(10{,}000)}{(0.8235 + 0.0001077 + 0.00001731)}$$

$$R_0 = 1.8$$

The reproductive ratio; $R_0 = 1.8$ obtained, is indeed very high and signify that HFMD is very contagious especially among children below the age of ten. Furthermore, the size of classes for nurseries and kindergartens level are very small; mostly below 20 in Sarawak. A $R_0 = 1.8$ would mean every new infected children would infected almost 2 other children during the outbreak.

Through the model analyses, we were able to show that the mathematical model built for the spread of HFMD in Sarawak is valid and stable. However we do admit that there are still rooms for improvement.

6 DISCUSSIONS

6.1 Conclusion

We have successfully developed an initial mathematical model for the spread of HFMD in Sarawak. The model is a preliminary model which we hope will be developed further into a better and precise model to predict the spread of HFMD. Despite its simplicity, the model was able to achieve the three objectives listed in section 1.2. The model was able to predict the number of persons infected during an outbreak. It was able to predict the duration of the outbreak. Finally, the model was able to determine that the critical parameters that can be used to help in the prevention of the outbreak are the number of susceptible and the transmission coefficient. These were shown and discussed in Chapter 4. We have successfully analyzed the mathematical model using the steady state and comparing the results with the actual data.

To conclude, the research is able to contribute to the following areas:

(i) The mathematical model is able to help the authorities concerned such as the Sarawak Health Department in predicting the number of infected during an outbreak of HFMD and thus enable them to plan appropriate actions for future outbreak.

(ii) Through the mathematical model, the dynamics of HFMD can be seen more clearly. We are able to determine that the transmission coefficient, β and the loss of immunity, δ played important parts in the dynamics of HFMD.

(iii)The model has shown that one of the factors that can help in reducing the outbreak of HFMD is to control the number of susceptible that will come into contact with the infective. This proved that the action taken by the authorities in year 2006; namely the

closure of nurseries, kindergartens and primary One to Three, was indeed the correct procedure to reduce the outbreak.

(iv) This research had opened a new area in the study of HFMD in Sarawak from mathematical modelling perspectives. We started off the research with a simple model and hope that more will follow to improve the model.

It should be stressed here that the mathematical model for HFMD is only as accurate as the data that we had used to build the model. Due to lacks of data regarding the transmission coefficient value and the rate for the loss of immunity, we can only use estimated values. Because of that, the results obtained from the model may not be that accurate. This is supported by Keeling M. J. (2005) which stated that "*Even if all the mechanism were understood and encoded, models would still be limited by the available data*" and "*It may be impossible to produce a good predictive model simply due to the lack of sufficiently detailed data*" (Keeling M. , 2006).

To conclude we quote Callahan (1996) "*Our goal is to gain insight into the workings of an epidemic and to suggest how we might intervene to reduce its effects. So we start off with a model while imperfect still captures some of the workings. The simplifications in the model will be justified if we are led to inferences which help us understand how an epidemic works and how we can deal with it if we wish, we can then refine the model, replacing the simple expressions with others that mirror the reality more fully.*"

We do hope that the authorities concerned can look into the use of this model in the next outbreak when it happens. From the usage, further improvements can be made so that a better

and more accurate mathematical model can be derived to model the spread of HFMD in Sarawak in years to come.

6.2 Future Work

As we progress through this project, we realized that there are still a lot of improvements that can be made to the modelling of HFMD. The model that we used in this research is an *open model* in which the demographic terms (birth and death rates) are taken into account. It is also known as *endemic model* (Hethcote, 2000). For comparison study, a *closed model* or an *epidemic model* can also be used to model the spread of HFMD as shown in figure 17.

