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SENSITIVITY ANALYSIS OF HAND FOOT MOUTH DISEASE MODEL WITH PUBLIC HEALTH RESOURCES

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Abstract

In this study, we proposed and analyzed a mathematical model to study the dynamics of hand foot mouth disease with effects of limited public health resources. The model is analysed using stability theory of differential equations and computer simulations. Sensitivity analysis is carried out to show the effects of model parameters to disease spread and control. The results showed that there were two equilibrium points; disease-free equilibrium and endemic equilibrium point. The qualitative behaviour results depended on the basic reproductive number (R_0). We obtained the basic reproductive number by using the next generation matrix. Stabilities of the model are determined by Routh-Hurwitz criteria. If $R_0 < 1$, , then the disease- free equilibrium point is local asymptotically stable, but if $R_0 > 1$, then the endemic equilibrium point is local asymptotically stable. The graphical representations are provided to qualitatively support the analytical results. It concluded that with an increase in the number of public health resources, the number of infected human will be reduced. Sensitivity analysis indicated that the transmission rate β was the most sensitive parameter to the basic reproductive number.‘

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1. Introduction

Hand Foot Mouth Disease(HFMD) is an acute viral illness that primary affects infants and children under the age of 10, but can also affect older children, teenagers and adults. HFMD is caused by several different viruses that belong to the enterovirus group, it is mostly caused by coxsakievirus(CV-A16), and human enterovirus(EV71)[1]. The virus of HFMD spreads easily through coughing, sneezing, and infected stool. It usually takes 3-7 days for a person to get symptoms of HFMD after being exposed to the virus of HFMD. Although many HFMD infected people remain asymptomatic, the symptoms of HFMD include sorein or on the mouth and on the hands, feet, and sometimes the buttocks and legs. The sores may be painful, and these sores may be eased with the use of medication[2]. During the outbreaks, the patients are advised to be quarantined at home or hospitalized. This is to avoid the direct contact with the patients as the virus can be easily transmitted through aerosol or ingestion and fomites [3]. The disease can transmitted through contact with contaminated environments such as water, food, or surfaces [4]. Most infected patients can recover in 7-10 days without medical treatment. However, the patients have been associated with meningitis and encephalitis. It can cause severe complications, including neurological, cardiovascular, and respiratory problems [5]. The delay in diagnosis and treatment may cause severe clinical symptoms which lead to the death of infected children. Nowadays, there are no specific vaccination or antivirus treatments available for curing the HFMD [5].

Mathematical model have been become important tools for investigating and understanding transmission dynamics and disease control. In 2015, Karaket et al proposed the SEIQR model of HFMD with effect of hand washing campaign [6]. Tan and Cao built and studied the dynamics and optimal control of a hand foot mouth disease model with vaccination [7]. Wu established a SEIR model with standard incidence rate to describe transmission of HFMD and also established a formula to estimate the basic reproductive number of HFMD. Chadsuthi and Wichapeng proposed a new model to investigate the effect of indirect transmission from contaminated environmental and the impact of asymptomatic individuals [8]. Li et al studied modeling and preventive measures of hand foot mouth disease in China [9]. In 2016 , Abdelrazec et al. formulated a model of dengue fever with nonlinear recovery rate, the impact of available resources of health system on the spread and control of the disease[10]. Therefore, it is important to study the impact of limited hospital resources capacity on HFMD. For this study, the objective is to propose a model to study the impact of limited public health resources on dynamics of HFMD and its control.

This paper is organized as follows. In section 2 we presented a modified

model from [9] by taking into account the limited public health resources. In section 3, we applied the model analysis to determine the equilibrium points, stability analysis and sensitivity analysis. In section 4, we carried out the numerical results to support the theoretical results by computer simulations. Finally, in section 5, we concluded both theoretical and numerical results of this study.

