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Global Stability of the Transmission of Hand-Foot-Mouth Disease According to the Age Structure of the Population

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Abstract

This study investigates a transmission model of Hand-Foot-Mouth disease (HFMD) where the age structure of the population is taken into account. Most infections in Thailand occur among children below the age of 10 years, whose immunity to HFMD is lower than people of age greater than 10 years. Therefore, a mathematical model was developed in which the population was separated into two groups with respect to age: one comprised of children aged less than 10 years, and another comprised of the rest of the population. The reproductive number was obtained by the next-generation matrix approach. Global asymptotical stability of the developed model was assured using Lyapunov's direct method. The model was validated by showing that the 2D and 3D trajectories of the numerical solutions for the different sub-population groups converged to the endemic equilibrium states when the reproduction number was greater than one, thus supporting the theoretical conclusions. Results show that the time series behaviors of the different normalized populations groups converge to the disease-free state when the values of the parameters are such that the basic reproductive number is 0.591481 (i.e., less than one) and to an endemic state when the values of the parameters are such that $R_0 = 54.4523$ and $R_0 = 192.575$ (i.e. greater than one). The results of this study can suggest ways for reducing the outbreak of this disease.

Keywords: Hand-Foot-Mouth Disease (HFMD); SEIR model; mathematical model; stability; age structure
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1. Introduction

Hand-Foot-Mouth Disease (HFMD) is a disease caused by enteroviruses, Coxsackie virus groups A and B [1-4]. The disease often is found in children because children have lower immunity. The disease only infects humans. The symptoms appear 3-7 days after the exposure to the virus [2, 5]. Most infected people exhibit only asymptomatic symptoms or a slight fever which is called Exanthematous fever. Some, however, will develop blisters in the mouth. When this happens, the sick person is said to be infected with Herpangina Hand-Foot-Mouth Disease, a viral haemorrhagic conjunctivitis disease. As we mentioned, most infected people do not show any symptoms. However, children of age less than 10 years are more susceptible to contract the disease than those older than 10 years of age since they may not have developed the immunity obtained from the asymptomatic infections. HFMD is transmitted through direct contact between the mouth and a hand or shared object such as spoon, glass or toy that has been contaminated with the mucus or saliva from the blister of an infected person. Most of this contact and spread occurs among children in nurseries or lower grades at schools. Children in higher grades and adults would have developed the immunity to the virus through exposure to it that they were unaware of [6]. HFMD became an important public health problem in Thailand in 1997, and outbreaks of Enterovirus 71 infections were reported in other countries in the Asia-Pacific region, such as Malaysia and Brunei [7]. In 1998 and 2000, outbreaks were reported in Taiwan and Singapore. Thailand reported outbreak beginning in 2003, and these have continued until the present [8-10]. Figure 1 shows the outbreaks of HFMD in Thailand over the period 2003-2018. The age distribution of the patients in 2020 was reported to be 93.37% for patients aged between 0-10 years, and 6.63% for patients older than 10 year of age [11]. As we see, the younger the child is, the higher the incidence of infection is. This is because they have not yet been exposed to the virus. If they had been exposed, they would have developed immunity to the disease. According to Figure 2, the study of HFMD divides participants into 2 groups; the first group is people between 0-10 years and the other group is people older than 10 years, because two groups have distinctly different infections.

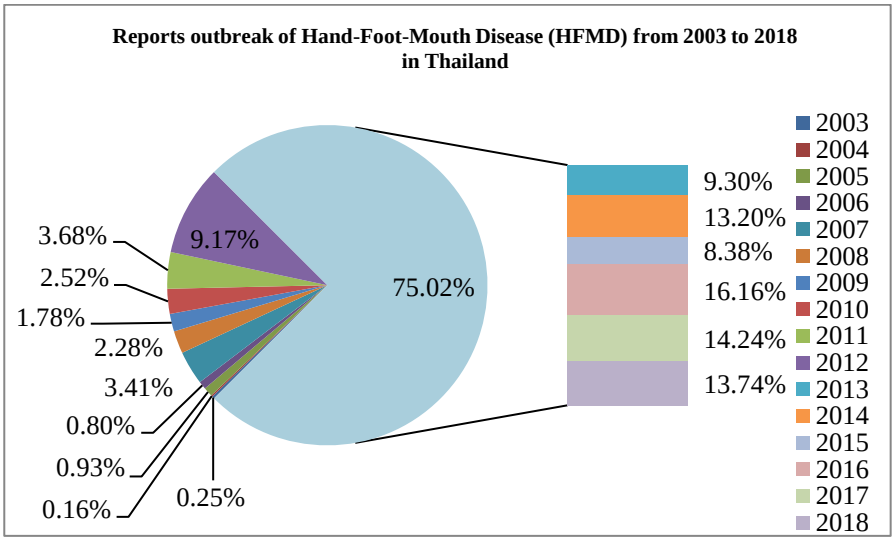

Figure 1. Reports on outbreaks of Hand-Foot-Mouth Disease (HFMD) from 2003 to 2018 in Thailand [12]

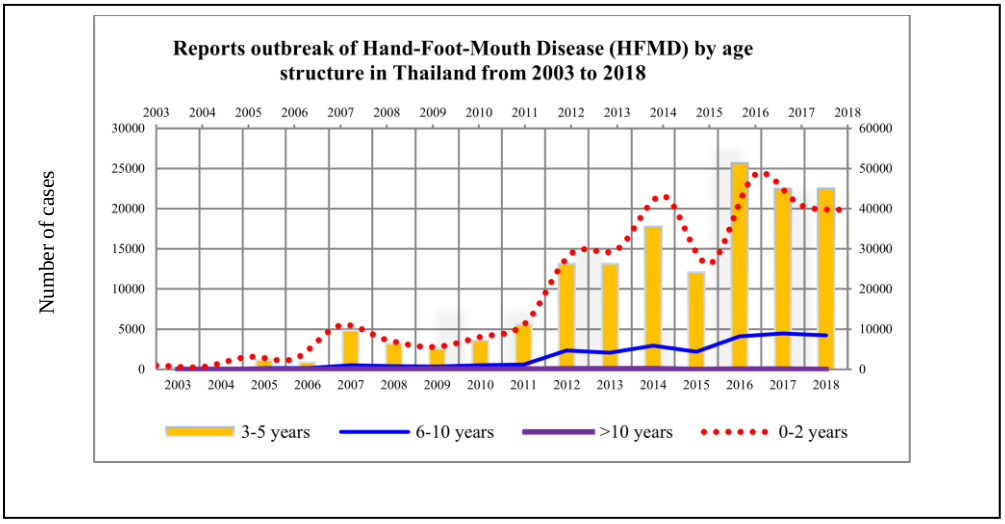

Figure 2. Reports on outbreaks of Hand-Foot-Mouth Disease (HFMD) by age structure in Thailand from 2003 to 2018 [13]

Several mathematical models to describe HFMD have been developed in the literature. In 2016, Li *et al.* [14] developed a SEIHR (S = Susceptible, E = Infected but not infectious, I = Infectious (clinical and subclinical), H = Hospitalized and R = Recovered) model to study HFMD in China. In their model, like ours, the population was divided in two groups; children (0-16 years) and adults (older than 16 years) and applied to the HFMD data for China from 2009 to 2014. Earlier, Wang *et al*. [3] conducted a time series analysis on its relationship with weather. They looked at the links between the admission of HFDM patients in the public hospitals in Hong Kong between 2008 and 2011 and the weather. In 2018, Tan and Cao [2] studied a dynamic model of HFMD which included the effects of vaccination in some children. They only considered children of age below 10 years since their immune systems were relatively intact (i.e. the antibodies to the HFMD virus were not present because of the unaware exposure to the asymptomatic form of the infections). Chadsuthi and Wichapeng [1] developed a mathematical model to study the effects of the contaminated environments in Bangkok and used it to understand the course of the HFMD from the reported information of individuals hospitalized with this disease. A number of age-structured models in the literature have also been developed, albeit for other diseases such as tuberculosis (TB) [15], Chikungunya [16] and HIV [17]. These models are based on the premise that the susceptibility of individuals varies with time, and consequently, involves the need for partial differential equations models. In this paper, the model of Pongsumpun and Wongvanich [18] is further developed. An assumption is that the susceptibility of individuals is quantized. In other words, the total population is divided into two groups, each with different finite susceptibility. The first group comprises population of children between 0-10 years, while the second group comprises a population of all other ages. The developed model is easier to analyze and interpret, and allows for global stability analysis to be conducted, which was not conducted in the previous works of Li *et al.* [14] and Pongsumpun and Wongvanich [18].

