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Optimal Control of Hand, Foot and Mouth Disease Model Using Variational Iteration Method

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Abstract. In this paper, the optimal control of transmission dynamics of hand, foot and mouth disease (HFMD), formulated by a compartmental deterministic SEIPR (Susceptible-Incubation (Exposed)- Infected - Post infection virus shedding - Recovered) model with vaccination and treatment as control parameters is considered. The objective function is based on the combination of minimizing the number of infected individuals and the cost involved in the interventions of vaccination given to the susceptible population and treatment given to the infected population. The existence for the optimal control pair is proved and the characterization of the optimal control pair is obtained by applying the Pontryagin's maximum principle. The variational iteration method is adopted to solve the non-linear Hamilton equations derived from the Pontryagin's maximum principle theory. These equations constitute a two-point boundary value problem. By considering the correction functionals of the Hamilton equations, the Lagrange multipliers are easily identified and practical iteration formulas are derived. An algorithm is developed, based on this formulas, to determine iteratively the solutions of the Hamilton equations with a desired accuracy. With the aid of solutions obtained, the optimal control law can be easily deduced. The results were analyzed and interpreted graphically using Maple.

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1. Introduction

Hand foot and mouth disease - a mild, contagious viral infection common in young children is characterized by sores in the mouth and a rash on the hands and feet. Hand foot and mouth disease is most commonly caused by a coxsackievirus. The coxsackievirus belongs to a group of viruses called nonpolio enteroviruses. Enterovirus 71 (EV-71) is the second-most common cause. Many other strains of coxsackievirus and enterovirus can also be responsible. Oral ingestion is the main source of coxsackievirus infection.

The usual period from initial infection to the onset of signs and symptoms (incubation period) is three to six days. A fever is often the first sign of hand foot and mouth disease, followed by a sore throat and sometimes a poor appetite and malaise. One or two days after the fever begins, painful sores may develop in the front of the mouth or throat. A rash on the hands and feet and possibly on the buttocks can follow within one or two days. Sores that develop in the back of the mouth and throat may suggest that your child is infected with a related viral illness called herpangina. Other distinguishing features of herpangina include a sudden high fever and in some instances, seizure. Sores that develop on the hands, feet or other parts of the body are very rare. The illness spreads by person-to-person contact with an infected person.

The first HFMD case was reported in New Zealand in 1957, which is now endemic worldwide. Research literature for past 25 years from Asia describes the epidemiology of HFMD, drawing on pediatric groups, national surveillance systems, outbreak investigations and clinical data. HFMD occurs in various countries that span stages of economic development and with climates that range from tropical to temperate [11]. This diversity complicates the attempts to identify and understand the general features of epidemiology and pathobiology of HFMD. Urashima et al.[21] tried to find the relationship between the out break of HFMD with the weather patterns in Taiwan and Tokyo, respectively. Hongwu Tan and Hui Cao[18] used mathematical modeling to gain some insights into the transmission dynamics of HFMD when the population is vaccinated.

Some mathematical modelers have developed models for analysing the dynamic behaviour of the HFMD. SEIR model was analysed theoretically by using numerical simulation which showed that the number of actively infective people at initial time and the disease transmission coefficient play more role on the transmission was done by Nandita Roy and Nilimesh Halder[16]. To curtail HFMD in Sarawak, a simple deterministic model has been studied [20]. To predict the real dynamics of Hand, Foot and Mouth infection, [4] hypothesized a model by including the incubation period and post infection virus shedding period. Liu[13] used the SEIQRS model to take into account the quarantine measure. Samanta [17] discussed a delay HFMD model with pulse vaccination strategy.