2. Model formulation

In this study, the total human population (N) at time t is divided into five compartments, namely: susceptible (S) represents the number of individuals who are susceptible to the disease; exposed (E) represents the number of asymptomatic infectious individuals who have been infected with the disease but do not show any sign of the symptoms; infected (I) represents the number of symptomatic infectious individuals who have been infected with the disease and not hospitalized; quarantined (Q) represents the number of symptomatic infectious individuals who have been infected with the disease and hospitalized, and recovered (R) represents the number of individuals who have recovered from the disease[9] as shown in Fig. 1.

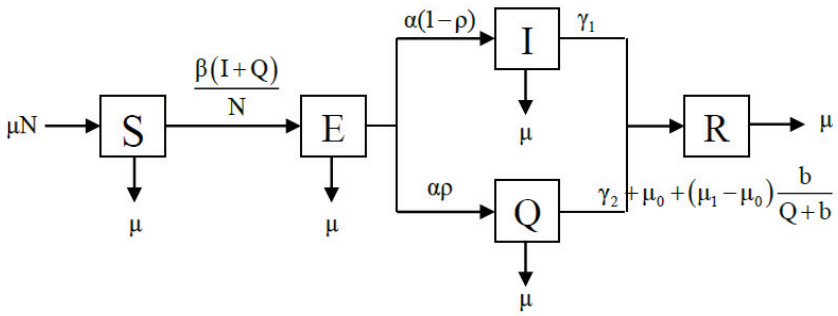


Fig.1.Flow chart of compartment of the HFMD model.

In order to understand the effect of limited resources such as hospital beds and their availabilityon the transmission and dynamics of HFMD. We introduce a recovery rate, denoted by μ, incorporating the impact of the capacity and limited resources of the health care system, in terms of hospital of bedpopulation ratio, which is denoted by $b > 0$. On the other hand, μ also depends on the number of infectious individual I, so that μ is a function of both b and I. It is obvious that the per capita recovery rate $\mu(b, I)$ is a decreasing function of I and increasing function of b, which is bounded above and below, respectively, by μ_0 and μ_1 for any $b > 0$. Here, μ_1 is the maximum per capita recovery rate due to the sufficient health care resource and few infectious individuals. μ_0 is

the minimum per capita recovery rate due to the function of basic clinical resources. If the number of new infectious individuals becomes larger and larger, the available resources cannot satisfy such large demand for treatment, but it is still possible that a certain amount of infectious individuals can be treated and get recovered, and minimum recovery rate μ_0 can be sustained. Based on above assumption, we start with the simple function in [9]. For this study, we introduce the function $\mu = \mu(Q, b) = \mu_0 + (\mu_1 - \mu_0)\frac{b}{Q+b}$

The dynamics of nonlinear of the model is described by the following system of nonlinear differential equations:

$$\frac{dS}{dt} = \mu N - \frac{\beta S(I+Q)}{N} - \mu S \tag{1}$$

$$\frac{dE}{dt} = \frac{\beta S(I+Q)}{N} - \alpha E - \mu E \tag{2}$$

$$\frac{dI}{dt} = \alpha(1-\rho)E - \gamma_1 I - \mu_1 I \tag{3}$$

$$\frac{dQ}{dt} = \alpha\rho E - \gamma_2 - \mu_2 Q - \mu_0 Q - (\mu_1 - \mu_0)\frac{bQ}{Q+b} - \mu Q \tag{4}$$

$$\frac{dR}{dt} = \gamma_1 I + \gamma_2 Q + \gamma_0 Q + (\mu_1 - \mu_0)\frac{bQ}{Q+b} - \mu R \tag{5}$$

where μ is the natural birth(death) rate; β is the transmission rate; α is the rate of progression to the infectious and not hospitalized; ρ is the proportion of the infectious and hospitalized; γ_1 is the recovery rate of the infectious and not hospitalized; γ_2 is the recovery rate of the infectious and hospitalized individuals; b is the impact of the capacity and limit resources of the health care system, in terms of hospital bed- population ratio; μ_0 is the minimum per capita recovery rate due to the function of basic clinical resources; μ_1 is the maximum per capita recovery rate due to the sufficient health care resource and few infectious individual.