The structure of this paper is as follows: Section 2 formulates the mathematical model in which the population groups are normalized and determines the positivity of solutions for the disease-free and endemic steady state. We used the next generation matrix method to find the basic reproductive number and used the Lyapounov function method to establish the global stability of the equilibrium point. Section 3 then shows the numerical simulation including some discussions. The paper is concluded in Section 4.

2. Materials and Methods

In this study, we use the Susceptible-Exposed-Infected-Recovered (SEIR) model to describe the dynamic transmission of Hand-Foot-Mouth Disease in Thailand. We assume that the human population is divided into two groups; group one consists of children in the age group between 0-10 years and group two is consists of people of age greater than 10 years. Each age group is divided into four subcategories; susceptible, exposed, infected and recovered. In this section, we used mathematical programs to help obtain the equilibrium point and basic reproductive number.

2.1 Parameter and Equations of the model

We suppose that N_h is the total human population at time t. At time t, there are susceptible children between 0-10 years old S_a, E_a are exposed children of ages between 0-10 years, I_a are the infected children in this age group and R_a are the recovered children in this age group. S_b, E_b, I_b and R_b are populations of the corresponding human population groups above the age of 10 years. The descriptions of the changes in the different groups within each population class are given as:

- To begin, rate of change in the total human populations is due to the birth rate times the total human population (ΛN_h). The rate of change in the number of susceptible children (S_a) depends upon the infection of a susceptible child when the child is exposed to an infected child (the exposure can be either direct or indirect). The rate of change is given by $\beta_1 S_a I_a$ where β_1 is the infection rate for human population of ages between 0-10 years, or by $\beta_2 S_b I_b$ where β_2 is the infection rate for human population of ages greater than 10 years. The number of susceptible children also decrease when they become 11 years old or when they die of natural causes. The rates of changes for these two factors are σS_a and μS_a, respectively. The rate of change in the number of exposed children E_a depends on the rate of exposure of a susceptible child to infected population regardless of which population the infected person belongs to, the rate at which the exposed child becomes an infected child (εE_a), ε being the incubation rate, the rate at which a child becomes 11 years (σE_a) and natural death of the exposed child (μE_a). The rate of change in the number of infected children (I_a) depends on the incubation rate of the child, the rate at which the child recovers from the infected (ϕI_a), the rate at which the infected child becomes 11 years (σE_a) and the natural death of the infected child (μI_a). The rate of change in the number of recovered children (R_a) depends on the rate of recovery, the natural death of recovered child (μR_a) and the rate at which the recovered child becomes 11 years (σR_a).
- Regarding the second group, the rate of change in the number of susceptible adults (people older than 10 years) S_b depends on the rate at which children (humans younger than 10 years old) become 11 years old, the rate at which any susceptible adult is exposed to an infected adult $(\beta_2 S_b I_b)$ and the death of the susceptible person. The rate of change in the number of exposed human population (E_b) depends on the rate at which infected human population are

exposed to the virus, the incubation rate (εE_b) and natural death rate human of exposed human (μE_b). The rate of change in the number of infected human populations (I_b) depends on the incubation rate (εE_b), the number of adults who recovered from the infected (ϕI_b) where ϕ is the rate of recovery and the death rate of infected adults (μI_b) who die of natural causes. The rate of change in the number of recovered human population (R_b) depends on the recovery rate from the infected and natural death rate of recovered human populations (μR_b). Definition of parameters in our model is shown in Table 1.

Table 1. Definition of parameters

Parameter	Biological meaning
Λ	Birth rate
β_1	Infected rate for human populations when the ages are between 0-10 years
ε	Incubation rate
ϕ	Recovery rate
σ	Rate at which the ages between 0-10 years changed to child above the age of 10 years
β_2	Infection rate for the human population whose age is greater than 10 years
μ	Natural death rate of human
N_h	Total human population

The mathematical description of the transmission of Hand-Food-Mouth Disease, which includes the age structure in Thailand, is given by the following systems of ordinary differential equations;

$$S_a'(t) = \Lambda N_h - \beta_1 S_a I_a - (\mu + \sigma) S_a \quad (1)$$

$$E_a'(t) = \beta_1 S_a I_a - (\mu + \varepsilon + \sigma) E_a \quad (2)$$

$$I_a'(t) = \varepsilon E_a - (\mu + \phi + \sigma) I_a \quad (3)$$

$$R_a'(t) = \phi I_a - (\mu + \sigma) R_a \quad (4)$$

$$S_b'(t) = \sigma(S_a + E_a + I_a + R_a) - \beta_2 S_b I_b - \mu S_b \quad (5)$$

$$E_b'(t) = \beta_2 S_b I_b - (\mu + \varepsilon) E_b \quad (6)$$

$$I_b'(t) = \varepsilon E_b - (\mu + \phi) I_b \quad (7)$$

$$R_b'(t) = \phi I_b - \mu R_b \quad (8)$$

The total population condition is also given by:

$$N_h'(t) = S_a'(t) + E_a'(t) + I_a'(t) + R_a'(t) + S_b'(t) + E_b'(t) + I_b'(t) + R_b'(t).$$

2.2 Positivity invariant sets of solutions of SEIR model

Proposition 1. Let $S_a(t)$, $E_a(t)$, $I_a(t)$, $R_a(t)$, $S_b(t)$, $E_b(t)$, $I_b(t)$, $R_b(t)$ be the trajectories of the respective functions of equations (1)-(8) with the initial conditions:

$S_a(0),\ E_a(0),\ I_a(0),\ R_a(0),\ S_b(0),\ E_b(0),\ I_b(0),\ R_b(0)$, and also invariant set

$\omega = \left\{ S_a(\mathrm{t}), E_a(\mathrm{t}), I_a(\mathrm{t}), R_a(\mathrm{t}), S_b(\mathrm{t}), E_b(\mathrm{t}), I_b(\mathrm{t}), R_b(\mathrm{t}) \in R_+^8; W_1 \le \Lambda N_h / (\mu+\sigma), W_2 \le \sigma W_1 / \mu. \right\}$

and ω is a positively invariant set for equations (1)-(8).

Proof. Combining by equations (1)-(8) by

$$W(\mathrm{t}) = \left(W_1(\mathrm{t}), W_2(\mathrm{t})\right)$$
$$= \left(S_a(\mathrm{t}) + E_a(\mathrm{t}) + I_a(\mathrm{t}) + R_a(\mathrm{t}),\ \ S_b(\mathrm{t}) + E_b(\mathrm{t}) + I_b(\mathrm{t}) + R_b(\mathrm{t})\right)$$

we have

$$W'(\mathrm{t}) = \left(W_1'(\mathrm{t}), W_2'(\mathrm{t})\right)$$
$$= \begin{pmatrix} \Lambda N_h - \beta_1 S_a I_a - (\mu+\sigma)S_a + \beta_1 S_a I_a - (\mu+\varepsilon+\sigma)E_a + \varepsilon E_a - (\mu+\phi+\sigma)I_a + \phi I_a - (\mu+\sigma)R_a, \\ \sigma(S_a + E_a + I_a + R_a) - \beta_2 S_b I_b - \mu S_b + \beta_2 S_b I_b - (\mu+\varepsilon)E_b + \varepsilon E_b - (\mu+\phi)I_b + \phi I_b - \mu R_b \end{pmatrix}$$
$$= \begin{pmatrix} \Lambda N_h - (\mu+\sigma)S_a - (\mu+\sigma)E_a - (\mu+\sigma)I_a - (\mu+\sigma)R_a, \\ \sigma(S_a + E_a + I_a + R_a) - \mu S_b - \mu E_b - \mu I_b - \mu R_b \end{pmatrix}$$
$$= \left(\Lambda N_h - (\mu+\sigma)W_1,\ \sigma W_1 - \mu W_2\right)$$

Hence, $W_1'(\mathrm{t}) = \Lambda N_h - (\mu+\sigma)W_1 \le 0 \quad$ for $\quad W_1 \ge \dfrac{\Lambda N_h}{(\mu+\sigma)}$ (9)

$$W_2'(\mathrm{t}) = \sigma W_1 - \mu W_2 \le 0 \quad \text{for} \quad W_2 \ge \frac{\sigma W_1}{\mu} \tag{10}$$

From the above equations (9)-(10), $W'(\mathrm{t}) \le 0$ whenever $W_1 \ge \dfrac{\Lambda N_h}{(\mu+\sigma)}$ and $W_2 \ge \dfrac{\sigma W_1}{\mu}$. Using an integrating factor, we have $0 \le \left(W_1(\mathrm{t}), W_2(\mathrm{t})\right) \le \left(\dfrac{\Lambda N_h}{(\mu+\sigma)} + W_1(0)\,\mathrm{e}^{-(\mu+\sigma)t}, \dfrac{\sigma W_1}{\mu} + W_2(0)\,\mathrm{e}^{-\mu t} \right)$.

