Transmission Dynamics and Optimal Control Strategies of a Hand-Foot-Mouth Disease Model with Treatment and Vaccination Interventions

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Abstract

In this article, the transmission dynamics of a Hand-Foot-Mouth disease model with treatment and vaccination interventions are studied. We calculated the basic reproduction number and proved the global stability of disease-free equilibrium when $R_0 < 1$, and the disease persistent when $R_0 > 1$. Meanwhile, we obtained the optimal control strategies minimizing the cost of intervention and minimizing the infected person. We also give some numerical simulations to verify our theoretical results.

Keywords

Hand-Foot-Mouth Disease, Optimal Control, Transmission Dynamic, Vaccination Interventions

1. Introduction

Hand-Foot-Mouth disease (HFMD) is a common childhood infectious disease, which was first reported in New Zealand in 1957 [1]. Since 1997, HFMD epidemics caused by EV-71 have been prevalent in the Asia-Pacific region, including China, Japan, Singapore, Malaysia, Vietnam, South Korea, Thailand, Cube, India and Cambodia. HFMD is caused by more than 20 different enteroviruses, such as Coxsackievirus A16 (CAV16), human enterovirus 71 (EV71), Coxsackie virus A4-A7, A9, A10, B1-B3, B5, and so on. CAV16 and EV71 are the most common aetiological agents, which being account for about 73% of HFMD cases [2].

Usually, the enterovirus has strong transitivity, high latent infection and causing large epidemics in short times. The HFMD transmits from person to person easily, mainly through fecal-oral and/or respiratory droplets, or by stool

touching, respiratory secretions, herpes solution and polluted staff of patients [3]. However, HFMD exhibits a self-limiting illness, not only affects children who younger than 10 years of age, but also affects adults. Infected adults are asymptomatic to the HFMD due to the antibodies in bodies, although they are infected. Many infected children are symptoms of HFMD including fever, intra-oral vesicales and erosions, and papulovesicles that favor the palms and soles. A small proportion children who infected, develop into neurological and systemic complications than that can be death.

As such, HFMD is a growing public health threat that causes a considerable disease burden and economic impact. Many HFMD cases are reported to the China Center for Disease Control and Prevention (CDC) during 2000-2022. In reaction, CDC imitated a surveillance program to reference HFMD cases with an unprecedented level of geographic detail. The EV71 vaccine was licensed in China in 2016, and other vaccines are still under development [4]. There are three recent phase 3 clinical trials of inactivated monovalent EV71 vaccines manufactured in China which were found to have high efficacy (90% - 97.4%) against EV71 associated HFMD in infants and young children [5]. Due to the change of HFMD virus, the antibodies against one enterovirus have no cross-protection against other enteroviruses. Therefore, the EV71 vaccines only offer high efficacy against EV71, and did not provide protection against HFMD caused by the other enteroviruses.

Epidemiological models are important tools to understand the spread and control of HFMD. Recently, many studies proposed compartmental models of HFMD to investigate the dynamics and to design evidence-based control strategies. Especially, there are fewer scholars established mathematical models to study HFMD with vaccination. Urashima *et al.* and Wang and Sung tried to find the relationship between the outbreak of HFMD with the weather patterns in Taiwan (China) and Tokyo, respectively [6] [7]. Tan and Cao built a HFMD model with treatment and vaccination interventions to study the transmission dynamics of HFMD [8]. Zhang and Rui *et al.* calculated the transmissibility of HFMD at county levels in Jiangsu Province and analyzed the differences of transmissibility and explored the possible influencing factors of its transmissibility [9]. Li and Wang *et al.* constructed a two stage-structured model to fit the HFMD data from 2009-2014 in China and obtain its optimal parameter values [10].

Motivated by the above facts, we formulate mathematical modeling to study the transmission dynamics of HFMD with treatment and vaccination interventions. The basic structure of this paper is as follows. In next section, we establish a HFMD model with vaccination and obtain the basic reproduction number R_0. In Section 3, we prove the global stability of disease-free equilibrium when $R_0 < 1$, while persistence of the disease when $R_0 > 1$. In Section 4, we apply the optimal control technique to minimize the number of the infected people. In Section 5, numerical simulations to demonstrate and support the theoretical results are given. Finally, we give the brief discussion of the results.

2. Model Formulation

In this section, we formulate a HFMD transmission model with infected people divided into two classes. HFMD caused by different enteroviruses, only EV71 vaccine was on market could prevent the HFMD induced by EV71. We consider the infectious individuals divided into two classes, which are infectious individuals I_1 infected by EV71 and infectious individuals I_2 infected by CVA16 or other enteroviruses serotypes.

We consider the total number of human population by $N(t)$ at time t, further divided into six categories: susceptible individuals $S(t)$, latent individuals $E(t)$, infectious individuals $I_1(t)$ and $I_2(t)$, vaccination individuals $V(t)$, and recovery individuals $R(t)$. It is obviously that the human population can be written as $N(t) = S(t) + E(t) + I_1(t) + I_2(t) + V(t) + R(t)$. The dynamical model for HFMD transmission as follows:

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = (1-p)b - \beta_1 S(t)\left(E(t) + I_1(t) + I_2(t)\right) - \mu S(t) + \gamma R(t)$$

$$\frac{\mathrm{d}E(t)}{\mathrm{d}t} = \beta_1 S(t)\left(E(t) + I_1(t) + I_2(t)\right) - \alpha E(t) - \delta E(t) - \mu E(t)$$

$$\frac{\mathrm{d}I_1(t)}{\mathrm{d}t} = q\alpha E(t) - \eta_1 I_1(t) - d_1 I_1(t) - \mu I_1(t)$$

$$\frac{\mathrm{d}I_2(t)}{\mathrm{d}t} = (1-q)\alpha E(t) - \eta_2 I_2(t) - d_2 I_2(t) - \mu I_2(t) \tag{1}$$