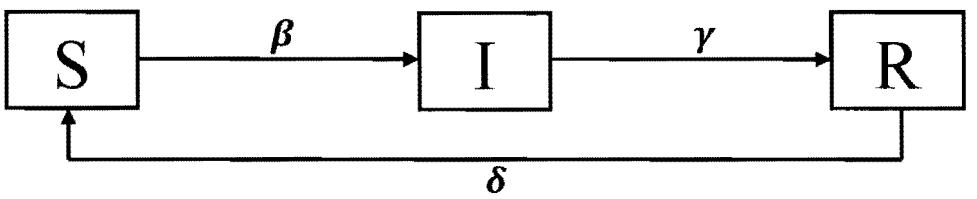


Figure 16: ***SIRS*** model without birth and death rate

These would simplify the mathematical equations to:

$$\frac{dS}{dt} = -\beta S(t)I(t) + \delta R(t) \qquad \text{Equation (19)}$$

$$\frac{dI}{dt} = \beta S(t)I(t) - \gamma I(t) \qquad \text{Equation (20)}$$

$$\frac{dR}{dt} = \gamma I(t) - \delta R(t) \qquad \text{Equation (21)}$$

Besides that our mathematical model used the concept of *mass action* to model the dynamic of the disease. Another approach is to use the *standard incidence formulation* (Hethcote, 2000). Based on *standard incidence formulation*, $s(t) = \frac{S(t)}{N}$, $i(t) = \frac{I(t)}{N}$ and $r(t) = \frac{R(t)}{N}$ are the susceptible, infectious and recovered fractions respectively with the total

population size; $N = S(t) + I(t) + R(t)$. $\beta \frac{I(t)}{N} = \beta i$ is the average number of contacts with the infective per unit of time of one susceptible, and $\beta \frac{I(t)}{N} S = \beta N i s$ is the number of new cases per unit time due to $S(t) = Ns$ susceptible. With these, the equations that are used in the model will need to be changed respectively.

Runge-Kutta method was used to solve the coupled nonlinear differential equations for the model because of its simplicity. However, Runge-Kutta method does not preserve the essential properties of the model namely positivity in which case ***S(t)***, ***I(t)*** and ***R(t)*** must be of positive values. Thus, it is better to solve the equations of the model using non-standard positivity-preserving-finite-difference-discretization method as proposed by Gumel, Mickens, & Corbett (2003) and Gumel, Patidar, & Spiteri (2005).

As mentioned in Chapter 3, the value for the transmission coefficient ($\beta = 0.00015$) that was used in this model was just an estimate. The estimation is made based on Callahan (1996) and Allman & Rhodes (2004) view on the general values for transmission coefficient for disease spread. So far the only literature that offers an insight into the transmission coefficient value is Wang & Sung (2004). However they determine the value using transformation function of seasonal factors in which case is not relevant to our model which is deterministic in nature. From the modelling view, we realized that by controlling or understanding the value of β, we might be able to curb the spread of HFMD. So we hope there will be some researches to look into the transmission coefficient of HFMD in Sarawak. Recalling that the transmission coefficient is the product of the contact rate and the probability of transmitting the virus during those contacts so further works can be focus on the contact rate. Chang, et al. (2004) did a study on the transmission rate for HEV71 in Taiwan which is limited to houshold contact. They

investigated patients at a children's hospital in Taiwan and family members of these patients who had signs and symptoms suggestive of HEV71. Patients and household members underwent clinical evaluations, virological studies, questionaire-based interview, and were followed up for 6 months. Their ideas could be used to determine the contact rate for HFMD in Sarawak. As for the probability of transmitting the virus during the contact, we might be able to made use of the incidence rate formula published by the Sarawak Health Department on HFMD as discussed in section 3.4.

Most literatures admitted that HFMD has no permanent immunity but no literatures hold any insight to the value for the loss of immunity at the moment. Thus, the precise value of δ is unknown. Using the mathematical model, we were able to prove that there is no permanent immunity against HFMD and also that the loss of immunity is not one day as proposed in Wang & Sung (2004). Based on the model, we concluded that the immunity against HFMD is roughly around 100 days after recovery. We hope there will be some researches either clinically or mathematically to determine the exact value for the loss of immunity. With further works on these two parameters a more precise model for the spread of HFMD in Sarawak can be obtained.

Finally, some focus should also be given to analyse the phase plane. The use of next generation method or standard linearization to establish the local asymptotic stability of the disease-free equilibrium, by way of finding the reproduction number is recommended.