As $t \to \infty$, and hence $0 \le \left(W_1(\mathrm{t}), W_2(\mathrm{t})\right) \le \left(\dfrac{\Lambda N_h}{(\mu+\sigma)}, \dfrac{\sigma W_1}{\mu} \right)$. The other case is similar. Thus ω is a positively invariant set. We can see that all equations described by equations (1)-(8) in the non-negative octant R_+^8 are positively invariant [19].

Note that the infection rate does not introduce exogenous mortality in the population, and the latter is assumed to be constant in size at any given time. Therefore the rate of change of the total human populations is zero, and consequently the birth and death rates are equivalent. Then we have $\Lambda = \mu$.

We introduce the normalized variables:

$$s_a = \frac{S_a}{N_h}, e_a = \frac{E_a}{N_h}, i_a = \frac{I_a}{N_h}, r_a = \frac{R_a}{N_h},\ s_b = \frac{S_b}{N_h}, e_b = \frac{E_b}{N_h}, i_b = \frac{I_b}{N_h}, r_b = \frac{R_b}{N_h}.$$

Then we have the reduced equations as follows:

$$s_a'(\mathrm{t}) = \Lambda - \beta_1 N_h s_a i_a - (\mu+\sigma)s_a \tag{11}$$

$$e_a'(\mathrm{t}) = \beta_1 N_h s_a i_a - (\mu+\varepsilon+\sigma)e_a \tag{12}$$

$$i_a'(\mathrm{t}) = \varepsilon e_a - (\mu+\phi+\sigma)i_a \tag{13}$$

$$r_a'(\mathrm{t}) = \phi i_a - (\mu+\sigma)r_a \tag{14}$$

$$s_b^{'}(t) = \sigma(s_a + e_a + i_a + r_a) - \beta_2 N_h s_b i_b - \mu s_b \quad (15)$$

$$e_b^{'}(t) = \beta_2 N_h s_b i_b - (\mu + \varepsilon) e_b \quad (16)$$

$$i_b^{'}(t) = \varepsilon e_b - (\mu + \phi) i_b \quad (17)$$

$$r_b^{'}(t) = \phi i_b - \mu r_b \quad (18)$$

where we have the conditions $s_a + e_a + i_a + r_a + s_b + e_b + i_b + r_b = 1.$

2.3 Equilibrium points

Equations (11)-(18) are the reduced equations. Equilibrium points are obtained by setting the right hand side of equation (11)-(18) to zero. Then we have two equilibriums:

i) The disease-free steady state:

$$T^* = (s_a^{0^*}, e_a^{0^*}, i_a^{0^*}, r_a^{0^*}, s_b^{0^*}, e_b^{0^*}, i_b^{0^*}, r_b^{0^*}) = \left(\frac{\Lambda}{\mu + \sigma}, 0, 0, 0, \frac{\Lambda\sigma}{\mu(\mu + \sigma)}, 0, 0, 0 \right)$$

when $R_0 < 1.$

ii) Endemic steady state: $Q^* = (s_a^{1^*}, e_a^{1^*}, i_a^{1^*}, r_a^{1^*}, s_b^{1^*}, e_b^{1^*}, i_b^{1^*}, r_b^{1^*})$

where

$$s_a^{1^*} = \frac{(\varepsilon + \mu + \sigma)(\mu + \sigma + \phi)}{\beta_1 \varepsilon N_h},$$

$$e_a^{1^*} = \frac{\Lambda\beta_1\varepsilon N_h - (\mu + \sigma)(\varepsilon + \mu + \sigma)(\mu + \sigma + \phi)}{(\varepsilon + \mu + \sigma)\beta_1 \varepsilon N_h},$$

$$i_a^{1^*} = \frac{\Lambda\varepsilon}{(\varepsilon + \mu + \sigma)(\mu + \sigma + \phi)} - \frac{(\mu + \sigma)}{\beta_1 N_h},$$

$$r_a^{1^*} = \frac{\Lambda\phi\varepsilon}{(\mu + \sigma)(\varepsilon + \mu + \sigma)(\mu + \sigma + \phi)} - \frac{\phi}{\beta_1 N_h},$$

$$s_b^{1^*} = \frac{(\mu + \varepsilon)(\mu + \phi)}{\beta_2 \varepsilon N_h},$$

$$e_b^{1^*} = \frac{\varepsilon(\alpha\beta_2\sigma N_h - \mu(\mu + \sigma)(\mu + \phi)) - \mu^2(\mu + \sigma)(\mu + \phi)}{\beta_2 \varepsilon N_h (\mu + \varepsilon)(\mu + \sigma)},$$

$$i_b^{1^*} = \frac{\Lambda\varepsilon\sigma}{(\mu + \varepsilon)(\mu + \sigma)(\mu + \phi)} - \frac{\mu}{\beta_2 N_h},$$

$$r_b^{1^*} = \frac{\Lambda\varepsilon\sigma\phi}{\mu(\mu + \varepsilon)(\mu + \sigma)(\mu + \phi)} - \frac{\phi}{\beta_2 N_h}$$

when $R_0 > 1.$

2.4 Basic reproductive number

The basic reproductive number (R_0) is calculated by the next-generation matrix [20, 21]. We can write the right-hand side of equations (11)-(18) as F and V. Then we have gains and losses:

$$\begin{vmatrix} Gains\,to\,e_a: & \beta_1 N_h s_a i_a \\ Gains\,to\,i_a: & 0 \\ Gains\,to\,e_b: & \beta_2 N_h s_b i_b \\ Gains\,to\,i_b: & 0 \end{vmatrix}, \quad \begin{vmatrix} Losses\ from\,e_a: & (\mu+\varepsilon+\sigma)e_a \\ Losses\ from\,i_a: & -\varepsilon e_a + (\mu+\phi+\sigma)i_a \\ Losses\ from\,e_b: & (\mu+\varepsilon)e_b \\ Losses\ from\,i_b: & -\varepsilon e_b + (\mu+\phi)i_b \end{vmatrix}.$$

Where F is the Jacobian matrix of the gains matrix and V is the Jacobian matrix of the losses matrix,

$$F = \begin{bmatrix} 0 & \beta_1 N_h s_a & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_2 N_h s_b \\ 0 & 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \mu+\varepsilon+\sigma & 0 & 0 & 0 \\ -\varepsilon & \mu+\phi+\sigma & 0 & 0 \\ 0 & 0 & \mu+\varepsilon & 0 \\ 0 & 0 & -\varepsilon & \mu+\phi \end{bmatrix}.$$

When the disease-free steady state is

$T^* = (s_a^{0^*}, e_a^{0^*}, i_a^{0^*}, r_a^{0^*}, s_b^{0^*}, e_b^{0^*}, i_b^{0^*}, r_b^{0^*}) = \left(\frac{\Lambda}{\mu+\sigma}, 0, 0, 0, \frac{\Lambda\sigma}{\mu(\mu+\sigma)}, 0, 0, 0 \right)$ and substitute T^* in F and V above and determine $H = FV^{-1}$, we have

$$H = \begin{bmatrix} \frac{\Lambda\beta_1 N_h (\varepsilon^2 + \varepsilon\mu)}{(\mu+\varepsilon)(\mu+\sigma)(\mu+\varepsilon+\sigma)(\mu+\phi+\sigma)} & \frac{\Lambda\beta_1 N_h}{(\mu+\sigma)(\mu+\phi+\sigma)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\Lambda\beta_2 N_h \varepsilon\sigma}{\mu(\mu+\varepsilon)(\mu+\sigma)(\mu+\phi)} & \frac{\Lambda\beta_2 N_h \sigma}{\mu(\mu+\phi)(\mu+\sigma)} \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

R_0 is the eigenvalues of the matrix $H = FV^{-1}$.