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = pb + \eta_1 I_1(t) - \mu V(t)$$

$$\frac{\mathrm{d}R(t)}{\mathrm{d}t} = \delta E(t) + \eta_2 I_2(t) - \gamma R(t) - \mu R(t)$$

where $b > 0$ is the birth rate of the population; $p \geq 0$ is the vaccine rate of the population; $\beta_1 > 0$ is the transmission coefficient of the infectious individuals infected; $\gamma \geq 0$ is loss of immunity rate of recovery individuals; $\mu > 0$ is the nature death rate; $\alpha > 0$ is the per-capita rate of the progression from latent individuals to infectious individuals; $q \geq 0$ is the percentage of individuals infected with EV-A71 from latent individuals to infectious individuals; $0 \leq 1-q \leq 1$ is the percentage of individuals infected with CV-A16 or other human enteroviruses; $\delta \geq 0$ is the treatment rate of the latent individuals; $\eta_1, \eta_2 \geq 0$ are the treatment rate of infectious individuals I_1 and I_2, respectively; $d_1, d_2 \geq 0$ are the death rate induced by infectious individuals I_1 and I_2, respectively.

3. Model Analysis

By using $N(t) = S(t) + E(t) + I_1(t) + I_2(t) + V(t) + R(t)$, we have

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = b - d_1 I_1(t) - d_2 I_2(t) - \mu N(t) \leq b - \mu N(t).$$

Obviously, $\limsup\limits_{t \to +\infty} N(t) \leq \dfrac{b}{\mu}$, which implies that $N(t) \leq \dfrac{b}{\mu}$.

From biological considerations, the dynamics of system (1) will be studied in

the following feasible region:

$$\Omega = \left\{ \left(S(t), E(t), I_1(t), I_2(t), V(t), R(t) \right) \in R_+^6 : 0 \le S(t) + E(t) + I_1(t) + I_2(t) + V(t) + R(t) \le \frac{\mu}{b} \right\}$$

where R_+^6 represents the non-negative cone of R^6. Then, all the solutions of the system (1) starting in Ω remain in the region Ω for all $t \ge 0$. Therefore, Ω is a positively invariant and bounded.

According to van den Diessche and Watmough [11] [12], we can obtain the basic reproduction number:

$$R_0 = \frac{\beta_1 b (1-p)}{\mu(\alpha+\delta+\mu)} \left[1 + \frac{q\alpha}{d_1+\eta_1+\mu} + \frac{\alpha(1-q)}{d_2+\eta_2+\mu} \right],$$

which means average new cases generated by a typical infectious member in the entire infection period.

For the system (1) in the absence of vaccination and recovery, means that $p=0$. Then, the basic reproduction number is proportional to the transmission coefficient β_1 and is given as

$$R_0 \big|_{p=0} = \frac{\beta_1 b}{\mu(\alpha+\delta+\mu)} \left[1 + \frac{q\alpha}{d_1+\eta_1+\mu} + \frac{\alpha(1-q)}{d_2+\eta_2+\mu} \right].$$

It is clear that

$$R_0 - R_0 \big|_{p=0} = \frac{\beta_1 b}{\mu(\alpha+\delta+\mu)} \left[-p - \frac{pq\alpha}{d_1+\eta_1+\mu} - \frac{p\alpha(1-q)}{d_2+\eta_2+\mu} \right] \le 0$$

which implies that the vaccination have a great contributed to decrease of the basic reproduction number R_0. That is, the vaccination is helpful to slow down the HFMD spread.

By directly calculation system (1), we get the disease-free equilibrium $P_0 = \left(S^0, E^0, I_1^0, I_2^0, V^0, R^0 \right)$, where $S^0 = \frac{b(1-p)}{\mu}$, $E^0 = I_1^0 = I_2^0 = R^0 = 0$, $V^0 = \frac{pb}{\mu}$.

Using Theorem 2 in [12], we have

Theorem 1. P_0 of the system (1) is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.

Next, we prove the global stability of the disease-free equilibrium when $R_0 < 1$.

Theorem 2. The disease-free equilibrium P_0 of system (1) is global asymptotically stable when $R_0 < 1$.

Proof: By Theorem 1, we only need to prove the disease-free equilibrium P_0 is a global attractor. Supposed $\limsup_{t \to +\infty} E(t) = m > 0$. For any $\varepsilon > 0$, there exist $\tau_1 > 0$ such that

$$E(t) \le m + \varepsilon, \text{ for all } t \ge \tau_1. \tag{2}$$

From the third equation of system (1) and (2), we have

$$\frac{dI_1(t)}{dt} \le q\alpha(m+\varepsilon) - (d_1+\eta_1+\mu)I_1(t), \text{ for all } t \ge \tau_1.$$

Then, there exists $\tau_2 \ge \tau_1$, such that

$$I_1(t) \le \frac{q\alpha(m+\varepsilon)}{d_1+\eta_1+\mu} + \varepsilon, \text{ for all } t \ge \tau_2. \tag{3}$$

From the fourth equation of system (1) and (2), we have

$$\frac{dI_2(t)}{dt} \le (1-q)\alpha(m+\varepsilon) - (d_2+\eta_2+\mu)I_2(t), \text{ for all } t \ge \tau_2.$$

Thus, there exists $\tau_3 \ge \tau_2$ such that

$$I_2(t) \le \frac{(1-q)\alpha(m+\varepsilon)}{d_2+\eta_2+\mu} + \varepsilon, \text{ for all } t \ge \tau_3. \tag{4}$$