3. Model analysis

3.1 Disease-free equilibrium point (DFE)

To find the disease-free equilibrium point (DFE) which is denoted by 0 E .We equated the right hand side of equation (1)-(5) to zero. In the absence of the disease in the community, $I = 0$ and solving for the state variables:

$$S = N,\ E = 0,\ Q = 0,\ R = 0$$

Therefore, the disease-free equilibrium point $E_0(N, 0, 0, 0, 0)$.

3.2 Disease endemic equilibrium point (DEE)

In case of the disease is presented in the community, $I^* > 0$. To obtained it, we equated equation (1)-(5) to zero. We denoted the disease endemic equilibrium point (DFE) by $E_1(S^*, E^*, I^*, Q^*, R^*)$. Then, we obtain $S^* = \frac{\alpha\rho'\mu N - \psi_1\psi_2 I^*}{\alpha\rho'\mu}$, $E^* = \frac{\psi_1 I^*}{\alpha\rho'}$, $Q^* = \frac{\psi_1\psi_2\beta I^{*2} + (\psi_1\psi_2 - \beta\alpha\rho')\mu N^*}{\beta\alpha\rho'\mu N - \psi_1\psi_2\beta I^*}$, $R^* = \frac{\psi_1\psi_2\beta(\rho\psi_1 + \rho'(\gamma_1+\mu)I^{*2} - (\rho\psi_1\beta\alpha\rho'\mu + \rho'^2\gamma_1\beta\alpha\mu - \rho'\mu^2\psi_1\psi_2 + \rho^2\mu^2\beta\alpha)NI^*}{\rho'\mu\beta(\psi_1\psi_2 I^* - \rho'\alpha\mu N)}$ and the value of I^* is the positive solution of cubic equation $AI^*3 + BI^{*2} + CI^* + D = 0$, where $\psi_1 = \gamma_1 + \mu, \psi_2 = \alpha + \mu, \rho' = 1 - \rho, \Delta\mu = \mu_1 - \mu_2, q_1 = \psi_1\psi_2\beta$, $q_2 = \psi_1\psi_2\mu N, q_3 = \beta\alpha\rho'\mu N, q_4 = \gamma_2 + \mu_0 + \mu, q_5 = \frac{\rho\psi_1}{\rho'}, q_6 = q_2 - q_3$, $A = q_4 q_1^2, B = 2q_1 q_4 q_6 - bq_4 q_1^2 - \Delta\mu b q_1^2 - q_1 q_3 q_5 + q_5 q_1^2 + q_1 q_5 q_6 - bq_5 q_1^2$, $C = q_4 q_6^2 + bq_1 q_3 q_4 - bq_1 q_4 q_6 + \Delta\mu b q_1 q_3 - q_3 q_5 q_6 + 2bq_1 q_3 q_5, D = bq_3 q_4 q_6 + \Delta\mu b q_3 q_6 - bq_5 q_3^2$.

3.3 Basic reproductive number (R_0)

In epidemiology, the basic reproductive number (R_0) is the average number of secondary infected individuals that are produced by a single infection in an entirely susceptible population[11]. We obtained the basic reproductive number by using the next generation matrix [12]. Rewriting the system model in matrix form:

$$\frac{dX}{dt} = F(X) - V(X)$$

$$F(X) = \begin{bmatrix} 0 \\ \frac{\beta S(I+Q)}{N} \\ N \\ 0 \\ 0 \\ 0 \end{bmatrix} \text{ and } V(X) = \begin{bmatrix} \frac{\beta S(I+Q)}{N} + \mu S - \mu N \\ \psi_2 E \\ \psi_1 I - \alpha\rho' E \\ q_4 Q + \frac{b\Delta\mu Q}{Q+b} - \alpha\rho E \\ \mu R + \mu Q - \gamma_1 I - q_4 Q - \frac{b\Delta\mu Q}{Q+b} \end{bmatrix}$$

