Mathematical Model of Hand-Foot-Mouth Disease (HFMD) in Thailand

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Abstract

The Susceptible-Infected-Recovered (SIR) Model is a mathematical model which has been adopted to predict the spread of a disease. The purpose of this study was to predict the hand, foot and mouth disease (HFMD) outbreak by using the fraction of the population SIR epidemiological model.

This study used secondary data from the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health Thailand that had been retrieved between 1st January 2008 and 31st December 2011, in population aged less than 5 years. Then Susceptible-Infected-Recovered (SIR) Model was built from data.

The results from SIR simulation show that the estimated reproductive ratio (R_0) equals to 1.42813. This ratio is greater than 1 indicating that the disease outbreak will be spread out in Thailand. The susceptible group population should be infected during an outbreak. In summary, HFMD will persist in Thailand under the R_0 condition. This suggests that investigating the preventive measures to control the HFMD quickly and the number of infections would decline rapidly over a period of outbreak time.

Keywords: SIR model, Mathematical model, HFMD, Reproductive ratio

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Introduction

Hand-Foot-Mouth Disease (HFMD) is a common febrile illness of early childhood, which is caused by viruses that belong to the enterovirus genus (group). This group of viruses includes polioviruses, coxsackieviruses, echoviruses, and enteroviruses. The most common viruses causing HFMD are coxsackievirus A16 (COX A16) and enterovirus 71 (EV71) (Zhu, Hao, Ma, Yu, & Wang, 2011). Sometimes, HFMD may be caused by other enteroviruses. But most patients with fatal complications are infected by EV71.

Usually the enterovirus exhibits strong transitivity, the latent infection is high and the transmission paths are complicated. These lead to epidemic outbreaks in short times. The disease causes fever, tetter and ulceration on hand, foot and mouth, and many further develop into myocarditis, pulmonary edema, aseptic meningoencephalitis, and other complications. HFMD is spread through direct contact with nose discharge, saliva, feces and fluid from the blisters.

Since the first HFMD case was reported in New Zealand in 1957, subsequent outbreaks have been reported worldwide. For example presently, the outbreak of HFMD has been affected children aged 5 years and younger. The cumulative reported of HFMD cases ratio of year 2012 per 2011 were 1.6, 1.5, 1.5, 0.1, 0.7, and 2.8 in China, Hong Kong, Macao, Japan, Republic of Korea, and Singapore, respectively. Although the number of cases has been well increased in Japan, the high incidence of HFMD was found in China, Macao (China), Republic of Korea, and Singapore (World Health Organization Western Pacific Region, 2012).

In Thailand, Ministry of Public Health reveals that between 1st January 2012 and 4th August 2012, there were 26,572 persons with signs and symptoms of HFMD and 2 deaths (Bureau of Epidemiology Department of Disease Control Ministry of Public Health, 2012). Not only the HFMD causes health problems, but also has a great social and economic impact. Therefore, it needs to get the information of the HFMD dynamics among susceptible populations. This information could help policy makers could taking an effective measurement to manage the epidemic in order to reduce the adverse impact of the disease.

Unfortunately, there is no specific treatment for HFMD. Owing to its global spread and the associated morbidity and mortality, much attention has been focused on devising methods for controlling the spread of HFMD (Liu, 2011). In the absence of effective anti-HFMD therapeutic treatment and vaccine, HFMD control strategies are based on taking appropriate preventive measures. These measures include quarantine mechanisms and personal protection against exposure to infected persons.

The foundations of mathematical modeling of human and mammalian disease epidemics were first established by Kermarck and McKendrick (Kermack & McKendrick, 1991a, Kermack & McKendrick, 1991b, Kermack & McKendrick, 1991c). The importance of mathematical models in disease epidemics has been discussed extensively by many researchers (Anderson, 1991; Bradley, 1982, Heesterbeek, Roberts, Heesterbeek, & Roberts, 1995). Several studies Chuo, Sing, & Labadin, (2008) Roy & Halder (2010) Urashima, Shindo, & Okabe (2003) and Wang & Sung (2004) are investigated the spread of HFMD among the young children. Chuo et al. (2008) established a simple deterministic SIR model of HFMD to predict disease outbreak. They estimated critical population density for the outbreak of HFMD in Sarawak, Malaysia in 2006. In the study of Wang & Sung. (2004), SIR model of HFMD has been used to analyze the occurrence of enterovirus complications among the severe ill cases in Taiwan. Urashima et al.(2003) attempted to established nonlinear mathematical models to simulate the impact of global warming on the incidences of HFMD in Tokyo. Numerical analysis has been shown to find the relationship between the outbreaks of HFMD with the weather patterns each countries in those models. Roy and Halder (2010) formulated a compartmental SEIR model for HFMD using computer algebra providing the analytical results obtained from the model. In this paper, using systems of differential equations that describe the basic formulation of an SIR model to estimate the fraction of the population hand, foot and mouth disease.