We have $R_0 = \max\left\{ \frac{\Lambda\beta_1\varepsilon N_h}{(\mu+\sigma)(\mu+\varepsilon+\sigma)(\mu+\phi+\sigma)}, \frac{\Lambda\beta_2\varepsilon\sigma N_h}{\mu(\mu+\varepsilon)(\mu+\sigma)(\mu+\phi)} \right\}$. (19)

2.5 Global stability of the equilibrium states

Theorem 1. If $R_0 < 1$, then the disease-free equilibrium point $T^* = (s_a^{0^*}, e_a^{0^*}, i_a^{0^*}, r_a^{0^*}, s_b^{0^*}, e_b^{0^*}, i_b^{0^*}, r_b^{0^*}) = \left(\frac{\Lambda}{\mu+\sigma}, 0, 0, 0, \frac{\Lambda\sigma}{\mu(\mu+\sigma)}, 0, 0, 0 \right)$ of equations (11)-(18) is globally asymptotically stable in the ω. We assume that

$$\begin{cases} \beta_1 = \dfrac{(\mu+\sigma)}{N_h s_a^{0^*}} \\ \beta_2 = \dfrac{\mu}{N_h s_b^{0^*}} \\ \Lambda = (s_a + e_a + i_a + r_a)(\mu+\sigma) \end{cases}. \quad (20)$$

Proof. We consider the Lyapunov function

$$\mathrm{L(t)} = (s_a - s_a^{0^*} \ln s_a) + e_a + i_a + r_a + (s_b - s_b^{0^*} \ln s_b) + e_b + i_b + r_b$$

$$
\begin{aligned}
L^{'}(\mathrm{t}) &= s^{'}_{a}\left(1-\frac{s^{0*}_{a}}{s_a}\right)+e^{'}_{a}+i^{'}_{a}+r^{'}_{a}+s^{'}_{b}\left(1-\frac{s^{0*}_{b}}{s_b}\right)+e^{'}_{b}+i^{'}_{b}+r^{'}_{b} \\
&= \left(\Lambda-\beta_1 N_h s_a i_a-(\mu+\sigma)s_a\right)\left(1-\frac{s^{0*}_{a}}{s_a}\right)+\left(\beta_1 N_h s_a i_a-(\mu+\varepsilon+\sigma)e_a\right)+\left(\varepsilon e_a-(\mu+\phi+\sigma)i_a\right) \\
&\quad +\left(\phi i_a-(\mu+\sigma)r_a\right)+\left(\sigma(s_a+e_a+i_a+r_a)-\beta_2 N_h s_b i_b-\mu s_b\right)\left(1-\frac{s^{0*}_{b}}{s_b}\right)+\left(\beta_2 N_h s_b i_b-(\mu+\varepsilon)e_a\right) \\
&\quad +\left(\varepsilon e_b-(\mu+\phi)i_b\right)+\left(\phi i_b-\mu r_b\right) \\
&= \Lambda\left(1-\frac{s^{0*}_{a}}{s_a}\right)-\beta_1 N_h s_a i_a+\beta_1 N_h s^{0*}_{a} i_a-(\mu+\sigma)s_a+(\mu+\sigma)s^{0*}_{a}+\beta_1 N_h s_a i_a-(\mu+\varepsilon+\sigma)e_a+\varepsilon e_a \\
&\quad -(\mu+\phi+\sigma)i_a+\phi i_a-(\mu+\sigma)r_a+\sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s^{0*}_{b}}{s_b}\right)-\beta_2 N_h s_b i_b+\beta_2 N_h s^{0*}_{b} i_b-\mu s_b \\
&\quad +\mu s^{0*}_{b}+\beta_2 N_h s_b i_b-(\mu+\varepsilon)e_b+\varepsilon e_b-(\mu+\phi)i_b+\phi i_b-\mu r_b \\
&= \Lambda\left(1-\frac{s^{0*}_{a}}{s_a}\right)-(\mu+\sigma)s_a+(\mu+\sigma)s^{0*}_{a}+\beta_1 N_h s^{0*}_{a} i_a-(\mu+\sigma)e_a-(\mu+\sigma)i_a-(\mu+\sigma)r_a \\
&\quad +\sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s^{0*}_{b}}{s_b}\right)-\mu s_b+\mu s^{0*}_{b}+\beta_2 N_h s^{0*}_{b} i_b-\mu e_b-\mu i_b-\mu r_b \\
&= \Lambda\left(1-\frac{s^{0*}_{a}}{s_a}\right)+(\mu+\sigma)s^{0*}_{a}\left(1-\frac{s_a}{s^{0*}_{a}}\right)+\beta_1 N_h s^{0*}_{a} i_a-(\mu+\sigma)e_a-(\mu+\sigma)i_a-(\mu+\sigma)r_a \\
&\quad +\sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s^{0*}_{b}}{s_b}\right)+\mu s^{0*}_{b}\left(1-\frac{s_b}{s^{0*}_{b}}\right)+\beta_2 N_h s^{0*}_{b} i_b-\mu e_b-\mu \mathrm{i}_b-\mu r_b \\
&= \Lambda\left(1-\frac{s^{0*}_{a}}{s_a}\right)+(\mu+\sigma)s^{0*}_{a}\left(1-\frac{s_a}{s^{0*}_{a}}\right)+i_a(\beta_1 N_h s^{0*}_{a}-(\mu+\sigma))-(\mu+\sigma)e_a-(\mu+\sigma)r_a \\
&\quad +\sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s^{0*}_{b}}{s_b}\right)+\mu s^{0*}_{b}\left(1-\frac{s_b}{s^{0*}_{b}}\right)+i_b(\beta_2 N_h s^{0*}_{b}-\mu)-\mu e_b-\mu r_b.
\end{aligned}
$$

From equation (20), we have

$$
\begin{aligned}
L^{'}(\mathrm{t}) &= \Lambda\left(1-\frac{s^{0*}_{a}}{s_a}\right)+(\mu+\sigma)s^{0*}_{a}\left(1-\frac{s_a}{s^{0*}_{a}}\right)+\sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s^{0*}_{b}}{s_b}\right)+\mu s^{0*}_{b}\left(1-\frac{s_b}{s^{0*}_{b}}\right) \\
&\quad -(\mu+\sigma)e_a-(\mu+\sigma)r_a-\mu e_b-\mu r_b.
\end{aligned}
$$

From $s^{0*}_{a}=\dfrac{\Lambda}{(\mu+\sigma)}$, $s^{0*}_{b}=\dfrac{\Lambda\sigma}{\mu(\mu+\sigma)}$, we have

$$
\begin{aligned}
L^{'}(\mathrm{t}) &= \Lambda\left(1-\frac{s^{0*}_{a}}{s_a}\right)+(\mu+\sigma)\frac{\Lambda}{(\mu+\sigma)}\left(1-\frac{s_a}{s^{0*}_{a}}\right)+\sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s^{0*}_{b}}{s_b}\right)+\mu\frac{\Lambda\sigma}{\mu(\mu+\sigma)}\left(1-\frac{s_b}{s^{0*}_{b}}\right) \\
&\quad -(\mu+\sigma)e_a-(\mu+\sigma)r_a-\mu e_b-\mu r_b.
\end{aligned}
$$