Besides that, we hope this project has paved a new road for more researches to come. We believe that the HFMD model can be modified to look into the effect of weather in the outbreak of HFMD in Sarawak as was done in Taiwan by Wang & Sung (2004) and also to support claim that outbreak of HFMD in Sarawak will happen every three years (Podin, et al.,

2006). A more precise model of HFMD would surely be able to help authorities concerned in predicting the outbreak of HFMD and indirectly helping in curbing the spread of HFMD.

7 APPENDIX

APPENDIX A.

CLOSURE DIRECTIVE – DIRECTOR OF SARAWAK HEALTH DEPARTMENT

JABATAN KESIHATAN NEGERI SARAWAK
JALAN TUN ABANG HAJI OPENG
93590 KUCHING, SARAWAK, MALAYSIA

Tel: 082-246350 Fax: 082-247254

Ruj. Kami: JKNSWK/Ops/HFMD 2006/1/20
Tarikh: 3 Mac 2006

SEGERA

Pengarah
Jabatan Pelajaran Negeri Sarawak
Tingkat 10, Bangunan Tun Datuk Patinggi Tuanku Haji Bujang
Jalan Simpang Tiga
93604 Kuching.

Pengarah
Jabatan Kebajikan Masyarakat Negeri
Tingkat 11, Wisma Saberkas
Jalan Green
93564 Kuching.

Pengarah Perpaduan
Jabatan Perpaduan Negara dan Integrasi Nasional
Tingkat 9, Bangunan Sultan Iskandar
Jalan Simpang Tiga
93350 Kuching.

Pengarah
Jabatan Kemajuan Masyarakat
Persekutuan Negeri Sarawak (KEMAS)
Tingkat 6, Bangunan Sultan Iskandar
Jalan Simpang Tiga
93350 Kuching.

Tuan/Puan,

ARAHAN PENUTUPAN SERTAMERTA KE ATAS SEMUA TADIKA, PRA-SEKOLAH, TABIKA DAN TASKA SELURUH SARAWAK

Saya dengan hormatnya merujuk kepada perkara di atas.

2. Sehubungan dengan pengumuman yang dibuat oleh YB Menteri Kesihatan Malaysia hari ini, **SEMUA** TADIKA, pra-sekolah, TABIKA dan TASKA di seluruh negeri Sarawak hendaklah **ditutup sepenuhnya selama dua (2) minggu** berkuatkuasa sertamerta mulai hari ini **Jumaat 3 Mac 2006.**

3. Tindakan ini diambil bagi memutuskan transmisi jangkitan ini secara berkesan di samping memudahkan kerja-kerja pembersihan dijalankan di premis-premis tersebut.

4. Oleh itu, tuan/puan adalah diminta untuk memaklumkan kepada premis-premis di bawah jagaan masing-masing untuk berbuat demikian dan mematuhi arahan ini.

Sekian, terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menjalankan tugas,

DR. YAO SIK KING
PENGARAH KESIHATAN NEGERI
SARAWAK.

APPENDIX B.

TEXT ON THE PUBLIC ANNOUNCEMENT

BY
YB DATUK PATINGGI TAN SRI DR. GEORGE CHAN HONG NAM,
DEPUTY CHIEF MINISTER OF SARAWAK
ON
THE CLOSURE OF ALL PRIMARY ONE TO THREE CLASSES
IN ALL PRIMARY SCHOOLS AND PRE SCHOOLS
IN THE STATE OF SARAWAK

As the State Minister-in-charge of the State Disaster and Relief Committee, with the consent of the Chief Minister of Sarawak and the Minister of Health Malaysia, I would like to make the following orders:

1. I would like to announce that, after the current school holiday is over on 17th March 2006, I would like to order all primary one to three classes in all the Primary schools in the State of Sarawak to be closed from Monday 20th March 2006 to Sunday 26th March 2006. We believe this order of closure in the State of Sarawak will further help break the transmission of Hand, Foot and Mouth Disease in the State.