From the sixth equation of system (1), (2) and (4), we have

$$\frac{dR(t)}{dt} \le \delta E(t) + \eta_2 I_2(t) - \gamma R(t) - \mu R(t), \text{ for all } t \ge \tau_3.$$

Thus, there exists $\tau_4 \ge \tau_3$ such that

$$R(t) \le \frac{1}{\gamma+\mu}\left[\delta(m+\varepsilon) + \eta_2\left(\frac{\alpha(1-q)(m+\varepsilon)}{d_2+\eta_2+\mu} + \varepsilon\right)\right], \text{ for all } t \ge \tau_4. \tag{5}$$

Next, substituting (3) and (4) into the second equation of system (1), we have that

$$\frac{dE(t)}{dt} \le \beta_1 \frac{b(1-p)}{\mu}\left(m+\varepsilon + \frac{q\alpha(m+\varepsilon)}{d_1+\eta_1+\mu} + \varepsilon + \frac{(1-q)\alpha(m+\varepsilon)}{d_1+\eta_1+\mu} + \varepsilon\right), \text{ for } t \ge \tau_3.$$
$$- (\alpha+\delta+\mu)E(t)$$

Then, there exists $\tau_4 \ge \tau_3$ such that

$$E(t) \le \beta_1 \frac{b(1-p)}{\mu(\alpha+\delta+\mu)}\left(m+\varepsilon + \frac{q\alpha(m+\varepsilon)}{d_1+\eta_1+\mu} + \varepsilon + \frac{(1-q)\alpha(m+\varepsilon)}{d_1+\eta_1+\mu} + \varepsilon\right), \tag{6}$$

for all $t \ge \tau_4$.

Letting $\varepsilon \to 0$, the inequality (6) becomes

$$E(t) \le \frac{\beta_1 b(1-p)}{\mu(\alpha+\delta+\mu)}\left(m + \frac{q\alpha m}{d_1+\eta_1+\mu} + \frac{(1-q)\alpha m}{d_1+\eta_1+\mu}\right)$$
$$= \frac{\beta_1 b(1-p)}{\mu(\alpha+\delta+\mu)}\left(1 + \frac{q\alpha}{d_1+\eta_1+\mu} + \frac{(1-q)\alpha}{d_1+\eta_1+\mu}\right)m$$
$$= mR_0$$

From lemma 1, that is $R_0 < 1$. Therefore, $\limsup\limits_{t\to+\infty} E(t) < m$, which is a contradiction. So, we have $m = 0$. Following (3)-(6) and the non-negativity of the solutions, we get that

$$\limsup\limits_{t\to+\infty} E(t) = \limsup\limits_{t\to+\infty} I_1(t) = \limsup\limits_{t\to+\infty} I_2(t) = \limsup\limits_{t\to+\infty} R(t) = 0.$$

Then, substituting $E(t), I_1(t), I_2(t), R(t)$ into the system (1), we obtain the limiting system as follows:

$$\begin{cases} \dfrac{\mathrm{d}S(t)}{\mathrm{d}t} = (1-p)b - \mu S(t) \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = pb - \mu V(t) \end{cases} \tag{7}$$

Sloving the equations of the system (7), we can obtain that

$$\limsup_{t\to+\infty} S(t) = \frac{b(1-p)}{\mu}, \quad \limsup_{t\to+\infty} V(t) = \frac{pb}{\mu}.$$

By the theory of asymptotically autonomous semiflows [13], we obtain that the disease-free equilibrium P_0 is the global attractor of the system (1).

Theorem 3. If $R_0 > 1$, then the disease is uniformly persistent for system (1). That is, there is a positive constant $\varepsilon_0 > 0$, such that

$$\liminf_{t\to+\infty} E(t) > \varepsilon_0, \quad \liminf_{t\to+\infty} I_1(t) > \varepsilon_0, \quad \liminf_{t\to+\infty} I_2(t) > \varepsilon_0. \tag{8}$$

Proof: Define $\tilde{K} = \left\{(S, E, I_1, I_2, V, R) \in R_+^6\right\}$,

$$K_0 = \left\{(S, E, I_1, I_2, V, R) \in \tilde{K} : S \geq 0, E > 0, I_1 > 0, I_2 > 0, V \geq 0, R \geq 0\right\},$$

and $\partial K_0 = \tilde{K} \setminus K_0$. Let $x(t, t_0, x_0)$ be the unique solution of system (1) with the initial value

$$x_0 = (S_0, E_0, I_{10}, I_{20}, V_0, R_0) \text{ at time } t_0.$$

Define poincare map $P: \tilde{K} \to \tilde{K}$ associated with system (1) as follows:

$$P(x_0) = x(t_0 + 1, x_0), \quad \forall x_0 \in \tilde{K}.$$

Set $M_\partial = \left\{x_0 \in \partial K_0 \middle| P^m(x_0) \in \partial K_0, \forall m \in Z_+\right\}$.

We claim that $M_\partial = \left\{(S, 0, 0, 0, V, R) \middle| S \geq 0, V \geq 0, R \geq 0\right\}$.

Clearly, $\left\{(S, 0, 0, 0, V, R) \middle| S \geq 0, V \geq 0, R \geq 0\right\} \subseteq M_\partial$.

Next, we need to demonstrate

$$M_\partial \setminus \left\{(S, 0, 0, 0, V, R) \middle| S \geq 0, V \geq 0, R \geq 0\right\} = \varnothing \tag{9}$$

If (9) does not hold, then there exists a point

$$(S_0, E_0, I_{10}, I_{20}, V_0, R_0) \in M_\partial \setminus \left\{(S, 0, 0, 0, V, R) \middle| S \geq 0, V \geq 0, R \geq 0\right\}. \tag{10}$$

To show (10) hold, we divided into two cases to discuss for three initial values E_0, I_{10}, I_{20}.