And we have assumed that $\Lambda=(s_a+e_a+i_a+r_a)(\mu+\sigma)$, thus

$$
\begin{aligned}
L^{'}(\mathrm{t}) &= \Lambda\left(1-\frac{s_a^{0*}}{\mathrm{s}_a}\right)+\Lambda\left(1-\frac{s_a}{s_a^{0*}}\right)+\sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s_b^{0*}}{\mathrm{s}_b}\right)+\sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s_b}{s_b^{0*}}\right)-(\mu+\sigma)e_a \\
&\quad -(\mu+\sigma)r_a-\mu e_b-\mu r_b \\
&= \Lambda\left(2-\frac{s_a^{0*}}{\mathrm{s}_a}-\frac{s_a}{s_a^{0*}}\right)+\sigma(s_a+e_a+i_a+r_a)\left(2-\frac{s_b^{0*}}{\mathrm{s}_b}-\frac{s_b}{s_b^{0*}}\right)-(\mu+\sigma)e_a-(\mu+\sigma)r_a-\mu e_b-\mu r_b \\
&= -\Lambda\left(\frac{\left(s_a^{0*}-\mathrm{s}_a\right)^2}{s_a s_a^{0*}}\right)-\sigma(s_a+e_a+i_a+r_a)\left(\frac{\left(s_b^{0*}-\mathrm{s}_b\right)^2}{s_b s_b^{0*}}\right)-(\mu+\sigma)e_a-(\mu+\sigma)r_a-\mu e_b-\mu r_b \\
&= -\left[\Lambda\left(\frac{\left(s_a^{0*}-s_a\right)^2}{s_a s_a^{0*}}\right)+\sigma(s_a+e_a+i_a+r_a)\left(\frac{\left(s_b^{0*}-s_b\right)^2}{s_b s_b^{0*}}\right)+(\mu+\sigma)e_a+(\mu+\sigma)r_a+\mu e_b+\mu r_b\right]\le 0
\end{aligned}
\tag{21}
$$

So, $L^{'}(\mathrm{t})\le 0$ .Using LaSalle's extension to Lyapunov's method [22], if and only if $s_a^{0*}=\mathrm{s}_a$, $e_a=0, i_a=0,\ r_a=0, s_b^{0*}=\mathrm{s}_b,\ e_b=0, i_b=0, r_b=0$. Then the equilibrium steady state $T^*=(s_a^{0*},e_a^{0*},i_a^{0*},r_a^{0*},s_b^{0*},e_b^{0*},i_b^{0*},r_b^{0*})=\left(\frac{\Lambda}{\mu+\sigma},0,0,0,\frac{\Lambda\sigma}{\mu(\mu+\sigma)},0,0,0\right)$ is globally asymptotically stable in the ω .

Theorem 2. If $R_0>1$, then the positive endemic equilibrium point $Q^*=(s_a^{1*},e_a^{1*},i_a^{1*},r_a^{1*},s_b^{1*},e_b^{1*},i_b^{1*},r_b^{1*})$ of equations (9)-(16) is globally asymptotically stable in the ω. Assume that

$$
\begin{cases}
M=\dfrac{\mu}{\varepsilon} \\
\Lambda=\dfrac{(\mu+\sigma)(\varepsilon+\mu+\sigma)(\mu+\sigma+\phi)}{\beta_1\varepsilon N_h} \\
\mu=\dfrac{\sigma(\mathrm{s}_a+e_a+i_a+\mathrm{r}_a)}{s_b^{1*}} \\
\beta_1=\dfrac{\mu}{N_h s_a^{1*}} \\
\beta_2=\dfrac{M\phi}{N_h s_b^{1*}}
\end{cases}
\quad .
\tag{22}
$$

Proof We consider the Lyapunov function:

$$K=(s_a-s_a^{1*}\ln s_a)+e_a+i_a+(s_b-s_b^{1*}\ln s_b)+e_b+Mi_b$$

$$K^{'}(\mathrm{t})=s_a^{'}\left(1-\frac{s_a^{1*}}{\mathrm{s}_a}\right)+e^{'}_a+i^{'}_a+s^{'}_b\left(1-\frac{s_b^{1*}}{\mathrm{s}_b}\right)+e^{'}_b+Mi^{'}_b$$

$$K^{'}(\mathrm{t}) = \left(\Lambda - \beta_1 N_h s_a i_a - (\mu+\sigma)s_a\right)\left(1-\frac{s_a^{1^*}}{s_a}\right) + \left(\beta_1 N_h s_a i_a - (\mu+\varepsilon+\sigma)e_a\right) + \left(\varepsilon e_a - (\mu+\phi+\sigma)i_a\right) +$$

$$\left(\sigma(s_a+e_a+i_a+r_a) - \beta_2 N_h s_b i_b - \mu s_b\right)\left(1-\frac{s_b^{1^*}}{s_b}\right) + \left(\beta_2 N_h s_b i_b - (\mu+\varepsilon)e_b\right) + M\left(\varepsilon e_b - (\mu+\phi)i_b\right)$$

$$= \Lambda - \beta_1 N_h s_a i_a - (\mu+\sigma)s_a - \Lambda\frac{s_a^{1^*}}{s_a} + \beta_1 N_h s_a i_a \frac{s_a^{1^*}}{s_a} + (\mu+\sigma)s_a\frac{s_a^{1^*}}{s_a} + \beta_1 N_h s_a i_a - \mu e_a - \varepsilon e_a - \sigma e_a + \varepsilon e_a$$

$$- \mu i_a - \phi i_a - \sigma i_a + \sigma(\mathrm{s}_a+e_a+i_a+r_a) - \beta_2 N_h s_b i_b - \mu s_b - \sigma(s_b+e_a+i_a+r_a)\frac{s_b^{1^*}}{s_b}$$

$$+ \beta_2 N_h s_b i_b \frac{s_b^{1^*}}{s_b} + \mu s_b \frac{s_b^{1^*}}{s_b} + \beta_2 N_h s_b i_b - \mu e_b - \varepsilon e_b + M\varepsilon e_b - M\mu \mathrm{i}_b - M\phi \mathrm{i}_b$$

$$= \Lambda\left(1-\frac{s_a^{1^*}}{s_a}\right) - (\mu+\sigma)s_a\left(1-\frac{s_a^{1^*}}{s_a}\right) - \beta_1 N_h s_a i_a + \beta_1 N_h i_a s_a^{1^*} + \beta_1 N_h s_a i_a - \mu e_a - \sigma e_a - \mu i_a - \phi i_a - \sigma i_a$$

$$+ \sigma(\mathrm{s}_a+e_a+i_a+r_a)\left(1-\frac{s_b^{1^*}}{s_b}\right) - \mu s_b\left(1-\frac{s_b^{1^*}}{s_b}\right) - \beta_2 N_h s_b i_b + \beta_2 N_h i_b s_b^{1^*} + \beta_2 N_h s_b i_b - \mu \mathrm{e}_b - \varepsilon \mathrm{e}_b + M\varepsilon e_b$$

$$- M\mu i_b - M\phi i_b$$

$$= \Lambda\left(1-\frac{s_a^{1^*}}{s_a}\right) + (\mu+\sigma)s_a^{1^*}\left(1-\frac{s_a}{s_a^{1^*}}\right) + \beta_1 N_h i_a s_a^{1^*} - \mu e_a - \sigma e_a - \mu i_a - \phi i_a - \sigma i_a + \sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s_b^{1^*}}{s_b}\right)$$

$$+ \mu s_b^{1^*}\left(1-\frac{s_b}{s_b^{1^*}}\right) + \beta_2 N_h i_b s_b^{1^*} - \mu e_b - \varepsilon e_b + M\varepsilon e_b - M\mu i_b - M\phi i_b.$$

From $s_a^{1^*} = \dfrac{(\varepsilon+\mu+\sigma)(\mu+\sigma+\phi)}{\beta_1 \varepsilon N_h}$, we have

$$K^{'}(\mathrm{t}) = \Lambda\left(1-\frac{s_a^{1^*}}{s_a}\right) + (\mu+\sigma)\frac{(\varepsilon+\mu+\sigma)(\mu+\sigma+\phi)}{\beta_1 \varepsilon N_h}\left(1-\frac{s_a}{s_a^{1^*}}\right) + \beta_1 N_h i_a s_a^{1^*} - \mu e_a - \sigma e_a - \mu i_a - \phi i_a - \sigma i_a$$

$$+ \sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s_b^{1^*}}{s_b}\right) + \mu s_b^{1^*}\left(1-\frac{s_b}{s_b^{1^*}}\right) + \beta_2 N_h i_b s_b^{1^*} - \mu e_b - \varepsilon e_b + M\varepsilon e_b - M\mu i_b - M\phi i_b.$$