2. Similarly, following the announcement by the Minister of Health on the 3rd March 2006, on the closure of all TASKA and similar premises I would like this closure to continue until 26th March 2006 for the following:

i) TASKA
ii) TADIKA
iii) TABIKA
iv) CHILD CARE CENTRES
v) NURSERIES
vi) CHILD DAY CARE CENTRES
vii) PLAY SCHOOLS
viii) PRA SEKOLAH
ix) TUITION CENTRES CATERING TO STUDENTS BELOW 10 YEARS OLD

I hope that all concerned will understand that this step is necessary in order to control the outbreak of Hand, Foot and Mouth Disease in the State of Sarawak.

I also hope that everybody will cooperate and abide by this order, so that we will not need to extend the duration of this closure order in future.

THANK YOU.

APPENDIX C.

THE BORNEO POST 11 April 2008 (Thursday) HOME

Outbreak of HFMD expected next year

Disease due to EV 71 occurs once in every three years

KUCHING: The Health Department is expecting an outbreak of the EV 71-caused hand, foot and mouth disease (HFMD) next year.

This is because the outbreak due to Enterovirus 71 (EV 71) occurs once in every three years, and the last one was in early 2006.

In a statement released yesterday, the department said necessary steps were being taken to prevent and control the outbreak.

"All districts have been asked to step up their prevention and control measures," the statement pointed out.

Among other things, the department advises and gives health education to the operators of child care centres so that they know how to take preventive measures, for example, keeping the premises clean and disinfected, and practise personal hygiene.

Early detection of cases and prompt notification and strengthening of laboratory-based surveillance for HFMD will also be taken into very serious account, the statement stressed.

The districts must also investigate all reported cases, focusing on determining the source of infection and focusing on preventing the transmission of the disease to others.

Active case detection (ACD) especially at child care centres, nurseries and pre-schools will also be stepped up.

Appropriate management of cases in observation and isolation wards will also be taken very seriously.

The districts have also been directed to conduct weekly analysis of the disease reported in their areas and take necessary preventive actions, the statement said.

The department said HFMD was caused by infection with human enteroviruses.

The most common members of the enterovirus genus that cause HFMD include coxsackie virus group A and B, the echovirus and EV 71.

It pointed out that HFMD is under the Prevention and Control of Infectious Disease Act 1988. Thus the nearest medical officer should be notified within 24 hours.

The department said in the first 13 weeks of this year a cumulative total of 1,368 cases were reported compared to 2,583 during the corresponding period last year.

The highest number of cases were reported in Bintulu (450 cases), followed by Miri (227), Kuching (281) and Sibu (191).

It also said that laboratory investigation conducted by Universiti Malaysia Sarawak (Unimas) showed that out of 111 specimens collected, 64 cases were positive of enterovirus and only one case positive with EV 71.

APPENDIX D.

A2 SATURDAY, MAY 10, 2008 WORLD

Death toll from EV71 outbreak reaches 34

Outbreak's spread slows down, new cases less severe: Health Ministry

BEIJING: The number of Chinese children confirmed dead from hand, foot and mouth disease has risen to 34 with nearly 25,000 people infected but the outbreak's spread may be slowing, state media said yesterday.

Xinhua news agency reported four new deaths, including an eight-month-old girl in southern China's Guangdong province and a one-year-old boy in the southwestern Guangxi region.

Two more children also had died in the hard-hit eastern province of Anhui, it said, adding the number of contractions he had risen to 24,971 as of Thursday.

However, the national Health Ministry said those discharged from hospitals in Anhui now exceeded new cases for the first time.

More new cases there also were less severe than previously, it said in a statement on its website.

Symptoms of the highly contagious disease include fever and sores. It can result in death in children due to their low developed immune systems.

The disease is common in China. More than 80,000 cases were reported last year, with 17 deaths.

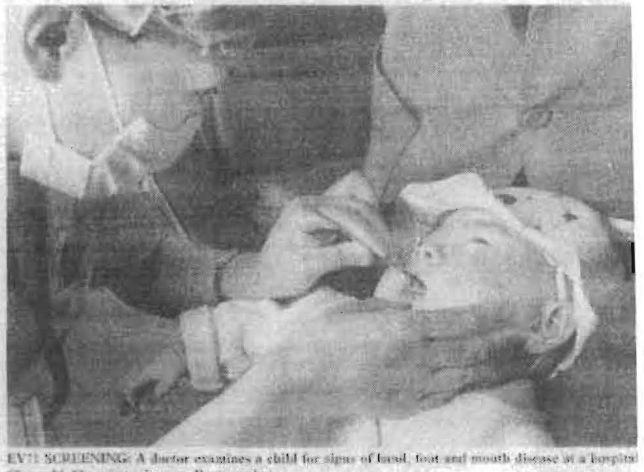
However, as rapid spread across a vast region, including the capital Beijing just months before the city hosts the Olympics in August, has prompted the government to issue a national alert.