Optimal control theory is used extensively in controlling the spread of infectious diseases. It is a powerful mathematical tool that can be used to make decisions involving complex biological situation. It is often used in the control of the spread of most diseases for which either vaccine or treatment is available. Gaff and Schaefer [7] applied optimal control theory to a set of epidemiological models in their attempt to find the most effective control strategy to minimize the number of individuals who become infected in the course of an epidemic using both treatment and vaccination as control measures. Zaman et al.[24] concentrated on an SIR model using only vaccination as their control. Blayneh et al.[2] considered prevention

and treatment as controls and studied optimal control of a vector-borne disease. Ebenezer et al.[3] applied control theory to study about the reduction of the Ebola infection using three different controls. Bakare [1] analyzed SIR epidemic model and derived basic reproduction number and applied optimal control theory to minimize the total number of infective individuals and the cost associated with the use of educational campaign and treatment. Tunde Tajudeen Yusuf and Francis Benyah[23], in their paper addressed how to optimally combine the vaccination and the treatment strategies such that the cost of the implementation of the two interventions is minimized while the disease is eradicated within specified period. Devipriya and Kalaivani [5] considered immune boosting and pathogen suppressing drugs as their controls for the multiple transmission of water-borne disease and obtained optimal solution in minimizing the number of infected individuals and the cost of the drug dose usage in the eradication of water-borne disease.

Several methods are available in the literature to solve optimal control problems. On one side, analytical theories, even if problems are in general solved numerically, include Variational Calculus [22], Hamilton-Jacobi and Pontryagin's principle of minimum or maximum [15] for systems described by continuous state-space models and dynamic programming. Non-linear differential equations can be solved easily and with high accuracy by means of the variational iteration method proposed by He [8], a good approximate solutions can be achieved by using practical iterative formulas derived from the correction functionals.

To the best of our knowledge, the optimal control of HFMD model by He's variational iteration method is nevertheless considered. Thus, an attempt is made in this paper. The mathematical formulation of HFMD model is given in section 2. In section 3, the controlled SEIPR model is considered and the existence optimal control pair is proved followed by its characterization with aid of Pontryagin's maximum principle. The optimality system so obtained is a two point nonlinear boundary value problem which is numerically solved using variational iteration method in section 4. In section 5, the results are analyzed and graphically interpreted using Maple.

2. Mathematical formulation of hand, foot and mouth disease

The mathematical model of HFMD is formulated by improving standard SIR model [20] by adding the compartments of the incubation group and post-infection virus shedding group which is a a simple deterministic SEIPR model to deal with the periodic infected cases. The population is split into five compartments namely the susceptible group (S), the incubation group (E), the infectious group (I), the post-infection virus shedding group (P) and the fully recovered group (R). The susceptible class increases through the natural birth and fully recovered individuals who have lost their immunity. Meanwhile, the susceptible class also decreases through the natural death, the moving to incubation group, infectious group and post-infection virus shedding group. The susceptible (S) gains the HFMD infection through the contact with the asymptomatic patients (E), symptomatic patients (I) or with those carrying post-infection virus individuals (P) [14]. Once infected, the asymptomatic patients will move to incubation group (E). During this incubation period, HFMD patients have no symptom shown. Symptoms can be developed within few days [14, 20], however after many simulations ran, it was assumed that symptoms are developed in about one day and the patients are moved to the infected group (I). Another one week, when the symptoms subside then they will move to the post-infection virus shedding group (P) where the patients are said to be clinically recovered and do not exhibit any symptoms, but the virus may

continue to shed. One more week later, the patients are fully recovered and will move to fully recovered group (R) [12]. An individual will attain an immunity from HFMD after recovery, however the patient can be infected again through different HFMD viruses. Thus, the recovered patient returns to susceptible class and capable to be infected again. Now let us formulate the Mathematical model of HFMD by the following system of nonlinear differential equations[4]:

$$\begin{aligned}
\frac{dS(t)}{dt} &= k_1 + \beta_7 R(t) - \beta_1 S(t)E(t) - \beta_5 S(t)I(t) - \beta_6 S(t)P(t) - k_2 S(t) \\
\frac{dE(t)}{dt} &= \beta_1 S(t)E(t) + \beta_5 S(t)I + \beta_6 S(t)P - \beta_2 E(t) - k_2 E(t) \\
\frac{dI(t)}{dt} &= \beta_2 E(t) - \beta_3 I(t) - (k_2 + k_3)I(t) \\
\frac{dP(t)}{dt} &= \beta_3 I(t) - \beta_4 P(t) - k_2 P(t) \\
\frac{dR(t)}{dt} &= \beta_4 P(t) - k_2 R(t) - \beta_7 R(t)
\end{aligned} \tag{1}$$