Substituting the relations in equations (22), we have $\Lambda = \dfrac{(\mu+\sigma)(\varepsilon+\mu+\sigma)(\mu+\sigma+\phi)}{\beta_1 \varepsilon N_h}$ and

$$\mu = \frac{\sigma(\mathrm{s}_a+e_a+i_a+\mathrm{r}_a)}{s_b^{1^*}}$$

$$K^{'}(\mathrm{t}) = \Lambda\left(1-\frac{s_a^{1^*}}{s_a}\right) + \Lambda\left(1-\frac{s_a}{s_a^{1^*}}\right) + \beta_1 N_h i_a s_a^{1^*} - \mu e_a - \sigma e_a - \mu i_a - \phi i_a - \sigma i_a + \sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s_b^{1^*}}{s_b}\right)$$

$$+ \sigma(s_a+e_a+i_a+r_a)\left(1-\frac{s_b}{s_b^{1^*}}\right) + \beta_2 N_h i_b s_b^{1^*} - \mu e_b - \varepsilon e_b + M\varepsilon e_b - M\mu i_b - M\phi i_b$$

$$= -\Lambda\frac{(s_a^{1^*}-s_a)^2}{s_a s_a^{1^*}} + \beta_1 N_h i_a s_a^{1^*} - \mu e_a - \sigma e_a - \mu i_a - \phi i_a - \sigma i_a - \sigma(s_a+e_a+i_a+r_a)\frac{(s_b^{1^*}-\mathrm{s}_b)^2}{s_b s_b^{1^*}}$$

$$+ \beta_2 N_h i_b s_b^{1^*} - \mu e_b - \varepsilon e_b + M\varepsilon e_b - M\mu i_b - M\phi i_b$$

$$K^{'}(\mathrm{t}) = -\Lambda\frac{(s_a^{1^*}-s_a)^2}{s_a s_a^{1^*}} - \sigma(s_a+e_a+i_a+r_a)\frac{(s_b^{1^*}-s_b)^2}{s_b\, s_b^{1^*}} + i_a(\beta_1 N_h s_a^{1^*}-\mu) + i_b(\beta_2 N_h s_b^{1^*}-M\phi)$$
$$+ e_b(M\varepsilon-\mu) - \mu e_a - \sigma e_a - \phi i_a - \sigma i_a - \varepsilon e_b - M\mu i_b.$$

Substituting the relations in equations (22), we have

$$K^{'}(\mathrm{t}) = -\Lambda\frac{(s_a^{1^*}-s_a)^2}{s_a s_a^{1^*}} - \sigma(s_a+e_a+i_a+r_a)\frac{(s_b^{1^*}-s_b)^2}{s_b s_b^{1^*}} - \mu e_a - \sigma e_a - \phi i_a - \sigma i_a - \varepsilon e_b - M\mu i_b$$
$$= -\left[\Lambda\frac{(s_a^{1^*}-s_a)^2}{s_a s_a^{1^*}} + \sigma(s_a+e_a+i_a+r_a)\frac{(s_b^{1^*}-s_b)^2}{s_b s_b^{1^*}} + \mu e_a + \sigma e_a + \phi i_a + \sigma i_a + \varepsilon e_b + M\mu i_b\right] \le 0 \qquad (23)$$

Hence, the condition (23) show that $K^{'}(\mathrm{t}) \le 0$ of all terms. Then the equilibrium steady state $Q^* = (s_a^{1^*}, e_a^{1^*}, i_a^{1^*}, r_a^{1^*}, s_b^{1^*}, e_b^{1^*}, i_b^{1^*}, r_b^{1^*})$ is globally asymptotically stable in the ω.

3. Results and Discussion

In this section, we simulate the dynamic behavior of HFMD in Thailand by numerically solving the equations (11)-(18),where thevalues of the parameter values are listed in Table 2.

Table 2. Values of the parameter of our HFMD model

Parameter	The disease-free	Endemic (case 1)	Endemic (case 2)	Reference
Λ	$1/(75*365)$	$1/(74*365)$	$1/(74*365)$	[14]
β_1	0.00045	0.0329	0.045	Assumption
ε	$1/5$	$1/5$	$1/5$	[14],[23]
ϕ	$1/14$	$1/14$	$1/14$	[2],[23]
σ	0.0002	0.0002	0.0002	[2]
β_2	0.005	0.0492	0.058	Assumption
μ	$1/(75*365)$	$1/(70*365)$	$1/(70*365)$	[14]
N_h	10	100	300	Estimated
R_0	0.591481	54.4523	192.575	

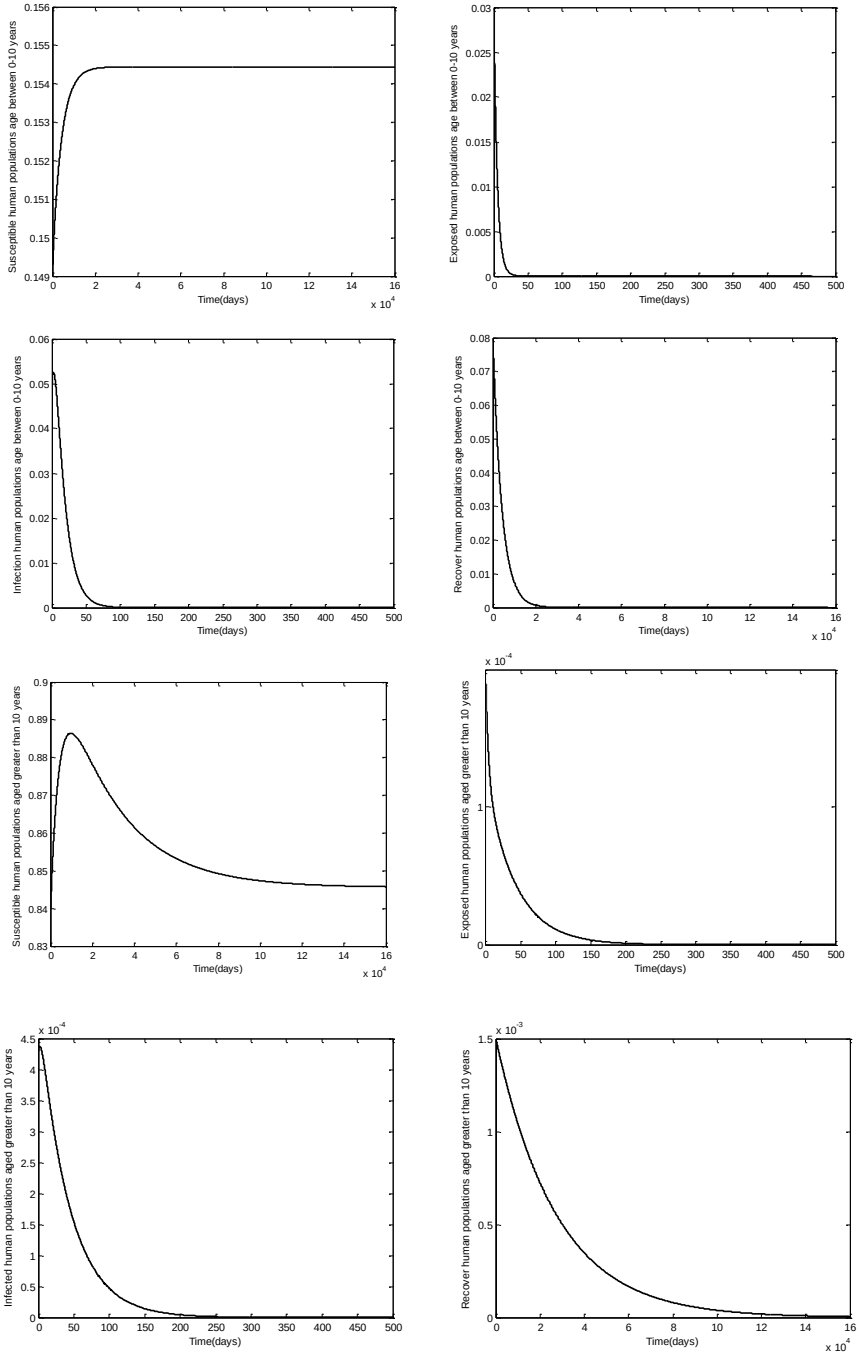

Figure 3. Solutions to the fractional of the global stability of T^* from equations (11)-(18) when $R_0 = 0.591481$