The World Health Organisation has said there is little fear of a devastating outbreak.

The China Daily newspaper yesterday quoted a US official as saying the Department of Health and Human Services had offered its help in containing the disease, which will be on the agenda during a visit to Beijing next week by the department's chief Mike Leavitt.

Most of the deaths have involved enterovirus 71, or EV71, which can lead to acute hand, foot and mouth disease and was identified early on by China as a key factor in severity of the outbreak.

However, it seems now to be mutated into a severe general form hand, foot and mouth disease according to state press reports. AFP



EV71 SCREENING: A doctor examines a child for signs of hand, foot and mouth disease at a hospital in Changzhi, Shanxi province. — Reuters photo

MAY 2008 WORLD W39

THE STAR, 6 MAY 2008, TUES

Over 6,300 EV71 cases reported, toll reaches 26

BEIJING: Authorities have reported more than 6,300 cases in a deadly viral outbreak and yesterday raised the death toll to 26 children.

The latest fatality was in coastal Zhejiang province. The provincial Health Ministry's website said that in addition to the one death, 1,198 children had been stricken with enterovirus 71.

The ministry appealed for any sick children "to be sent immediately to health clinics" and for people to "report the case immediately to health and education departments".

There have already been 5,151 cases reported in neighbouring Anhui province, where 22 children have died, according to the official Xinhua News Agency. Most of the cases were in or near Fuyang, a fast-growing city in the rural heartland of Anhui in central China.

Xinhua has also reported three deaths in Guangdong.

Enterovirus 71, also known as EV-71, causes a severe form of hand, foot and mouth disease with symptoms including fever, mouth sores and rashes with blisters. It is easily spread by sneezing or coughing. The viruses mainly strike children ages 10 and younger. Some cases can lead to fatal swelling of the brain.

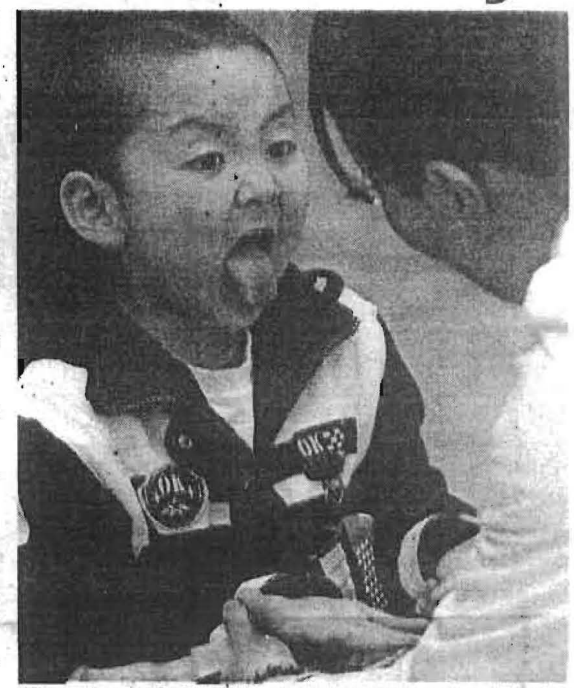
The illness is not related to foot and mouth disease, which afflicts livestock. – AP

APPENDIX E.

What's with these body parts?

Due to its tendency to cause large outbreaks and some deaths, Hand, Foot and Mouth Disease has become an important public health issue in certain parts of the world, especially in Asia.

Dr Koh Mia Tuang ... We shouldn't be unduly worried, but at the same time we should not be complacent. We should know what to look out for and seek early help.