(i) One initial value is equal to zero, and the others are larger than zero. Without loss of generality, suppose $E_0 = 0, I_{10} > 0, I_{20} > 0$.

It is obvious that $S(t) > 0, I_1(t) > 0, I_2(t) > 0$ for any $t > t_0$. By the second equation of system (1), we obtain that

$$\left.\frac{\mathrm{d}E(t)}{\mathrm{d}t}\right|_{t=t_0} = \beta_1 S(t_0)(I_{10} + I_{20}) > 0.$$

Thus, $(S, E, I_1, I_2, V, R) \notin \partial K_0$, for $0 < t - t_0 \ll 1$.

This is a contradiction. The other subcases can be similarly proved.

(ii)Two initial values are equal to zero, and the other one is larger than zero.

Without loss of generality, suppose $E_0 = I_{10} = 0, I_{20} > 0$.

It is obvious that $S(t) > 0, I_2(t) > 0$ for any $t > t_0$. By the second equation of system (1), we have that

$$\left. \frac{dE(t)}{dt} \right|_{t=t_0} = \beta_1 S(t_0) I_{20} > 0.$$

So, $E(t) > 0$ for $0 < t - t_0 \ll 1$. From the third equation of system (1), we get that $\left. \frac{dI_1(t)}{dt} \right|_{t=t_0} = q\alpha E(t) > 0$, which means $I_1(t) > 0$ for $0 < t - t_0 \ll 1$.

Therefore, we have $(S, E, I_1, I_2, V, R) \notin \partial K_0$, for $0 < t - t_0 \ll 1$. This is a contradiction. Similarly, the others subcases can be proved.

Therefore, we proved $(S, E, I_1, I_2, V, R) \notin \partial K_0$, for $0 < t - t_0 \ll 1$.

In what follows, we use contradiction to prove that there exists for $\xi > 0$, such that

$$\limsup_{m \to +\infty} d\left(p^m(x_0), p^0 \right) \geq \xi, \quad \forall x_0 \in K_0, m \in Z^+, \tag{11}$$

where $p_0 = \left(S^0, 0, 0, 0, V^0, R^0 \right)$.

It follows from Theorem 2 in [12], that

$$R_0 > 1 \Leftrightarrow \rho\left(FV^{-1} \right) > 1 \Leftrightarrow \rho\left(\exp(F - V) \right) > 1.$$

Therefore, if $R_0 > 1$, we choose $\varepsilon > 0$, sufficiently small such that

$$\rho\left(\exp(F - V - M_\varepsilon) \right) > 1, \tag{12}$$

where $M_\varepsilon = \begin{pmatrix} \varepsilon & \varepsilon & \varepsilon \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$.

If (11) does not hold, then for any $\varsigma > 0$, we obtain $\limsup_{m \to +\infty} d\left(p^m(x_0), p_0 \right) < \varsigma$, for some $x_0 \in K_0$. Without loss of generality, we suppose that $d\left(p^m(x_0), p_0 \right) < \varsigma, \forall \varsigma > 0, \forall m \in Z_+$.

By the continuity of the solution with respect to the initial conditions, we get that

$$\left\| x\left(t, P^m(x_0) \right) - x(t, P_0) \right\| \leq \varepsilon, \quad \forall t \in [t_0, t_0 + 1], \forall m \in Z_+. \tag{13}$$

For $\forall t \geq t_0$, there exists an integer $l \in Z_+$ such that $t - t_0 = l + \hat{t}$, where $\hat{t} \in [0, 1)$. From (13), we have

$$\left\| x\left(t, P^m(x_0) \right) - x(t, P_0) \right\| = \left\| x\left(t_0 + \hat{t}, P^{m+l}(x_0) \right) - x(t_0 + \hat{t}, P_0) \right\| \leq \varepsilon.$$

Thus, we have

$$S(t) \geq S^0 - \varepsilon, \text{ for all } t \geq t_0. \tag{14}$$

By system (1) and (14), we obtain

$$\frac{\mathrm{d}E(t)}{\mathrm{d}t} \geq \beta_1 \left(S^0 - \varepsilon \right) \left(E(t) + I_1(t) + I_2(t) \right) - (\alpha + \delta + \mu) E(t)$$

$$\frac{\mathrm{d}I_1(t)}{\mathrm{d}t} = q\alpha E(t) - (d_1 + \eta_1 + \mu) I_1(t) \tag{15}$$

$$\frac{\mathrm{d}I_2(t)}{\mathrm{d}t} = (1-q)\alpha E(t) - (d_2 + \eta_2 + \mu) I_2(t)$$

Clearly, system (15) is an irreducible cooperative system. Consider the following auxiliary system

$$\frac{\mathrm{d}\hat{Z}(t)}{\mathrm{d}t} = \left(F - V - M_\varepsilon \right) \hat{Z}(t), \tag{16}$$

where $\hat{Z}(t) = \left(\hat{E}(t), \hat{I}_1(t), \hat{I}_2(t) \right)^{\mathrm{T}}$ and

$$F - V - M_\varepsilon = \begin{pmatrix} \beta_1 \left(S^0 - \varepsilon \right) - (\alpha + \delta + \mu) & \beta_1 \left(S^0 - \varepsilon \right) & \beta_1 \left(S^0 - \varepsilon \right) \\ q\alpha & -(d_1 + \eta_1 + \mu) & 0 \\ (1-q)\alpha & 0 & -(d_2 + \eta_2 + \mu) \end{pmatrix}.$$