where $F(X)$ is the non- negative matrix of new infection terms and $V(X)$ is the non-single matrix of remaining transfer terms. Setting

$$F = \left[\frac{\partial F_i(E_0)}{\partial X_i}\right] \text{ and } V = \left[\frac{\partial V_i(E_0)}{\partial X_i}\right]$$

for all $i, j = 1, 2, 3, 4, 5$ be the Jacobian matrix of $F(X)$ and $V(X)$ at E_0.

The basic reproductive number of the model can be evaluated through the spectral radius (the largest eigenvalues) of FV^{-1} is denoted by $\rho(FV^{-1})$. Then, we get the basic reproductive number R_0, where

$$R_0 = \frac{\beta\alpha(1-\rho)}{(\gamma_1+\mu)(\alpha+\mu)} + \frac{\beta\alpha\rho}{(\gamma_2+\mu+\mu_1)(\alpha+\mu)}$$

3.4 Sensitivity analysis of the model parameters

On the basic parameters, we carried out sensitivity analysis. This helped us to check and identify parameters that can impact the basic reproductive number. To obtained sensitivity analysis, we followed the technique outlined by [13]. This technique develops a formula to obtain the sensitivity index of all the basic parameters, defined as $\Delta_x^{R_0} = (\frac{\partial R_0}{\partial x})(\frac{x}{R_0})$, for x represents all the basic parameters. For example, the sensitivity index of R_0 with respect to β is $\Delta_\beta^{R_0} = (\frac{\partial R_0}{\partial \beta})(\frac{\beta}{R_0}) = 1$. With respect to the remaining parameters, $\Delta_\mu^{R_0}, \Delta_\rho^{R_0}, \Delta_\alpha^{R_0}, \Delta_{\gamma_1}^{R_0}, \Delta_{\gamma_2}^{R_0}$, and $\Delta_{\mu_1}^{R_0}$, are obtained and evaluated at

$$\mu = 0.000039139, \beta = 1, \rho = 0.01, \alpha = 1, \gamma_1 = 0.7348,$$

$$\gamma_2 = 0.2013, \mu_0 = 0.1, \mu_1 = 2, b = 1.$$

Their sensitivity indices are in Table 1.

Table 1: Sensitivity indices of model parameters

Parameter	Description	Sensitivity index
β	the transmission rate	+1.00
γ_1	the recovery rate of the infectious and hospitalized individuals	-0.996586
ρ	the proportion of the infectious and hospitalized	-0.006706
μ_1	the maximum per capita recovery rate due to the sufficient health care resource and few infectious individuals	-0.003053
γ_2	the recovery rate of the infectious and hospitalized individuals	-0.000307
μ	the natural birth(death) rate	-0.000092
α	the rate of progression to the infectious and not hospitalized	+0.000039
b	the impact of the capacity and limit resources of the health care system, in terms of hospital bed- population ratio	0
μ_0	the minimum per capita recovery rate due to the function of basic clinical resources	0

3.4.1 Interpretation of sensitivity Indices

The sensitivity indices of the basic reproductive number with respect to main parameters are arranged orderly in Table 1. Those parameters that have positive indices (β and α) show that they have great impact on spreading the disease in the community if there are increasing. Due to the reason that the basic reproductive number increase as their values increase, it means that the average number of secondary cases of infection increases in the community. And also those parameters in which their sensitivity indices are negative ($\gamma_1, \rho, \mu_1, \gamma_2$ and μ) have an influence of minimizing the burden of the HFMD in the community as their values increase while the other are left constant. And also as their values increase, the basic reproductive number decrease, which leads to minimizing the endemicity of the HFMD in community.