HFMD usually starts off with a mild fever, three to seven days after contact with the virus. Two or three days later, red spots begin to appear on the palms and ulcers can develop on the lips, in the throat and on the tongue.

By LIM WEY WEN
starhealth@thestar.com.my

As the countdown to the Beijing Olympics continues, the Chinese government is dealing with yet another concern – a biological one this time.

The Hand, Foot and Mouth disease (HFMD) has once again broke out in Asia, infecting 16,778 in China since January this year, the official press agency of the People's Republic of China reported on Thursday.

Starting in the Chinese city of Fuyang in the Anhui province, the disease has now been reported in neighbouring provinces such as Shanghai, Zhejiang, Henan, Hebei and JiangXi.

In Southeast Asia, increased infection rates have been recorded since in Singapore and Vietnam. But there were no reports of deaths from the disease in Singapore while Vietnam health officials say that there were some deaths but no specific figure was given.

With headlines like "deadly virus" and "killer disease", HFMD often creates worry in most parents. But out of almost 16,000 infections in China by the coxsackie virus A16 and enterovirus-71 (that causes HFMD), the disease had caused 28 deaths – most of them children under six – since the outbreak started on Mar 20.

So, what do these figures tell us?

It may kill, but most recover

According to Emeritus Professor Datuk Dr Lam Sai Kit, a senior research fellow at the University of Malaya, HFMD caused by enteroviruses other than EV-71 is mild and seldom, if ever, gives rise to complications.

However, in HFMD cases caused by EV-71, less than 1% has been shown to present with severe complications, including deaths.

Although she could not cite facts and figures, Madam Zhen Wai Mun – housewife, grandmother and a nanny of a four-year-old – knows that although HFMD is common, certain precautions must be taken.

"It is a common illness among children, mostly for those below six years old. Most of them get infected in nurseries and kindergartens, and most of them recover after a while," said Zhen, who has a grandson and a granddaughter.

"But when my granddaughter got fever and rashes two years ago, it took us a few days to suspect that HFMD may be the cause," Zhen said.

Having experience of baby-sitting for working moms for over 20 years now, Zhen took her feverish 4-year-old granddaughter to the nearest clinic once she noticed rashes on her hands and feet.

"The general practitioner could not give us a definite answer, so we took her to a paediatrician, and she was diagnosed with HFMD," she added.

But Zhen did not worry overmuch. "We were told that the virus she was infected with is not a dangerous one, but the doctor told us to monitor my granddaughter closely and get her admitted if the fever does not subside after medication.

"About a week or so, she recovered," said Zhen.

Zhen alerted the parents of the child under her care to monitor their child.

She subsequently sought treatment for her grandson at the first sign of fever. "The doctor told me that HFMD is very contagious, so I practised good hygiene and monitored the children at home," she said.

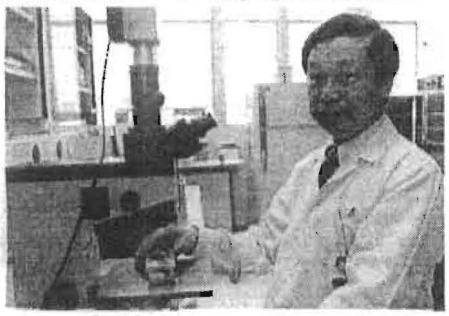
However, Zhen was concerned that her granddaughter could have infected other children in her kindergarten.

"If we had known that there was an infection in the kindergarten, we would have sought treatment for my granddaughter earlier," said Zhen, who then asked the kindergarten principal to alert parents about the infection at the morning assembly.

"At least parents can be on the lookout for signs and symptoms for them to seek treatment immediately when their child experiences them," she added.

Hand, Foot and Mouth Disease

Typically a benign and common illness, HFMD has become an important public health disease in countries such as Malaysia, due to its tendency to cause outbreaks and some deaths among children and infants.



According to Emeritus Professor Datuk Dr Lam Sai Kit, HFMD caused by enteroviruses other than EV-71 is mild, and seldom, if ever, give rise to complications.

It is caused by a group of viruses called enteroviruses, which include coxsackie virus A16 (most common) and EV-71.