From [13], there exists a positive vector v such that $\hat{Z}(t) = v\exp(\eta t)$ is a solution of system (16), where $\eta = \ln\rho\left(\exp\left(F - V - M_\varepsilon \right) \right)$. By (12), we have $\eta > 0$ and thus $\hat{Z}(t) \to +\infty$ as $t \to +\infty$, *i.e.* $\hat{E}(t) \to +\infty$, $\hat{I}_1(t) \to +\infty$, $\hat{I}_2(t) \to +\infty$ as $t \to +\infty$. Applying the comparison principle [14], we get that when $E(0) > 0$, $I_1(0) > 0$, $I_2(0) > 0$, then $E(t) \to +\infty$, $I_1(t) \to +\infty$, $I_2(t) \to +\infty$ as $t \to +\infty$. This is a contradiction. Thus (11) holds and P is weakly uniformly persistent with respect to $(K_0, \partial K_0)$. Therefore, $W^s(P_0) \bigcap K_0 = \varnothing$. Every solution in M_∂ converges to P_0. According to Zhao [15], we know that P is uniformly persistent with respect to $(K_0, \partial K_0)$. Therefore, we get $\liminf\limits_{t \to +\infty} E(t) > \varepsilon_0$, $\liminf\limits_{t \to +\infty} I_1(t) > \varepsilon_0$, $\liminf\limits_{t \to +\infty} I_2(t) > \varepsilon_0$. This completes the proof of Theorem 3.

4. Optimal Control

The purpose of this section is to controlling HFMD. We introduce the time dependent controls in the model (1) and study the strategies that curtail HFMD epidemic. For the optimal control problem of system (1), we add three control functions $u_1(t), u_2(t)$ and $u_3(t)$. Then, we consider the HFMD model with controls is given as follows:

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = \left(1 - u_1(t) \right) b - \beta_1 S(t) \left(E(t) + I_1(t) + I_2(t) \right) + \gamma R(t) - \mu S(t),$$

$$\frac{\mathrm{d}E(t)}{\mathrm{d}t} = \beta_1 S(t) \left(E(t) + I_1(t) + I_2(t) \right) - \alpha E(t) - \delta E(t) - \mu E(t),$$

$$\frac{\mathrm{d}I_1(t)}{\mathrm{d}t} = q\alpha E(t) - d_1 I_1(t) - \eta_1 I_1(t) - \mu I_1(t) - u_2(t) I_1(t),$$

$$\frac{\mathrm{d}I_2(t)}{\mathrm{d}t} = (1-q)\alpha E(t) - d_2 I_2(t) - \eta_2 I_2(t) - \mu I_2(t) - u_3(t) I_2(t),$$

$$\frac{dV(t)}{dt} = u_1(t)b + \eta_1 I_1(t) - \mu V(t) + u_2(t)I_1(t),$$

$$\frac{dR(t)}{dt} = \delta E(t) + \eta_2 I_2(t) - \gamma R(t) - \mu R(t) + u_3(t)I_2(t). \tag{17}$$

where

(i) $u_1(t)$ represents the control variable based on vaccination of EV-A71;

(ii) $u_2(t), u_3(t)$ represents the control variable to measure the effectiveness of treatment of $I_1(t), I_2(t)$, respectively.

We apply control theory [16] as a mathematical tool to make decision involving complex biological situations. For the system (17), we consider the control variables $u_1(t), u_2(t)$ and $u_3(t)$ are bounded and measured with

$$U = \left\{ (u_1(t), u_2(t), u_3(t)) \middle| u_i(t) \text{ is Lebesgue measurable}, 0 \le u_i(t) \le 1, t \in [0, T], i = 1, 2, 3 \right\}$$

where T is the control period.

From the control problem, the objective functional is given by

$$J(u_1(t), u_2(t), u_3(t)) = \int_0^T \left(A_1 I_1(t) + A_2 I_2(t) + \frac{B_1}{2} u_1^2(t) + \frac{B_2}{2} u_2^2(t) + \frac{B_3}{2} u_3^2(t) \right) dt, \tag{18}$$

where the constants B_1, B_2 and B_3 are a measure of the relative cost of the interventions associated with the controls $u_1(t)$, $u_2(t)$ and $u_3(t)$, respectively. A_1 and A_2 are the constants represent a measure of the relative cost of the interventions over the interval $[0, T]$.

In order to find the optimal values $u_1^*(t), u_2^*(t)$ and $u_3^*(t)$ of the controls variables $u_1(t)$, $u_2(t)$ and $u_3(t)$, which are minimizing cost functional (18), *i.e.*

$$J(u_1^*(t), u_2^*(t), u_3^*(t)) = \min \left\{ J(u_1(t), u_2(t), u_3(t)) \middle| (u_1(t), u_2(t), u_3(t)) \in U \right\}.$$

Next, we use Pontryagin's Maximum Principle [16] to solve this optimal control problem.

Using Pontryagin's Maximum Principle converts the system of (17) and (18) into a problem of minimizing a Hamiltonian (H) with respect to $u_1(t)$, $u_2(t)$ and $u_3(t)$ as follows:

$$\begin{aligned} H(t, X(t), u(t), \lambda(t)) = {} & A_1 I_1(t) + A_2 I_2(t) + \frac{B_1}{2} u_1^2(t) + \frac{B_2}{2} u_2^2(t) + \frac{B_3}{2} u_3^2(t) \\ & + \lambda_1(t) \frac{dS(t)}{dt} + \lambda_2(t) \frac{dE(t)}{dt} + \lambda_3(t) \frac{dI_1(t)}{dt} \\ & + \lambda_4(t) \frac{dI_2(t)}{dt} + \lambda_5(t) \frac{dV(t)}{dt} + \lambda_6(t) \frac{dR(t)}{dt}, \end{aligned} \tag{19}$$

where

$$\begin{cases} X(t) = (S(t), E(t), I_1(t), I_2(t), V(t), R(t)), \\ u(t) = (u_1(t), u_2(t), u_3(t)), \\ \lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t), \lambda_6(t)). \end{cases}$$

The adjoint equations are obtained by

$$\frac{\mathrm{d}\lambda_i}{\mathrm{d}t} = -\frac{\partial H}{\partial X(t)},$$

with transversality condition $\lambda_i(T) = 0$, where $i = 1, 2, 3, 4, 5, 6$.