Objective

This study was to predict the HFMD outbreak by using the fraction of the population SIR epidemiological model that needs to control of disease in similar future epidemic.

Methods

This study applied the susceptible-infectious-recovered (SIR) model proposed Kermack and MacKendrick that provides an established basis to model the transmission dynamics of infectious diseases (Kermack & McKendrick, 1991a). The SIR model classifies individuals as susceptible (S), infectious (I), and recovered (R). Susceptible individuals in contact with the virus enter the infectious class at the rate $\beta I(t)/N$ where β is the transmission rate, $I(t)$ is the number of infectious individuals at time t and N (t) = S (t) + I (t) + $R(t)$ is the total population at time t. This assumes that the disease latency period is negligible. The classical SIR model assumes homogeneous mixing between individuals and, therefore, the fraction $I(t)/N$ is the probability that a random contact would be with an infectious individual. This study assume that the time-scale of the epidemic is much faster than those of demographic processes. Moreover, recovered individuals are assumed to acquire immunity to the disease for at least the duration of the outbreak. The SIR transmission process (single outbreak) can then be modeled using the system of nonlinear differential equations:

$$\left.\begin{aligned} \frac{dS}{dt} &= -\beta S(t)I(t)/N \\ \frac{dI}{dt} &= \beta S(t)I(t)/N - \gamma I(t) \\ \frac{dR}{dt} &= \gamma I(t\,) \end{aligned}\right\} \tag{1}$$

where the dot denotes the time derivatives.

The dynamics of the HFMD outbreak in Thailand is modeled using the following based on the characteristics of HFMD. The SIR model is adopted to model the spread of the disease. Slight modifications were made on the SIR model. This describe the behavior of the disease as interpreted from the clinical studies of the disease. The compartmental model that describes the population dynamics of the HFMD is shown below.

$$\left.\begin{aligned} \frac{dS}{dt} &= \alpha N - \beta S(t)I(t)\text{-}\delta S(t) \\ \frac{dI}{dt} &= \beta S(t)I(t) - (\gamma+\delta)I(t) \\ \frac{dR}{dt} &= \gamma I(t)\text{-}\delta R(t) \end{aligned}\right\} \qquad (2)$$

The parameters that are used in the model;

dS/dt means change in susceptibles population per small unit time dt;

dI/dt means change in infective population per small unit time dt;

dR/dt means change in infective population per small unit time dt;

$S(t)$ is the number of susceptible population at time;

$I(t)$ is the number of infective population at time;

$R(t)$ is the number of recovered population at time;

α is the general population birth rate;

β is the infection rate of population;

γ is the recovery rate of population;

δ is the natural death rate of population.

The nonlinear system of differential equations formulated above has initial conditions

$S(0) = S_0$, $I(0) = I_0$, $R(0) = 0$

With $N = S(t) + I(t) + R(t)$. Dividing the equations in (2) by the constant total population size N such

s_t = $S(t)/N$ (The susceptible fraction of the population at time t.)

i_t = $I(t)/N$ (The infected fraction of the population at time t.)

r_t = $R(t)/N$ (The recovered fraction of the population at time t.) that

$$\begin{aligned} \frac{ds}{dt} &= \alpha - \beta si - \delta s \\ \frac{di}{dt} &= \beta si - (\gamma+\delta)i \\ \frac{dr}{dt} &= \gamma i\text{-}\delta r \end{aligned} \qquad (3)$$

With $s(t) + i(t) + r(t) = 1$

to compute the basic reproduction number:

$$R_0 = \frac{\beta}{\gamma+\delta} \qquad (4)$$

Population and Sample

This study use secondary data from data on website from Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health in Thailand. The data is through investigated for all cases in all health units and filled the investigation from laboratory samples cases tested by the Department of Medical Science, Ministry of Public Health.University laboratories have identified Coxsackievirus A and Enterovirus 71 (EV71) as main causes of infections. All data is analyzed and detailed monthly reports of cases in Table1.