"They are called enteroviruses (gut-viruses) because they multiply in the gut," said consultant paediatrician Dr Koh Mia-Tuang, who specialises in childhood infectious diseases. But although it multiplies in the gut, diarrhoea is not a prominent feature in enterovirus infections, he added.

The name – HFMD – is descriptive of organs that are commonly affected in the disease, which is characterised by sores or rashes on the hands, wrists, feet, buttocks and in the mouth.

According to the US Centers of Disease Control and Prevention (CDC), this moderately contagious disease can put everyone at risk of an infection, but not everyone who is infected becomes ill.

The disease can spread from person to person by direct contact with nose and throat discharges, saliva, fluid from blisters or the stool of infected persons.

A person is most contagious during the first week of the illness, but HFMD is not transmitted to or from pets or other animals.

The disease in its usual, classical form, does not kill. It is the complications, usually caused by EV-71, that kills, Dr Koh said.

"The reason why it kills is because the virus can attack the central nervous system. It usually causes paralysis, drowsiness, aseptic meningitis (inflammation of the protective membranes covering the brain and spinal cord), and can also cause inflammation of the heart muscles," he added.

The classical form of HFMD – usually due to the coxsackie virus infection – often resolve completely by themselves after a week to 10 days without any specific treatment.

As there are currently no effective vaccines or medications to cure HFMD, medications will usually be prescribed to help with the fever and pain.

"The disease (HFMD) is a spectrum. It can be very mild to very severe," said Dr Koh. The severe cases are usually associated with EV-71, and patients may have conditions that affect the brain, the heart, and the nervous system, he added.

HFMD usually starts off with a mild fever, three to seven days after contact with the virus. Two or three days later, red spots begin to appear on the palms and ulcers can develop on the lips, in the throat and on the tongue.

Because of these painful lesions (sores), a child may refuse to eat or drink, Dr Koh continued.

Some of the spots can be filled with fluid a few days later. "Within this fluid there are a lot of viral particles, so the disease can also be spread by it," said Dr Koh.

However, not all patients go through all stages of the disease. "Some of them may just have ulcers in the tongue or on the cheek, but most of them do have a combination of ulcers in the lips and painful red spots over the palms and the soles," said Dr Koh.

When the child has sores in his mouth, it is painful for him to drink and eat solid food. "The trick is to give small amounts of fluid frequently. Parents can also give a child ice water or ice cubes to suck on," said Dr Koh.

Danger signs parents should look out for in a child with HFMD are:

- Refusal of fluids or any oral intake
- Passing less urine or passing urine less frequently.
- Appear unusually lethargic, listless, disinterested, feeling very weak
- Continuous fever (more than five days) with high temperature (more than 38.5°C)
- Rapid breathing or difficulty in breathing
- Cool extremities
- Drowsiness and convulsions

> SEE NEXT PAGE

APPENDIX F.

Additional Information on HFMD

1. **Agent of infection;**

   a. It is a disease caused by viruses from enterovirus group specifically from EV71 and Coxsackie group A16.

2. **Clinical Signs and Symptoms.**

   a. The signs and symptoms of the infection are fever, sore throat, loss of appetite, ulcer at the throat and mouth as well as blister rashes on the hands, feet and diaper area (papulovesicular lesions).

   b. It affects mostly children below 10 years of age. Duration of infection normally lasts 7 to 10 days.

3. **Mode of Spread.**

   HFMD is spread by;

   a. Direct contact with droplets from infected person through coughing and sneezing, or oral secretion and nasal discharge, or through contaminated hands to mouth.

   b. Touching blister on the body of an infected person.

4. **Incubation period.**

   a. A person will show signs and symptoms 3 to 7 days after exposure to the virus. Most patients will recover within a few days.

5. **Period of Infection.**

   a. It is very infectious at the acute stage especially from the cough and sneeze droplets, oral and nasal discharge and fluid from the blisters.

   b. The viruses may continue to be excreted in the stool of the infected persons for a few weeks.