By Equation (19), we have the adjoint equations

$$\frac{\mathrm{d}\lambda_1(t)}{\mathrm{d}t} = -\frac{\partial H}{\partial S(t)} = (\lambda_1(t) - \lambda_2(t))\beta_1(E(t) + I_1(t) + I_2(t)) + \mu$$

$$\frac{\mathrm{d}\lambda_2(t)}{\mathrm{d}t} = -\frac{\partial H}{\partial E(t)} = (\lambda_1(t) - \lambda_2(t))\beta_1 S(t) + \lambda_2(t)(\alpha + \delta + \mu)E(t) - \lambda_3(t)q\alpha - \lambda_4(t)(1-q)\alpha$$

$$\frac{\mathrm{d}\lambda_3(t)}{\mathrm{d}t} = -\frac{\partial H}{\partial I_1(t)} = -A_1 + (\lambda_1(t) - \lambda_2(t))\beta_1 S(t) + \lambda_3(t)(d_1 + \eta_1 + \mu + u_2(t)) - \lambda_5(t)(\eta_1 + u_2(t))$$

$$\frac{\mathrm{d}\lambda_4(t)}{\mathrm{d}t} = -\frac{\partial H}{\partial I_2(t)} = -A_2 + (\lambda_1(t) - \lambda_2(t))\beta_1 S(t) + \lambda_4(t)(d_2 + \eta_2 + \mu + u_3(t)) - \lambda_6(t)(\eta_2 + u_3(t))$$

$$\frac{\mathrm{d}\lambda_5(t)}{\mathrm{d}t} = -\frac{\partial H}{\partial V(t)} = \lambda_5(t)\mu$$

$$\frac{\mathrm{d}\lambda_6(t)}{\mathrm{d}t} = -\frac{\partial H}{\partial R(t)} = -\lambda_1(t)\gamma + \lambda_6(t)(\gamma + \mu)$$

(20)

The optimality of the control problem is obtained by

$$u_i^*(t) = \frac{\partial H}{\partial u_i(t)},$$

where $i = 1, 2, 3, 4, 5, 6$. The solution of $u_1^*(t), u_2^*(t)$ and $u_3^*(t)$ are presented in compact form as

$$u_1^*(t) = \max\left\{\min\left\{1, \frac{b(\lambda_1(t) - \lambda_5(t))}{B_1}\right\}, 0\right\}$$

$$u_2^*(t) = \max\left\{\min\left\{1, \frac{\lambda_3(t) - \lambda_5(t)}{B_2}I_1^*\right\}, 0\right\} \qquad (21)$$

$$u_3^*(t) = \max\left\{\min\left\{1, \frac{\lambda_4(t) - \lambda_6(t)}{B_3}I_2^*\right\}, 0\right\}$$

5. Numerical Simulations

In this section, we will make numerical simulations of the optimized control measures for HFMD system (17). Forward fourth-order Runge-Kutta scheme is used to solve system (17) over the time interval $(0, T]$ and transversality conditions $\lambda_i(T) = 0$, $i = 1, 2, 3, 4, 5, 6$. Then, system (20) is solved by a backward fourth-order Runge-Kutta scheme using the current iteration solution of system (17). Take the parameter values as follows: $p = 0.2$; $b = 16073$; $\beta_1 = 0.0353$; $\gamma = 3.4458 \times 10^{-5}$; $\mu = 3.9139 \times 10^{-5}$; $\alpha = 0.185185$; $\delta = 0.117647$; $q = 0.018$; $d_1 = 0.0113841$; $\eta_1 = \eta_2 = 0.117643$; $d_2 = 0.0011259$.

We numerically examine the effect of the optimal control strategy on the

spread of HFMD. In the simulation without control measure is labeled with bold line and the control by a dashed line. The weight constant values in the objective function are $A_1 = 400$; $A_2 = 800$; $B_1 = 30$; $B_2 = 20$; $B_3 = 150$. **Figure 1** showed the control strategy resulted in a decrease in the number of latent individuals E(t), infectious individuals I₁(t) and I₂(t), and increase the number of vaccination individuals V(t). In **Figure 2**, the optimal control profile for $u_1(t)$, $u_2(t)$ and $u_3(t)$ are showed.