with initial data

$$S(0) \geqslant 0; \quad E(0) \geqslant 0; \quad I(0) \geqslant 0; \quad P(0) \geqslant 0; \quad R(0) \geqslant 0,$$

where k_1 and k_2 represent natural birth and death rate, k_3 represents the death rate due to the disease, β_1 denote the transmission coefficient of susceptible individuals (S) getting infected by exposed individuals (E), β_2 denote the transmission coefficient of susceptible individuals (S) getting infected by infectious individuals (I), β_3 denote the transmission coefficient of susceptible individuals (S) getting infected by clinically recovered individuals (P). The rate at which an asymptomatic patient developing symptoms per unit time is given by α, the rate at which an infectious individual clinically recovered per unit time is given by ν_1, the rate at which a clinically recovered individual fully recovered per unit time is given by ν_2 and the rate at which a recovered individual loses its immunity is given by γ.

3. Controlled HFMD model

Consider the controlled SEIPR model

$$\begin{aligned}
\frac{dS(t)}{dt} &= k_1 + \beta_7 R(t) - \beta_1 S(t)E(t) - \beta_5 S(t)I(t) - \beta_6 S(t)P(t) - k_2 S(t) - u_1(t)S(t) \\
\frac{dE(t)}{dt} &= \beta_1 S(t)E(t) + \beta_5 S(t)I(t) + \beta_6 S(t)P(t) - \beta_2 E(t) - k_2 E(t) \\
\frac{dI(t)}{dt} &= \beta_2 E(t) - \beta_3 I(t) - (k_2 + k_3)I(t) - u_2(t)I(t) \\
\frac{dP(t)}{dt} &= \beta_3 I(t) - \beta_4 P(t) - k_2 P(t) \\
\frac{dR(t)}{dt} &= \beta_4 P(t) - k_2 R(t) - \beta_7 R(t) + u_1(t)S(t) + u_2(t)I(t)
\end{aligned} \tag{2}$$

with initial conditions

$$S(0) = 10000, E(0) = 4, I(0) = 4, P(0) = 4, R(0) = 0 \tag{3}$$

where $u_1(t)$ and $u_2(t)$ are controls representing treatment given to the infected individuals and vaccination given to the susceptible individuals, respectively.
The main objective is to minimize the number of infected and the cost involved in the intervention of vaccination and treatment. Thus, the objective functional is defined as

$$J(u_1(t), u_2(t)) = \int_0^T (A_1 I(t) + A_2 u_1^2(t) + A_3 u_2^2(t))dt \tag{4}$$

where A_1, A_2 and A_3 are positive weights that balance the size of terms. The term $A_2 u_1^2(t)$and $A_3 u_2^2(t)$ describe the cost associated with the intervention of vaccination and treatment. Here the aim is to minimize the number of infected and cost involved in control strategies, the optimal control pair $({u_1}^*(t), {u_2}^*(t))$ were obtained such that

$$J({u_1}^*(t), {u_2}^*(t)) = \min\big(J(u_1(t), u_2(t))/(u_1(t), u_2(t)) \in U\big) \tag{5}$$

where $U = \{(u_1(t), u_2(t))/u_i(t)$ is measurable, $0 \leqslant u_i(t) \leqslant 1, t \in [0, T]$, for $i = 1, 2\}$ is the adimissible control set. Here, the value $u_i(t) = 1, i = 1, 2$ represents the maximal control due to vaccination and treatment provided.

3.1 *Existence of an optimal control pair*

The existence of the optimal control pair for the state system (2) can be obtained by using a result by Fleming and Rishel [6].

Theorem 3.1 Consider the control problem with system (2). There exists a optimal control pair $(u_1^*(t), u_2^*(t)) \in U$ such that $J(u_1^*, u_2^*) = \min_{u_1, u_2 \in U} J(u_1, u_2)$.