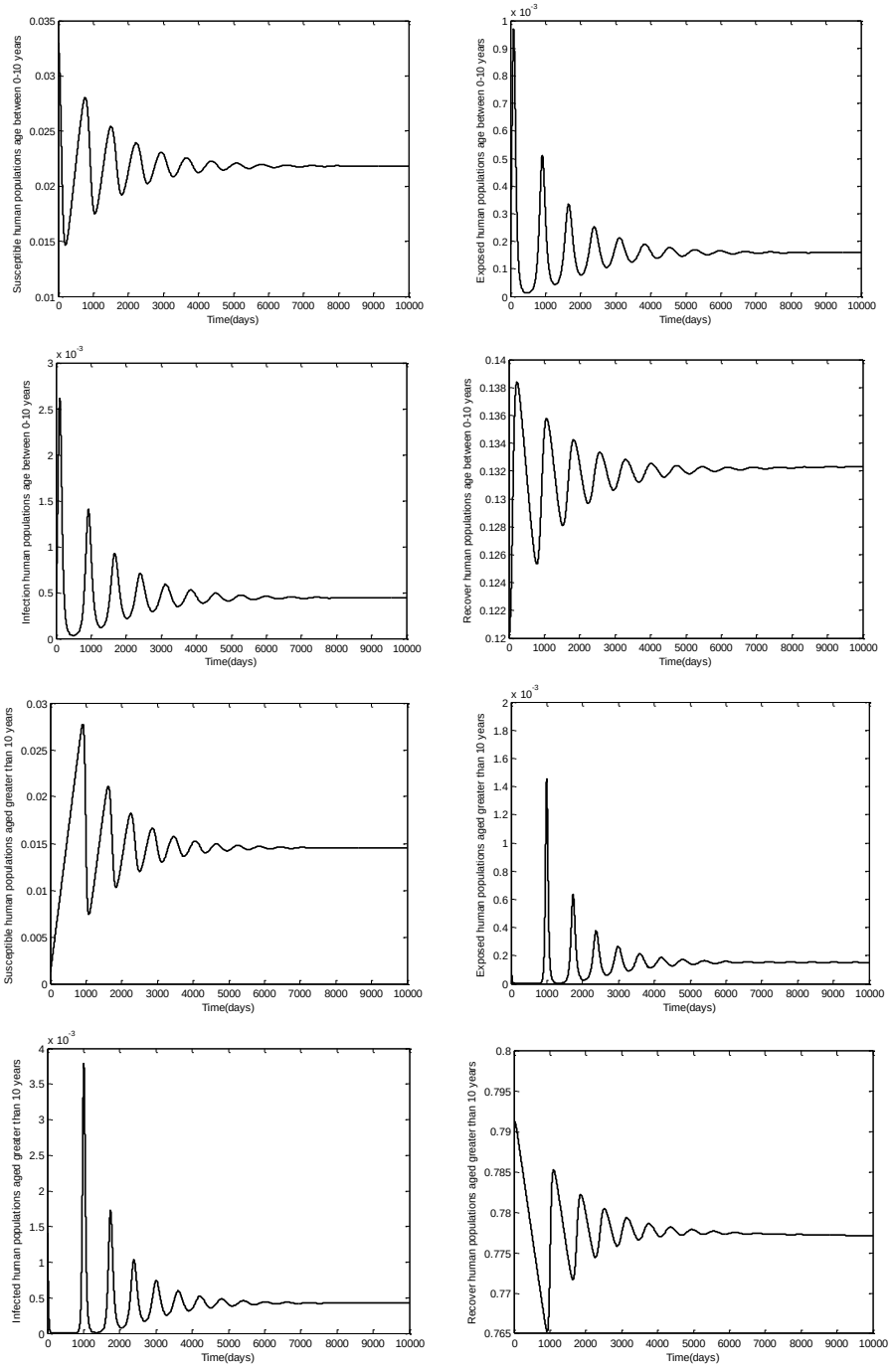

Figure 4. Solutions to the fractional of the global stability of Q^* from equations (11)-(18) when $R_0 = 54.4523$

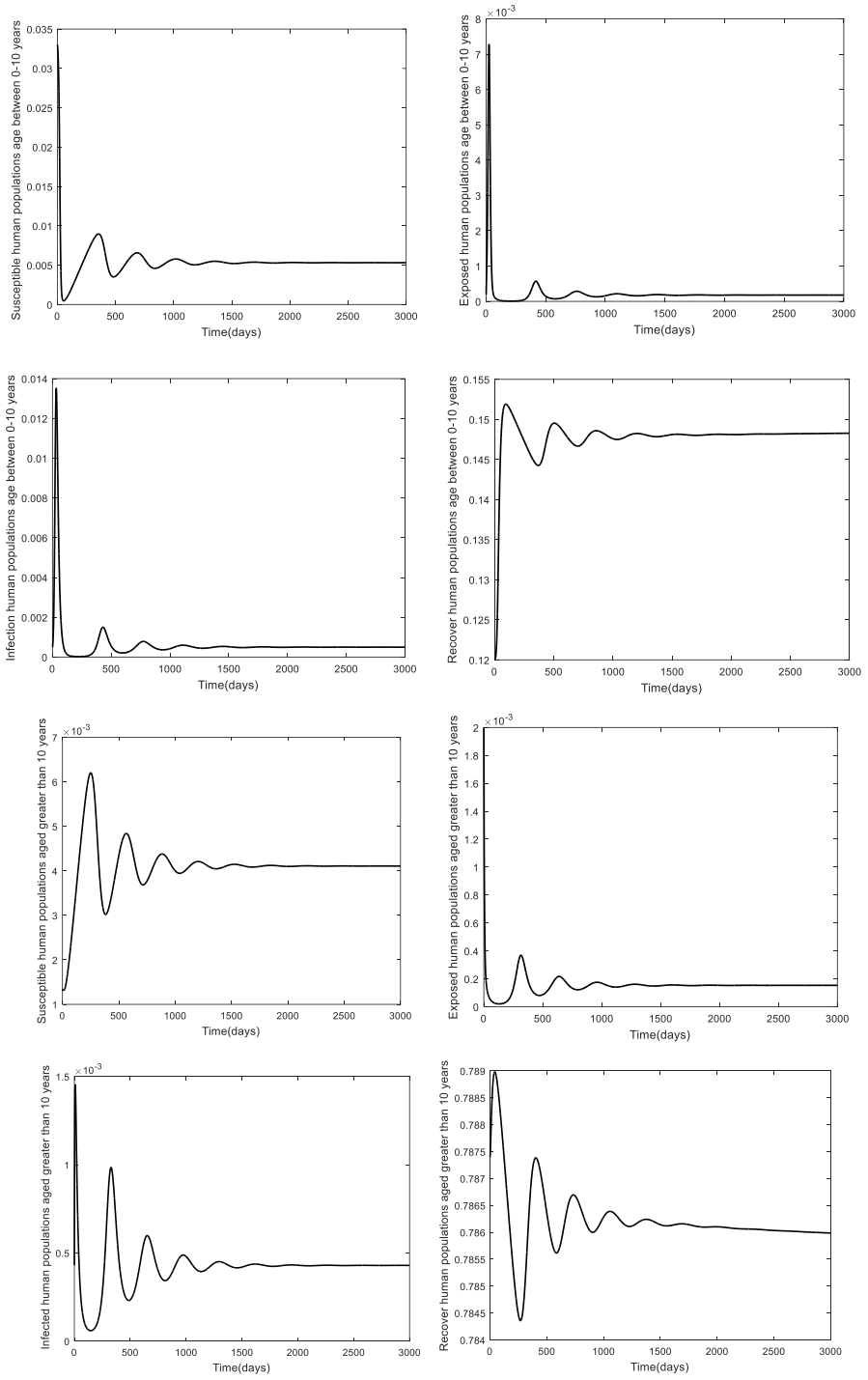

Figure 5. Solutions to the fractional of the global stability of Q^* from equations (11)-(18) when $R_0 = 192.575$