3.6 Stability analysis

The local stability of an equilibrium point is determined from the Jacobian matrix of the system of ordinary differential equation (1)-(5) evaluated at each equilibrium point. We find the Jacobian matrix of system (1)-(5) at the disease free equilibrium point E_0 as follows:

$$J_0 = \begin{bmatrix} -\mu & 0 & -\beta & -\beta & 0 \\ 0 & -\psi_2 & \beta & \beta & 0 \\ 0 & \alpha\rho' & -\psi_1 & 0 & 0 \\ 0 & \alpha\rho & 0 & -q_4 - \Delta\mu & 0 \\ 0 & 0 & \gamma_1 & q_4 + \Delta\mu - \mu & -\mu \end{bmatrix}$$

We obtained a characteristic polynomial from $\det(J_0 - \lambda I) = 0$.

$$\det(J_0 - \lambda I) = \begin{vmatrix} -\mu - \lambda & 0 & -\beta & -\beta & 0 \\ 0 & -\psi_2 - \lambda & \beta & \beta & 0 \\ 0 & \alpha\rho' & -\psi_1 - \lambda & 0 & 0 \\ 0 & \alpha\rho & 0 & -q_4 - \Delta\mu - \lambda & 0 \\ 0 & 0 & \gamma_1 & q_4 + \Delta\mu - \mu & -\mu - \lambda \end{vmatrix}$$

The eigenvalues of J_0 are obtained by solving $\det(J - \lambda I) = 0$. We obtained the characteristic equation:

$$(\lambda + \mu)^2(\lambda^3 + U\lambda^2 + V\lambda + W) = 0,$$

where

$U = q_4 + \Delta\mu + \psi_1 + \psi_2$

$V = (\psi_1 + \psi_2)(q_4 + \Delta\mu) + \psi_1\psi_2 - \alpha\beta$

$W = \psi_1\psi_2(q_4 + \Delta\mu) - \alpha\rho\beta\psi_1 - \alpha\rho'\beta(q_4 + \Delta\mu)$

Two eigenvalues are $\lambda_{1,2} = -\mu$. The other three eigenvalues are the solutions of the cubic equation $\lambda^3 + U\lambda^2 + V\lambda + W = 0$. The roots of this equation are negative if the coefficients satisfied the three conditions of Routh-Hurwitz criteria [14]. E_0 will be locally asymptotically stable when the coefficients satisfy this conditions $U > 0, V > 0, UV > W$.

Thus, the diseasefree equilibrium point will be locally asymptotically stable.

To determine the stability of the endemic equilibrium point E_1, we evaluate the Jacobian matrix of system (1)-(5) at the endemic equilibrium point E_1 to get

$$J_1 = \begin{bmatrix} -\frac{\beta(I^*+Q^*)}{N} & 0 & -\frac{\beta S^*}{N} & \frac{-\beta S^*}{N} & 0 \\ \frac{\beta(I^*+Q^*)}{N} & -\psi_2 & \frac{\beta S^*}{N} & \frac{\beta S^*}{N} & 0 \\ 0 & \alpha\rho' & -\psi_1 & 0 & 0 \\ 0 & \alpha\rho & 0 & -q_4 - \frac{b^2\Delta\mu}{(Q^*+b)^2} & 0 \\ 0 & 0 & \gamma_1 & q_4 + \frac{b^2\Delta\mu}{(Q^*+b)^2} - \mu & -\mu \end{bmatrix}$$

The characteristic equation of Jacobian matrix at E_1 becomes

$$(\lambda + \mu)(\lambda^4 + P_1\lambda^3 + P_2\lambda^2 + P_3\lambda + P_4) = 0,$$