Table 1 Number of cases and deaths related to outbreak in Thailand

Year	**Number of cases**												**Number of deaths**
	Jan	**Feb**	**Mar**	**Apr**	**May**	**June**	**July**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**	
2008	3,843	1,996	702	311	462	1,037	811	597	563	539	339	257	4
2009	356	662	1,003	433	529	1,614	668	514	734	642	780	862	2
2010	2,258	2,597	1,227	386	572	1,449	1,543	856	570	437	293	267	0
2011	280	256	316	226	585	3,091	3,144	2,804	3,380	1,840	1,216	1,058	6

Results

Between January 2008 and December 2011, a total of 47,372 HFMD cases less than 5 years old were reported and investigated by Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health in Thailand.

In this study, epidemic curves to show outbreak patterns of spread, magnitude of the outbreak and outbreak time trend are presented.

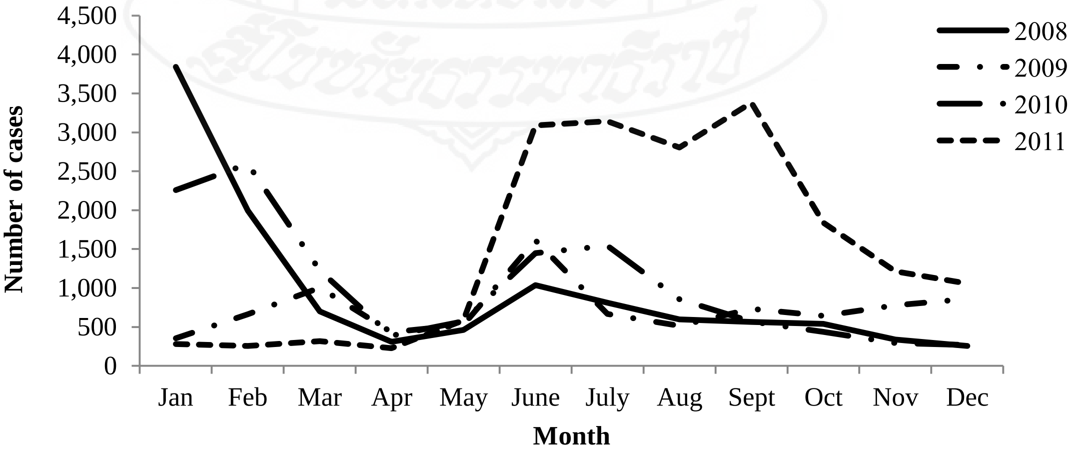

Figure 1 Monthly epidemic curves for HFMD between 2008 and 2011

An epidemic curve for HFMD outbreak shows in Figure 1. The classic epidemic curves from a propagated outbreak shows successively taller peaks, distanced one incubation period apart. However, the epidemic curve for this type of outbreak may not fit this exactly pattern. The monthly enteroviruses had a seasonal cycle between May and September, because the rainy season has temperature and humidity that reasonably effect distribution. In addition, case increases between January and February in 2008.

This study uses MATLAB program to run simulations; Susceptible-Infectious-Recovery (SIR) model for HFMD. For systems of nonlinear differential equations, that used the ode 15s build-in function which is the fourth order variable Runge-Kutta method. Model analysis is executed on the parameter values to find the effect of these values on the rate of spread in HFMD. The estimated parameters of the model that are used for the analysis are present in Table 2.

Table 2 Parameters used in simulation models of hand foot, and mouth disease

Parameters	Initial value	Illustration
Susceptible population (S)	0.95	Proportions for non-infected population less than 5 years, initial assumption= 0.95
Infection rate (β)	0.14286	1/Average latent period*
Recovered rate (γ)	0.1	1/Average duration of infectiousness*
General population birth rate (α)	3.18278x10^{-3}	Average birth rate,2008-2011**
Natural death rate (δ)	3.06605x10^{-5}	For population less than 5 years**

* " Situation of Hand Foot Mouth" by Bureau of Epidemiology Department of Disease Control Ministry of Public Health, 2012.

** "Health information" by Bureau of Policy and Strategy Ministry of Public Health, 2012.

The number of contacts between susceptibles and HFMD patients during infectious period is

$$\sigma = \frac{\beta}{\gamma} = \frac{0.14286}{0.1} \qquad (5)$$

$$\sigma = 1.4286$$

This means that on the average one HFMD patient contacts 1.4286 susceptible group people in Thailand during infectious period.

To analyze the data, reproductive number R_0 is calculated by substituting the parameter values in table 2 into equation (4). Reproductive number is 1.42813.