Proof To prove the existence of an optimal control, we use the result in [6]. Note that the control and the state variable are nonnegative values. In this minimizing problem, the necessary convexity of the objective functional in u_1, u_2 is satisfied. The set of all the control variable $(u_1, u_2) \in U$ is also convex and closed by definition. The optimal system is bounded which determines the compactness needed for the existence of the optimal control. In addition, the integrand in the functional (3), $A_1 I(t) + A_2 u_1^2(t) + A_3 u_2^2(t)$ is convex on the control set U. Also we can easily see that, there exist a constant $\omega > 1$ and positive numbers ω_1, ω_2 such that $J(u_1, u_2) \geqslant \omega_1(|u_1|^2 + |u_2|^2)^{\omega/2} - \omega_2$, because, the state variables are bounded, which completes the existence of an optimal control. ■

3.2 *Characterization of the optimal control pair*

According to the Pontryagin's Maximum Principle, we now derive the necessary conditions that a pair of optimal controls and corresponding states must satisfy.

To this purpose, we define the Hamiltonian function for the system:

$$\begin{aligned} H(t,S,E,I,P,R,\lambda_S,\lambda_E,\lambda_I,\lambda_P,\lambda_R) &= A_1 I(t) + A_2 u_1^2(t) + A_3 u_2^2(t) + \lambda_S(k_1 \\ &+ \beta_7 R(t) - \beta_1 S(t)E(t) - \beta_5 S(t)I(t) - \beta_6 S(t)P(t) - k_2 \\ &- u_1(t)S(t)) + \lambda_E(\beta_1 S(t)E(t) + \beta_5 S(t)I(t) + \beta_6 S(t)P(t) \\ &- \beta_2 E(t) - k_2 E(t)) + \lambda_I(\beta_2 E(t) - \beta_3 I(t) - (k_2+k_3)I(t) \\ &- u_2(t)I(t)) + \lambda_P(t)(\beta_3 I(t) - \beta_4 P(t) - k_2 P(t)) + \lambda_R(\beta_4 P(t) \\ &- k_2 R(t) - \beta_7 R(t) + u_1(t)S(t) + u_2(t)I(t)) \end{aligned} \tag{6}$$

Theorem 3.2 Given optimal controls $u_1{}^*(t)$ and $u_2{}^*(t)$ and solutions S(t),E(t),I(t),P(t) and R(t) of the corresponding state system, there exists adjoint variables $\lambda_S(t)$,$\lambda_E(t)$,$\lambda_I(t)$,$\lambda_P(t)$ and $\lambda_R(t)$ satisfying

$$\begin{aligned} \dot{\lambda_S}(t) &= \lambda_S(t)\beta_1 E(t) + \lambda_S(t)\beta_5 I(t) + \lambda_S(t)\beta_6 P(t) + \lambda_S(t)k_2 + \lambda_S(t)u_1(t) \\ &- \lambda_E(t)\beta_1 E(t) - \lambda_E(t)\beta_5 I(t) - \lambda_E(t)\beta_6 P(t) - \lambda_R(t)u_1(t) \\ \dot{\lambda_E}(t) &= \lambda_S(t)\beta_1 S(t) - \lambda_E(t)\beta_1 S(t) + \lambda_E(t)\beta_2 + \lambda_E(t)k_2 - \lambda_I(t)\beta_2(t) \\ \dot{\lambda_I}(t) &= -A_1 + \lambda_S(t)\beta_5 S(t) - \lambda_E(t)\beta_5 S(t) + \lambda_I(t)\beta_3 + \lambda_I(t)(k_2+k_3) \\ &+ \lambda_I(t)u_2(t) - \lambda_P(t)\beta_3 - \lambda_R(t)u_2(t) \\ \dot{\lambda_P}(t) &= \lambda_S(t)\beta_6 S(t) - \lambda_E(t)\beta_6 S(t) + \lambda_P(t)\beta_4 + \lambda_P(t)k_2 - \lambda_R(t)\beta_4 \\ \dot{\lambda_R}(t) &= -\lambda_S(t)\beta_7 + \lambda_R(t)k_2 + \lambda_R(t)\beta_7 \end{aligned} \tag{7}$$

and $\lambda_S(T) = \lambda_E(T) = \lambda_I(T) = \lambda_P(T) = \lambda_R(T) = 0$, the transversality conditions.
Furthermore

$$\begin{aligned} u_1{}^*(t) &= \min\left\{\max\left\{0, \frac{S(t)(\lambda_S(t) - \lambda_R(t))}{2A_2}\right\}, 1\right\} \\ u_2{}^*(t) &= \min\left\{\max\left\{0, \frac{I(t)(\lambda_I(t) - \lambda_R(t))}{2A_3}\right\}, 1\right\} \end{aligned} \tag{8}$$