where $j_1 = \frac{\beta(I^*+Q^*)}{N} + \mu$, $j_2 = \frac{\beta(I^*+Q^*)}{N}$, $j_3 = \frac{\beta S^*}{N}$, $j_4 = q_4 + \frac{b^2\Delta\mu}{(Q^*+b)^2}$, $j_5 = q_4 + \frac{b^2\Delta\mu}{(Q^*+b)^2} - \mu$, $P_1 = \psi_1 + \psi_2 + j_1 + j_4$, $P_2 = \psi_1\psi_2 - \alpha j_3 + \psi_1 j_1 + \psi_1 j_4 + \psi_2 j_4 + j_1 j_4$, $P_3 = \psi_1\psi_2 j_1 + \psi_1\psi_2 j_4 - \alpha\rho\psi_1 j_3 - \alpha\rho' j_3 j_4 - \alpha\mu j_3 + \psi_1 j_1 j_4 + \psi_2 j_1 j_4$, $P_4 = \psi_1\psi_2 j_1 j_4 - \alpha\rho\mu\psi_1 j_3 - \alpha\rho'\mu j_3 j_4$.

One of eigenvalues is $\lambda_1 = -\mu < 0$. The four eigenvalues of $\lambda^4 + P_1\lambda^3 + P_2\lambda^2 + P_3\lambda + P_4$ will have negative real part if they satisfy the Routh-Hurwitz criteria [14]. Thus, E_1 will be locally asymptotically stable for $R_0 > 1$ when $\lambda^4 + P_1\lambda^3 + P_2\lambda^2 + P_3\lambda + P_4 = 0$ satisfies the following conditions:

$$P_1 > 0, \quad P_3 > 0, \quad P_1P_2P_3 > P_3^2 + P_1^2P_4.$$

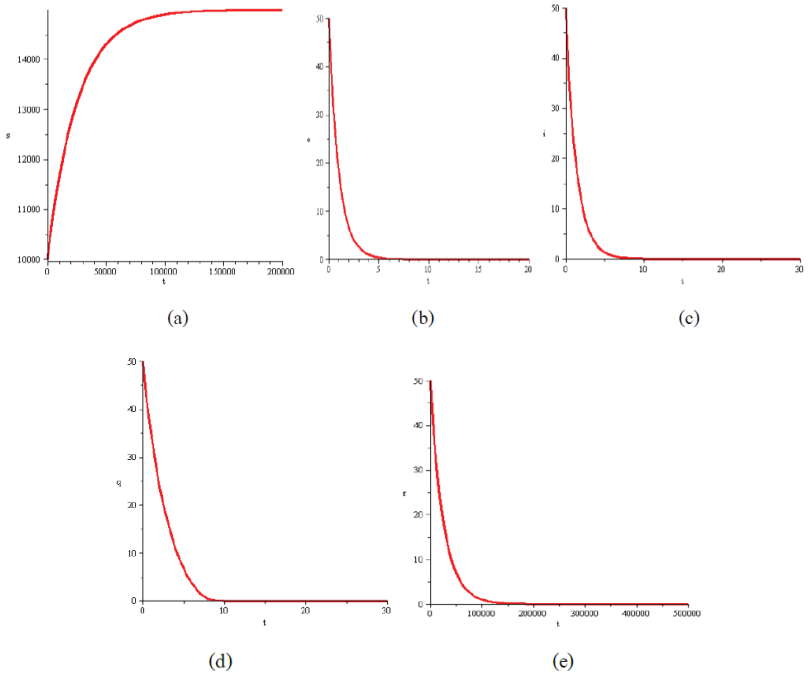
4. Numerical results

The parameters used in the numerical simulation are given in Table 2.

Table 2. Parameter values used in numerical simulation at disease free state.