Model analysis is executed on the parameter values to find the effect of these values on the rate of spread in HFMD. The estimated parameters of the model that used for the analysis are presented in table 2

In these simulations, the parameter values is given in Table 2 for the model equations.With the nature of an infectiveness into a susceptible group population of Thailand, the population changes from being infectious group independent to the state of endemicity. The dynamics of the disease by the use of simulations as the following instances: (i) The presence of infection group (ii) Increase in initial proportion of infection group in the population.

To depict the dynamics of the compartments during the outbreak, it can be assumed that the initial proportions of susceptible group, infected group and the recovered group condition are $s(t) = 0.95$, $i(t) = 0.05$ and$(t) = 0.0$, respectively.

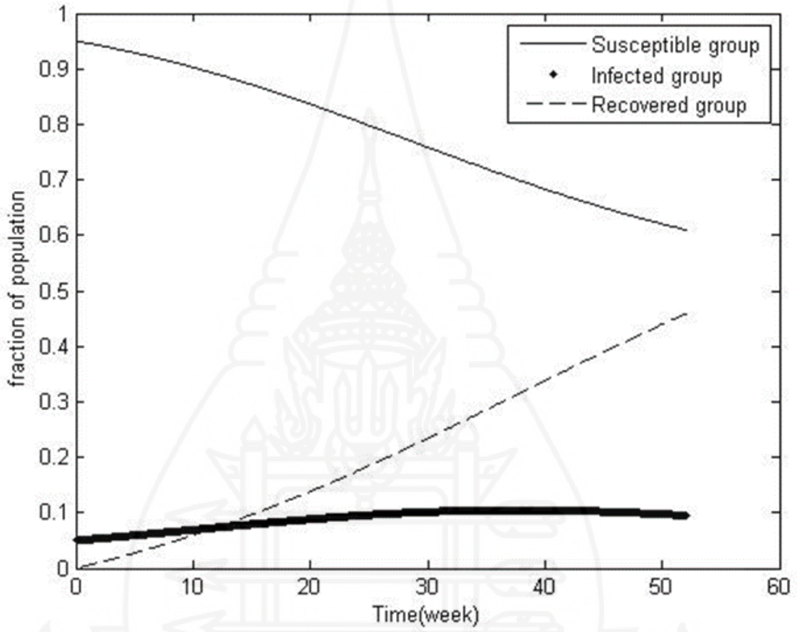

Figure 2 The dynamics of the various compartments during the outbreak

The initial proportion of infected group is 0.05 from Figure 2, the proportion of the susceptible group declines from an initial value of 0.95 decreases and gradually afterwards. On the other hand, the proportion of the infected group increase from the first week and remains that value onwards, and increases again between the 33'rd week and the 42'nd week. Also, the proportion of the recovered group increases from the first week and maintain that value onwards the 52'th week. Hence, the susceptible group decrease due to the introduction of the infected group. While susceptible group more infect, due to their high recovery rate, the number keeps on reducing. From the result, it can be concluded that fast and effective actions have to be taken by health authorities and policy makers in order to reduce the spread of HFMD.

Conclusion

There have been plenty of papers on how to control and prevent HFMD from a public health. However, there are few works constructing differential equations models to simulate data of HFMD (Chuo et al., 2008, Liu, 2011, Roy & Halder, 2010, Wang & Sung, 2004). All the parameters of the model are estimated using average number of adequate contacts of a person per time and depend on the population verifying the rationality of the parameters. Consequently, the demonstrated rationality of the parameters in this proposed model is consistence with real situation. Moreover, this study applies proportion of population per unit time.

Numerical simulations and model analysis is extensively helpful in the determination of the effect of the various parameters especially the transmission rate and recovery rate on the spread of the disease. From the basic reproductive number is larger than 1. Thus, this concludes that HFMD will persist in Thailand under the current conditions.

There is no effective vaccine or antiviral treatment specifically for HFMD. In addition Ministry of Public Health can provide some preventive measures to control the HFMD. If the preventive measures proposed in our paper is implemented, HFMD will be controlled quickly and the number of infection group will decline rapidly over a period of time outbreak.

Recommendation

Even though the SIR model provides a general framework to understand the spread of a disease, it may be too simple to accurately model a real epidemic like the outbreak of HFMD in Thailand. There are various limitations or shortcomings in this model, which are explained as follows:

1. There should be an exposed (but not yet infected) class; people have to be exposed to the disease before they can be infected and consequently become infectious. This is the case for the HFMD. A HFMD patient becomes infectious group only after the infected person develops the symptoms. Therefore, the limitations and flaws in the SIR model can be modified and extended to the Susceptible- Exposed-Infected-Recovered (SEIR) model. The model equation is kept simple: a deterministic, compartmental, mathematical model is formulated to describe the transmission dynamics of HFMD.