Proof The form of the adjoint equations and transversality conditions are standard results from Pontryagin's maximum principle. The adjoint system can be obtained as follows:

$$\begin{aligned} \dot{\lambda_S}(t) = -\frac{\partial H}{\partial S} &= \lambda_S(t)\beta_1 E(t) + \lambda_S(t)\beta_5 I(t) + \lambda_S(t)\beta_6 P(t) + \lambda_S(t)k_2 + \lambda_S(t)u_1(t) \\ &- \lambda_E(t)\beta_1 E(t) - \lambda_E(t)\beta_5 I(t) - \lambda_E(t)\beta_6 P(t) - \lambda_R(t)u_1(t) \\ \dot{\lambda_E}(t) = -\frac{\partial H}{\partial E} &= \lambda_S(t)\beta_1 S(t) - \lambda_E(t)\beta_1 S(t) + \lambda_E(t)\beta_2 + \lambda_E(t)k_2 - \lambda_I(t)\beta_2 \\ \dot{\lambda_I}(t) = -\frac{\partial H}{\partial I} &= -A_1 + \lambda_S(t)\beta_5 S(t) - \lambda_E(t)\beta_5 S(t) + \lambda_I(t)\beta_3 + \lambda_I(t)(k_2+k_3) \\ &+ \lambda_I(t)u_2(t) - \lambda_P(t)\beta_3 - \lambda_R(t)u_2(t) \end{aligned}$$

$$\begin{aligned}\dot{\lambda_P}(t) &= -\frac{\partial H}{\partial P} = \lambda_S(t)\beta_6 S(t) - \lambda_E(t)\beta_6 S(t) + \lambda_P(t)\beta_4 + \lambda_P(t)k_2 - \lambda_R\beta_4(t)\\ \dot{\lambda_R}(t) &= -\frac{\partial H}{\partial R} = -\lambda_S(t)\beta_7 + \lambda_R(t)k_2 + \lambda_R(t)\beta_7\end{aligned} \tag{9}$$

The optimality equations were given by:

$$\begin{aligned}\frac{\partial H}{\partial u_1} &= 2A_2u_1(t) - \lambda_S(t)S(t) + \lambda_R(t)S(t) = 0 \text{ at } {u_1}^*(t)\\ \frac{\partial H}{\partial u_2} &= 2A_3u_2(t) - \lambda_I(t)I(t) + \lambda_R(t)I(t) = 0 \text{ at } {u_2}^*(t)\end{aligned} \tag{10}$$

Hence,

$$\begin{aligned}{u_1}^*(t) &= \frac{S(t)(\lambda_S(t) - \lambda_R(t))}{2A_2}\\ {u_2}^*(t) &= \frac{I(t)(\lambda_I(t) - \lambda_R(t))}{2A_3}\end{aligned} \tag{11}$$

By using the bounds for the control u_1, we get

$${u_1}^*(t) = \begin{cases}\frac{S(t)(\lambda_S(t)-\lambda_R(t))}{2A_2} & \text{if } 0 \le \frac{S(t)(\lambda_S(t)-\lambda_R(t))}{2A_2} \le 1,\\ 0 & \text{if } \frac{S(t)(\lambda_S(t)-\lambda_R(t))}{2A_2} \le 0,\\ 1 & \text{if } \frac{S(t)(\lambda_S(t)-\lambda_R(t))}{2A_2} \ge 1.\end{cases} \tag{12}$$

In compact notation,

$${u_1}^*(t) = \min\left\{\max\left\{0, \frac{S(t)(\lambda_S(t) - \lambda_R(t))}{2A_2}\right\}, 1\right\} \tag{13}$$