6. Conclusion

In this paper, based on the mechanism and characteristics of HFMD transmission, we established a Hand-Foot-Mouth disease model with treatment and vaccination interventions and studied the effect of intervention strategy in controlling the spread of HFMD. The basic reproduction number of system (1) is obtained, and proved the disease would die out when $R_0 < 1$, and the disease would be endemic when $R_0 > 1$. By the optimal control theory, we studied the intervention strategy to determine the optimal integrated strategy. In addition, we use Pontryagin's Maximum Principle to analyze optimal control problem with three control variables. Numerical simulations illustrated the effectiveness of the proposed control problem.
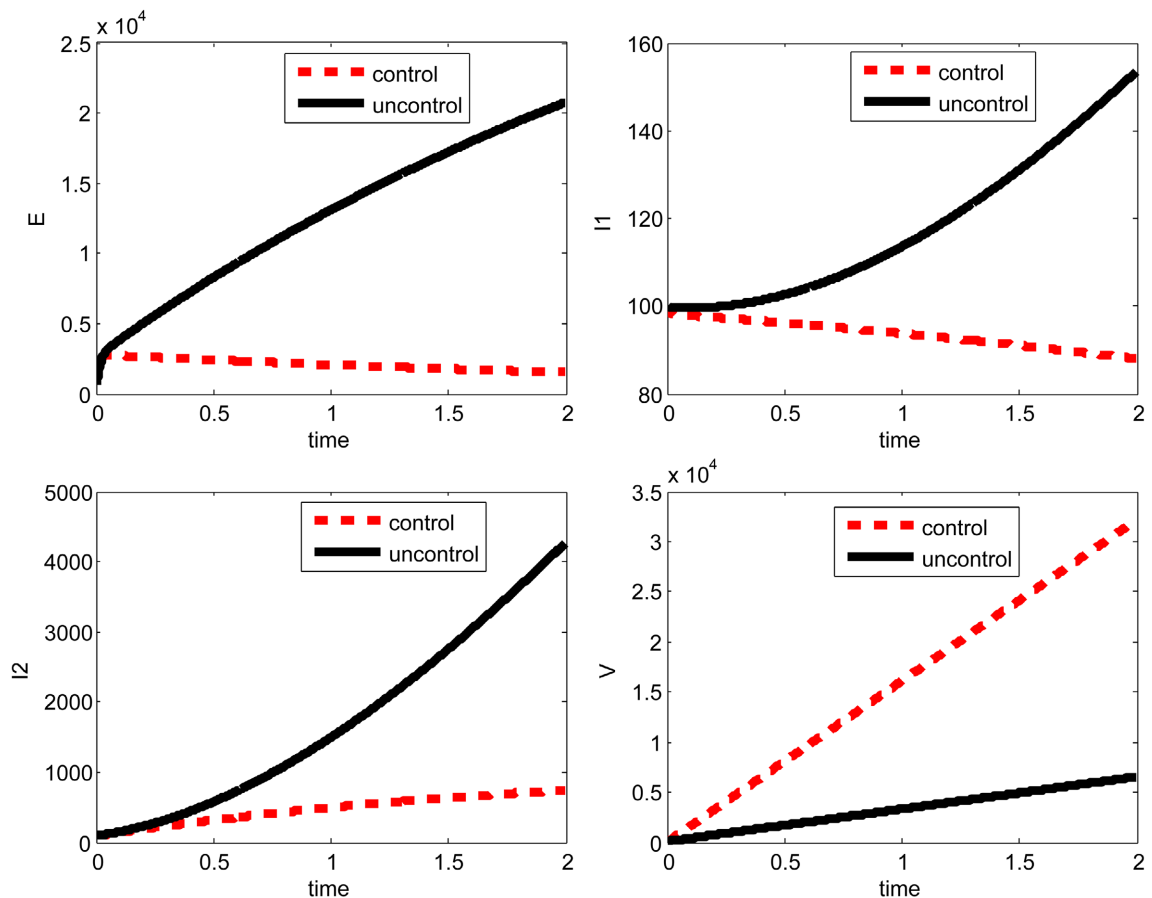
Figure 1. The plot represents population of $E(t)$, $I_1(t)$, $I_2(t)$, and $V(t)$ both with control and without control.
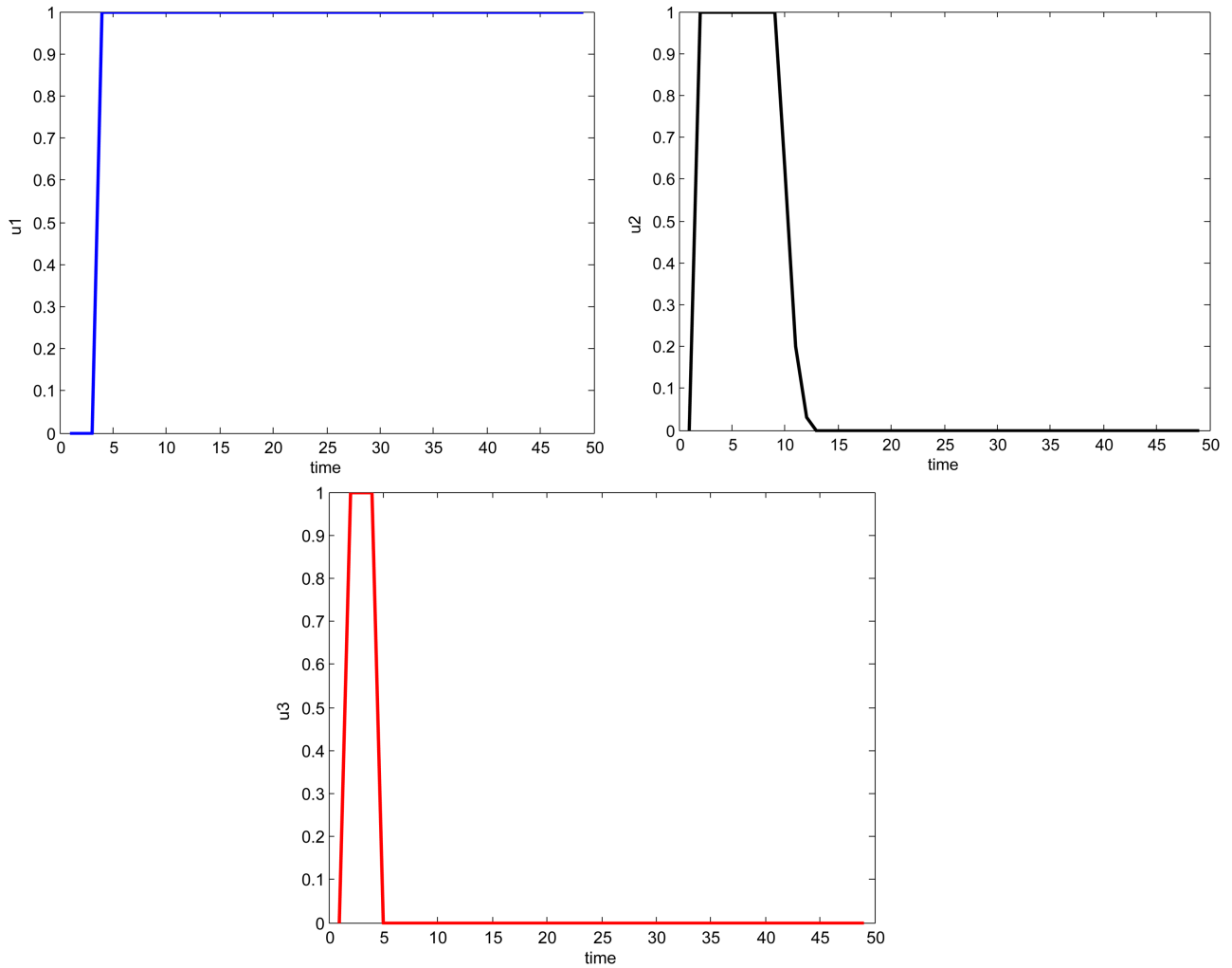
Figure 2. The plot represents the controls $u_1(t)$, $u_2(t)$ and $u_3(t)$.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Duff, M.F. (1968) Hand-Foot-and-Mouth Syndrome in Humans: Coxackie A10 Infections in New Zealand. *BMJ*, **2**, 661-664. https://doi.org/10.1136/bmj.2.5606.661