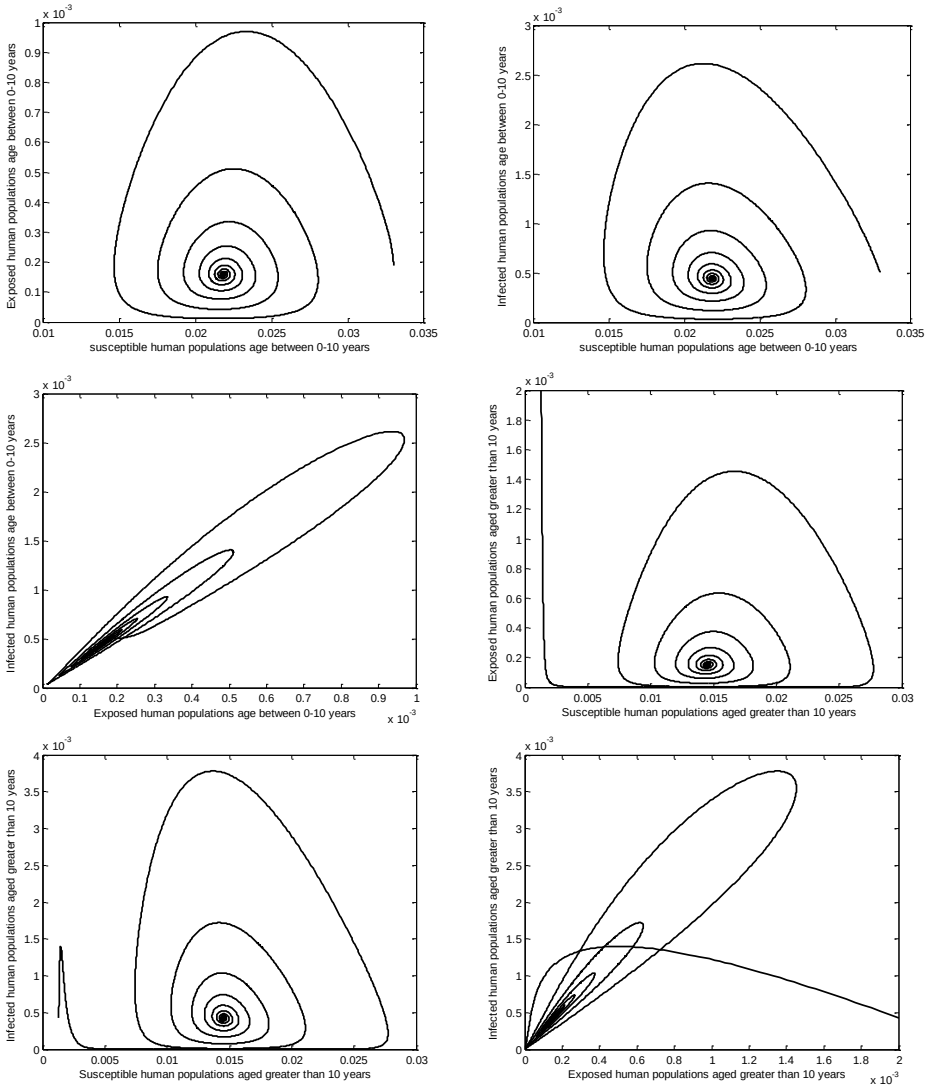

Figure 6. Solutions to the fractional projected onto the 2D of the global stability of Q^* from equations (11)-(18) when $R_0 = 54.4523$

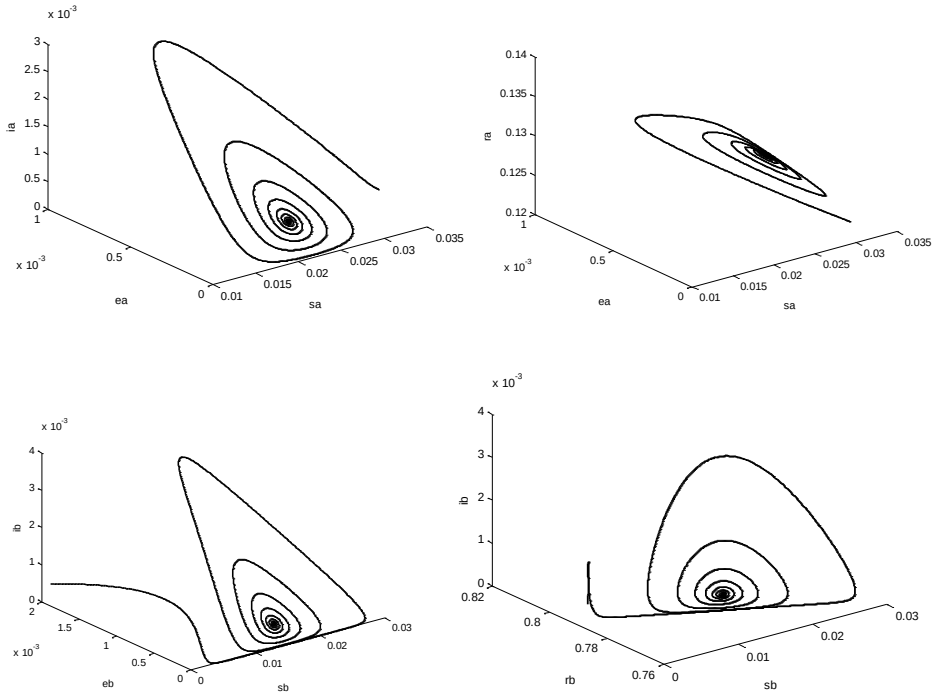

Figure 7. Solutions to the fractional projected onto the 3D of the global stability of Q^* from equations (11)-(18) when $R_0 = 54.4523$

For the numerical results, we used the values of the parameters shown in Table 2. When equilibrium state converge to the disease-free state $T^* = (0.1544, 0, 0, 0, 0.8456, 0, 0, 0)$, it is seen from Figure 3 that the equilibrium point for the susceptible lower age population (between 0-10 years) is lower than that for a larger age (>10 years). This implies that the children's age group is able to control the disease faster when $R_0 < 1$. Figures 4 and 5 then show the numerical trajectories for the global stability of the endemic state at different values of the basic reproductive number $R_0 = 54.45$ for Figure 4 and 192.575 for Figure 5. It is seen that as the basic reproductive number increases, the outbreak converges to the equilibrium point faster than an outbreak with a lower basic reproductive number. Figure 6 presents the 2D phase portrait trajectories of (s_a, e_a), (s_a, i_a), $(e_a, i_a), (s_b, e_b), (s_b, i_b)$ and (e_b, i_b) from the use of Matlab. Figure 7 shows the 3D phase portrait of (s_a, e_a, i_a), $(s_a, e_a, r_a), (s_b, e_b, i_b), (s_b, r_b, i_b)$, again with the use of Matlab. Both of these Figures depict clearly the convergence of the trajectories to the equilibrium when $R_0 > 1$. Note that these stability analyses are important from the control design perspective. In other words, if the system is deemed stable, then a simple controller would be required to track the desired disease trajectory. However, if the system is not stable, then a stabilizing controller must firstly be designed before a suitable controller could be implemented. Such a process is a lot more difficult to implement from the control perspective.

4. Conclusions

In this research, we have studied a transmission model of Hand-Foot-Mouth disease (HFMD) by creating the mathematical model of HFMD according to the data of the disease. We distributed human population into two groups; the first group is the children of ages between 0-10 years and the second group is people who are older than 10 years. Each age group is divided into four subclasses; susceptible, exposed, infected and recovered. From HFMD model, we assume the number of human population is constant. We establish 2 equilibrium states: a disease-free equilibrium state and endemic equilibrium state. The basic reproductive number (R_0) is determined using the next generation method and is denoted R_0. as

$$R_0 = \max\left\{\frac{\alpha\beta_1\varepsilon N_h}{(\mu+\sigma)(\mu+\varepsilon+\sigma)(\mu+\phi+\sigma)}, \frac{\alpha\beta_2\varepsilon\sigma N_h}{\mu(\mu+\varepsilon)(\mu+\sigma)(\mu+\phi)}\right\}.$$

When $R_0 < 1,$ the disease-free steady state is globally asymptotically stable as can be seen in theorem 1 and when $R_0 > 1,$ the endemic steady state is globally asymptotically stable as can be seen in theorem 2. Since Hand-Foot-Mouth Disease is often found in children, we created mathematical model and divided into two groups for the analysis of the disease of each population group. Moreover, our analysis for parameters revealed parameters that affected the outbreak which are the infection rate for human population when the ages are between 0-10 years, the infection rate of a child above the age of 10 years and total human population. The results of this study can suggest ways for reducing the outbreak of this disease. If the importance of the disease is not realized and action taken, outbreaks will continue to occur.

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