By using the bounds for the control u_2, we get

$${u_2}^*(t) = \begin{cases}\frac{I(t)(\lambda_I(t)-\lambda_R(t))}{2A_3} & \text{if } 0 \le \frac{I(t)(\lambda_I(t)-\lambda_R(t))}{2A_3} \le 1,\\ 0 & \text{if } \frac{I(t)(\lambda_I(t)-\lambda_R(t))}{2A_3} \le 0,\\ 1 & \text{if } \frac{I(t)(\lambda_I(t)-\lambda_R(t))}{2A_3} \ge 1.\end{cases} \tag{14}$$

In compact notation,

$${u_2}^*(t) = \min\left\{\max\left\{0, \frac{I(t)(\lambda_I(t) - \lambda_R(t))}{2A_3}\right\}, 1\right\} \tag{15}$$

Using (13) and (15), we have the following optimality system:

$$\begin{aligned}
\dot{S}(t) &= k_1 + \beta_7 R(t) - \beta_1 S(t)E(t) - \beta_5 S(t)I(t) - \beta_6 S(t)P(t) - k_2 S(t) \\
&\quad - \min\{\max\{0, \frac{S(t)(\lambda_S(t) - \lambda_R(t))}{2A_2}\}, 1\}S(t) \\
\dot{E}(t) &= \beta_1 S(t)E(t) + \beta_5 S(t)I(t) + \beta_6 S(t)P(t) - \beta_2(t)E(t) - k_2(t)E(t) \\
\dot{I}(t) &= \beta_2 E(t) - \beta_3 I(t) - (k_2 + k_3)I(t) - \min\{\max\{0, \frac{I(t)(\lambda_I(t) - \lambda_R(t))}{2A_3}\}, 1\}I(t) \\
\dot{P}(t) &= \beta_3 I(t) - \beta_4 P(t) - k_2 P(t) \\
\dot{R}(t) &= \beta_4 P(t) - k_2 R(t) - \beta_7 R(t) + \min\{\max\{0, \frac{S(t)(\lambda_S(t) - \lambda_R(t))}{2A_2}\}, 1\}S(t) \\
&\quad + \min\{\max\{0, \frac{I(t)(\lambda_I(t) - \lambda_R(t))}{2A_3}\}, 1\}I(t)
\end{aligned}$$

$$\begin{aligned}
\dot{\lambda_S}(t) &= \lambda_S(t)\beta_1 E(t) + \lambda_S(t)\beta_5 I(t) + \lambda_S(t)\beta_6 P(t) + \lambda_S(t)k_2 \\
&\quad + \lambda_S(t)\min\{\max\{0, \frac{S(t)(\lambda_S(t) - \lambda_R(t))}{2A_2}\}, 1\} - \lambda_E(t)\beta_1 E(t) \\
&\quad - \lambda_E(t)\beta_5 I(t) - \lambda_E(t)\beta_6 P(t) - \min\{\max\{0, \frac{S(t)(\lambda_S(t) - \lambda_R(t))}{2A_2}\}, 1\}\lambda_R(t) \\
\dot{\lambda_E}(t) &= \lambda_S(t)\beta_1 S(t) - \lambda_E(t)\beta_1 S(t) + \lambda_E(t)\beta_2 + \lambda_E(t)k_2 - \lambda_I(t)\beta_2 \\
\dot{\lambda_I}(t) &= -A_1 + \lambda_S(t)\beta_5 S(t) - \lambda_E(t)\beta_5 S(t) + \lambda_I(t)\beta_3 + \lambda_I v(k_2 + k_3) \\
&\quad + \min\{\max\{0, \frac{I(t)(\lambda_I(t) - \lambda_R(t))}{2A_3}\}, 1\}\lambda_I(t) - \lambda_P(t)\beta_3 \\
&\quad - \min\{\max\{0, \frac{I(t)(\lambda_I(t) - \lambda_R(t))}{2A_3}\}, 1\}\lambda_R(t) \\
\dot{\lambda_P}(t) &= \lambda_S(t)\beta_6 S - (t)\lambda_E(t)\beta_6 S(t) + \lambda_P(t)\beta_4(t) + \lambda_P(t)k_2 - \lambda_R(t)\beta_4 \\
\dot{\lambda_R}(t) &= -\lambda_S(t)\beta_7 + \lambda_R(t)k_2 + \lambda_R(t)\beta_7
\end{aligned} \tag{16}$$