Parameter	Description	Values
N	total number of human population	15,000 Human
μ	the natural birth(death) rate	0.000039139 per day
β	the transmission rate	0.5149 per day
ρ	the proportion of the infectious and hospitalized	0.01
α	the rate of progression to the infectious and not hospitalized	1 per day
γ_1	the recovery rate of the infectious and not hospitalized	0.7348 per day
γ_2	the recovery rate of the infectious and hospitalized individuals	0.2013 per day
μ_0	the minimum per capita recovery rate due to the function of basic clinical resources.	0.1 per day
μ_1	the maximum per capita recovery rate due to the sufficient health care resource and few infectious individuals	2 per day
b	the impact of the capacity and limit resources of the health care system, in terms of hospital bed- population ratio	10 bed

Fig. 2 Time series of (a) susceptible (S), (b) exposed (E), (c) infectious (I), (d) quarantined (Q), (e) recovered. The values of parameters are in Table 2 and $\lambda_{1,2} - 0.000039139$, $\lambda_3 = -0.14024$, $\lambda_4 = -1.58866024$, $\lambda_5 = -2.20732024$, $R_0 = 0.696002 < 1$.



We see that the solutions converge to the disease free equilibrium state $E_0(15,000, 0, 0, 0, 0)$ as shown.

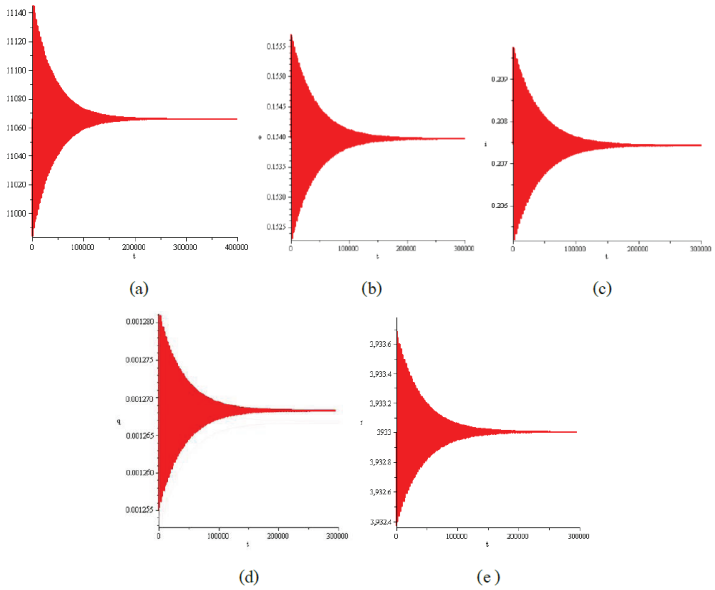


Fig. 3 Time series of (a) susceptible (S), (b) exposed (E), (c) infectious (I), (d) quarantined (Q), and (e) recovered. The values of parameters are in Table 2. except $\beta = 1$ and $b = 1.$, $\lambda_1 = -0.000039139$, $\lambda_2 = -1.74022$, $\lambda_{4,5} = -0.0000116644 \pm 0.00242884i$, $R_0 = 1.3555 > 1$.

We see that the solutions converge to the endemic equilibrium state $E_1(11,066.7, 0.153941, 0.207394, 0.0012687, 3932.97)$ as shown.

5. Discussion and Conclusions

In this paper, we proposed and analyzed the model for the dynamics of hand foot mouth disease by taking into account the limited public health resources. We obtained that when the basic reproductive number $R_0 < 1$ with $\beta = 0.5149$, $b = 10$, the trajectory solutions approached to disease-free equilibrium state as shown in Fig. 2. From this result, we can propose some preventive measures as follow, reducing the transmission rate β for the susceptible can effectively control the HFMD (see Fig. 2 c, d). So health care education such as washing hands before meals and after using the toilet, advocate good personal hygiene.

Kindergartens should clean and disinfect toys and appliances every day, which

the same result as in [9]. If $R_0 > 1$ with $\beta = 1,\ b = 1$, the trajectory solutions approached to endemic equilibrium state as shown in Fig. 3. In some hospital, when the number of physicians, nurses, hospital beds and isolation places is not enough, this imply the recovery rate is low [10]. For the sensitivity indices, we found that the most sensitivity parameter is the transmission rate (β). It then follows by the recovery rate of the infectious and not hospitalized (γ_1), and the proportion of the infectious and hospitalized (ρ), respectively.

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