APPENDIX G.

a. Creating M-file named HFMD2006

```
function f = HFMD2006(t, x)

%The default value for the parameters
alpha  = 0.000293;
muNull = 0.0001077;
muOne  = 0.00001731;
beta   = 0.00015;
gamma  = 0.8235;
delta  = 0.07;

% S(t) = x(1);
% I(t) = x(2);
% R(t) = x(3);

% dS/dt = f(1);
% dI/dt = f(2);
% dR/dt = f(3);

f = zeros (3, 1);
f(1) = alpha*x(1)- beta*x(1)*x(2)- muNull*x(1)+ delta*x(3);
f(2) = beta*x(1)*x(2) - gamma*x(2) -(muNull+muOne)*x(2);
f(3) = gamma*x(2)-delta*x(3)-muNull*x(3);
```

b. Initial values and calling the function *ode45*

```
>> %Initial value for the susceptible, infected and recovered class respectively
>> S0 = 10000;
>> I0 = 4;
>> R0 = 0;
>>
>> %Grouping the initial value into vector
>> x0 = [S0; I0; R0];
>> MaxTime = 52;
>> %Calling the M-file and ode45 function
>> [t,x] = ode45(@HFMD2006, [0,MaxTime], x0);
>>
>> %Ploting the infected line on the graph
>> plot(t,x(:,2));
```

APPENDIX H.

10 THURSDAY, NOVEMBER 29, 2007 — Central Region — THE BORNEO POST

Dept monitoring HFM in Sibu

24/1/2008 (Thursday)

Cases tend to increase towards year end; Health Dept wants to ensure situation under control

By Raymond Tan

THE BORNEO POST — Central Region — THURSDAY, JANUARY 24, 2008 7

Bracing for return of HFM

We are looking out for the cases and stepping up precautionary measures to prevent a spread: Health Dept

By Raymond Tan

APPENDIX I

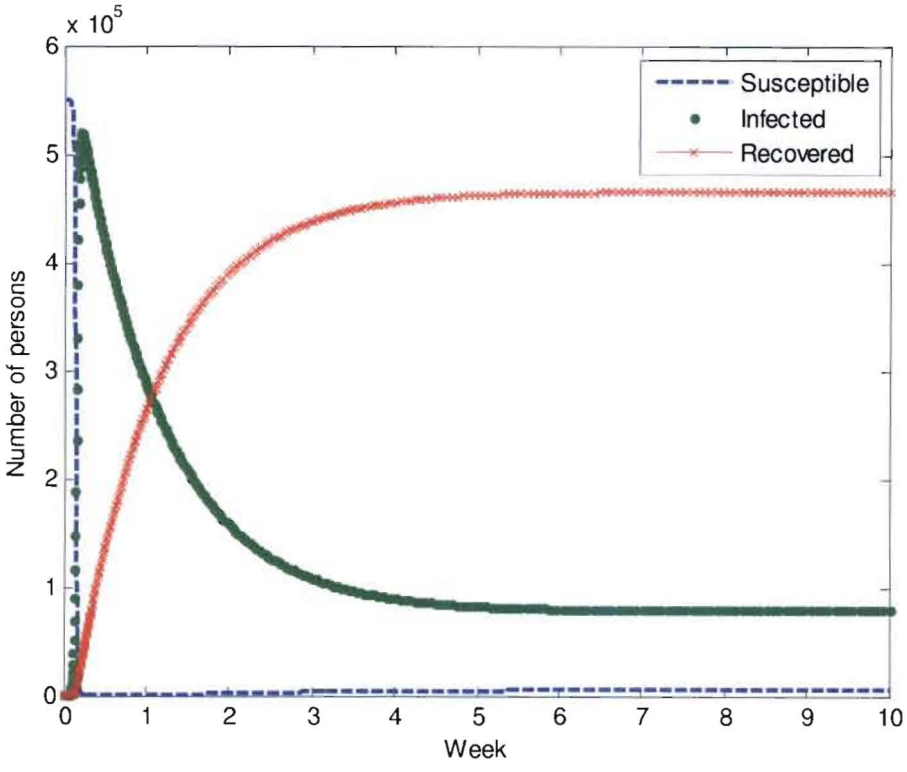


Figure 17: The result for HFMD model with $\boldsymbol{\delta = 0.14}$ or acquired immunity of 50 days

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