[2] Xing, W., Liao, Q., Viboud, C., Zhang, J., Sun, J., Wu, J.T., *et al.* (2014) Hand, Foot, and Mouth Disease in China, 2008-12: An Epidemiological Study. *The Lancet Infectious Diseases*, **14**, 308-318. https://doi.org/10.1016/S1473-3099(13)70342-6

[3]   Wang, J.-F., Guo, Y.-S., George, C., *et al.* (2011) Hand, Foot and Mouth Disease: Spatiotemporal Transmission and Climate. *International Journal of Health Geographics*, **10**, 1-10. https://doi.org/10.1186/1476-072X-10-25

[4]   Yang, B.Y., *et al.* (2017) Epidemiology of Hand, Foot and Mouth Disease in China, 2008 to 2015 Prior to the Introduction of EV-A71 Vaccine. *Eurosurveillance*, **22**, 38-47. https://doi.org/10.2807/1560-7917.ES.2017.22.50.16-00824

[5]   Li, R., Liu, L., Mo, Z., Wang, X., Xia, J., Liang, Z., *et al.* (2014) An Inactivated Enterovirus 71 Vaccine in Healthy Children. *The New England Journal of Medicine*, **370**, 829-837. https://doi.org/10.1056/NEJMoa1303224

[6]   Urashima, M., Shindo, N. and Okabe, N. (2003) Seasonal Models of Herpangina and Hand-Foot-Mouth Disease to Simulate Annual Fuctuations in Urban Warming in Tokyo. *Japanese Journal of Infectious Diseases*, **56**, 48-53.

[7]   Wang, Y.C. and Sung, F.C. (2004) Modeling the Infectious for Entero Viruses in Taiwan Area. http://gra103.aca.ntu.edu.tw/gdoc/D91844001a.pdf

[8]   Tan, H.W. and Cao, H. (2018) The Dynamics and Optimal Control of a Hand-Foot-Mouth Disease Model. *Computational and Mathematical Methods in Medicine*, **2018**, Article ID: 9254794. https://doi.org/10.1155/2018/9254794

[9]   Zhang, W., Rui, J. and Cheng, X.Q., *et al.* (2022) Transmissibility of Hand, Foot, and Mouth Disease in 97 Counties of China. *Scientific Reports* **12**, 1-15. https://doi.org/10.1038/s41598-022-07982-y

[10] Li, Y., Wang, L.W., *et al.* (2016) The Data Fitting and Optimal Control of a Hand, Foot and Mouth Disease (HFMD) Model with Stage Structure. *Applied Mathematics and Computation*, **276**, 61-74. https://doi.org/10.1016/j.amc.2015.11.090

[11] Diekmann, O., Heesterbeek, J.A.P. and Metz, J.A. (1990) On the Definition and the Computation of the Basic Reproduction Ratio R0 in Models for Infectious Disease in Heterogeneous Populations. *Journal of Mathematical Biology*, **28**, 365-382. https://doi.org/10.1007/BF00178324

[12] van den Driessche, P. and Watmough, J. (2002) Reproduction Numbers and Sub-Threshold Endemic Equilibria for Compartmental Models of Disease Transmission. *Mathematical Biosciences*, **180**, 29-48. https://doi.org/10.1016/S0025-5564(02)00108-6

[13] Xu, D. and Zhao, X.Q. (2005) Dynamics in a Periodic Competitive Model with Stage Structure. *Journal of Mathematical Analysis and Applications*, **311**, 417-438. https://doi.org/10.1016/j.jmaa.2005.02.062

[14] Smith, H. and Waltman, P. (1995) The Theory of the Chemostat. Cambridge University Press, Cambridge. https://doi.org/10.1017/CBO9780511530043

[15] Zhao, X.-Q. (2003) Dynamical Systems in Population Biology. Spring-Verlag, New York. https://doi.org/10.1007/978-0-387-21761-1

[16] Lenhart, S. and Workman, J.T. (2007) Optimal Control Applied to Biological Models. Mathematical and Computational Biology Series. Chapman & Hall/CRC Press, London/Boca Raton. https://doi.org/10.1201/9781420011418