2. The progression of HFMD within the total population can be simplified to four differential equations. These four equations represent four different groups of people: the susceptible group, the exposed group, the infective group, and the recovered group. The susceptible gruop (represented by "S") are people that have never come into contact with HFMD, the exposed group (represented by "E") are people who have come into contact with the disease but are not yet infective, the infective group (represented by "I") are people who have become infected with HFMD and are able to transmit the disease, and the recovered group (represented by "R") are people that have recovered from HFMD. Note that $S+E+I+R=N$, where N being the total population is constant. It is assumed that the population

is a value between zero and N, where N is the population at full capacity. It is further assumed that all individuals are equally likely to be infected by the infectious individuals in a case of contact except those who are immuned. The undetected or late detected infectious individuals are ones contributing to disease transmission and spread. Further research work is recommended particularly for non-constant and heterogeneous population.

References

Anderson, Roy M., May, Robert M. (1991). *Infectious diseases of humans : dynamics and control*. Oxford; New York: Oxford University Press.

Bradley, D. J. (1982). Epidemiological models — theory and reality. In R. Anderson (Ed.), *The Population Dynamics of Infectious Diseases: Theory and Applications* (pp. 320-333): Springer US.

Bureau of Epidemiology Department of Disease Control Ministry of Public Health (2012). Situation of Hand Foot Mouth. Retrived Aug 14, 2012, from http://www.boe.moph.go. th/urgent.php?cat=26.

Bureau of Policy and Strategy Ministry of Public Health. (2012). Health information. Aug 14, 2012, from http://bps.ops.moph.go.th/Healthinformation/index.htm

Chuo, F., Sing, T., & Labadin, J. (2008, 13-15 May 2008). A Simple Deterministic Model for the Spread of Hand, Foot and Mouth Disease (HFMD) in Sarawak. Paper presented at the Modeling & Simulation, 2008. AICMS 08. Second Asia International Conference on.

Heesterbeek, J. A. P., Roberts, M. G., Heesterbeek, J. A. P., & Roberts., M. G. (1995). *Mathematical Models for Microparasites of Wildlife Ecology of Infectious Diseases in Natural Populations*: Cambridge University Press.

Kermack, W. O., & McKendrick, A. G. (1991a). Contributions to the mathematical theory of epidemics--I. 1927. *Bull Math Biol, 53*(1-2), 33-55.

Kermack, W. O., & McKendrick, A. G. (1991b). Contributions to the mathematical theory of epidemics--II. The problem of endemicity.1932. *Bull Math Biol, 53* (1-2), 57-87.

Kermack, W. O., & McKendrick, A. G. (1991c). Contributions to the mathematical theory of epidemics--III. Further studies of the problem of endemicity. 1933. *Bull Math Biol, 53*(1-2), 89-118.

Liu, J. (2011). Threshold dynamics for a HFMD epidemic model with periodic transmission rate. *Nonlinear Dynamics, 64*(1-2), 89-95.
doi: 10.1007/s11071-010-9848-6

Roy, N., & Halder, N. (2010). Compartmental Modeling of Hand, Foot and Mouth Infectious Disease (HFMD).*Research Journal of Applied Sciences, 5*(3), 177-182. doi: 10.3923/rjasci.2010.177.182

Urashima, M., Shindo, N., & Okabe, N. (2003). Seasonal models of herpangina and Hand-Foot-Mouth Disease to simulate annual fluctuations in urban warming in Tokyo. *Jpn J Infect Dis*, *56*(2), 48-53.

Wang, Y.-C., & Sung, F.-C. (2004). Modeling the Infections for Enteroviruses in Taiwan. Retrieved January 15, 2012, from https://gra103.aca.ntu.edu.tw/gdoc/95/D91844001a.pdf?origin=publication_detail

World Health Organization Western Pacific Region. (2012). Emerging disease surveillance and response. Retrived Aug 14, 2012, from http://www.wpro.who.int/emerging_diseases/HFMD/en/index.html.

Zhu,Q., Hao, Y., Ma, J., Yu, S., & Wang, Y. (2011). Surveillance of Hand, Foot, and Mouth Disease in Mainland China (2008–2009). *Biomedical and Environmental Sciences*, *24*(4), 349-356.