with initial conditions

$$S(0) = 10000, E(0) = 4, I(0) = 4, P(0) = 4, R(0) = 0$$

and transversality conditions

$$\lambda_S(T) = \lambda_E(T) = \lambda_I(T) = \lambda_P(T) = \lambda_R(T) = 0$$

■

4. Numerical solution of controlled HFMD by He's variational iteration method

To study the behaviour of HFMD with controls, the optimality system (16) have to be solved. As it is a nonlinear two point boundary value problem(BVP), find-

ing exact solution is difficult. To overcome these difficulties numerical method is necessary. Hence we find numerical solution of system (16) by He's variational iteration method (VIM). By considering the correction functionals of the Hamilton equations, the Lagrange multipliers are easily identified and practical iteration formulas are derived. An algorithm is developed, based on this formulas, to determine iteratively the solutions of the Hamilton equations with a desired accuracy. Let us introduce the notation for the state and costate variables as follows: $S = x_1, E = x_2, I = x_3, P = x_4, R = x_5$; $\lambda_S = p_1, \lambda_E = p_2, \lambda_I = p_3, \lambda_P = p_4, \lambda_R = p_5$.

The corresponding correction functionals of the optimality system are

$$x_1^{(N+1)}(t) = x_1^{(N)}(t) + \int_0^t \lambda_{x_1}(\xi)\big[\dot{x}_1^{(N)}(\xi) - k_1 - \beta_7\tilde{x}_5^{(N)}(\xi) + \beta_1\tilde{x}_1^{(N)}(\xi)\tilde{x}_2^{(N)}(\xi) + \beta_5\tilde{x}_1^{(N)}(\xi)\tilde{x}_3^{(N)}(\xi) + \beta_6\tilde{x}_1^{(N)}(\xi)\tilde{x}_4^{(N)}(\xi) + k_2x_1^{(N)}(\xi) - \frac{1}{2A_2}\left(\tilde{p}_1^{N}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x_1}^{(N)}(\xi)\big]d\xi$$

$$x_2^{(N+1)}(t) = x_2^{(N)}(t) + \int_0^t \lambda_{x_2}(\xi)\big[\dot{x}_2^{(N)}(\xi) - \beta_1\tilde{x}_1^{(N)}(\xi)\tilde{x}_2^{(N)}(\xi) - \beta_5\tilde{x}_1^{(N)}(\xi)\tilde{x}_3^{(N)}(\xi) - \beta_6\tilde{x}_1^{(N)}(\xi)\tilde{x}_4^{(N)}(\xi) + \beta_2x_2^{(N)}(\xi) + k_2x_2^{(N)}(\xi)\big]d\xi$$

$$x_3^{(N+1)}(t) = x_3^{(N)}(t) + \int_0^t \lambda_{x_3}(\xi)\big[\dot{x}_3^{(N)}(\xi) - \beta_2\tilde{x}_2^{(N)}(\xi) + \beta_3x_3^{(N)}(\xi) + (k_2+k_3)x_3^{(N)}(\xi) + \frac{1}{2A_3}\left(\tilde{p}_3^{(N)}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x}_3^{(N)}(\xi)\big]d\xi$$

$$x_4^{(N+1)}(t) = x_4^{(N)}(t) + \int_0^t \lambda_{x_4}(\xi)\big[\dot{x}_4^{(N)}(\xi) - \beta_3\tilde{x}_3^{(N)}(\xi) + \beta_4x_4^{(N)}(\xi) + k_2x_4^{(N)}(\xi)\big]d\xi$$

$$x_5^{(N+1)}(t) = x_5^{(N)}(t) + \int_0^t \lambda_{x_5}(\xi)\big[\dot{x}_5^{(N)}(\xi) - \beta_4\tilde{x}_4^{(N)}(\xi) + k_2x_5^{(N)}(\xi) + \beta_7x_5^{(N)}(\xi) - \frac{1}{2A_2}\left(\tilde{p}_1^{N}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x_1}^{(N)}(\xi) - \frac{1}{2A_3}\left(\tilde{p}_3^{(N)}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x}_3^{(N)}(\xi)\big]d\xi$$

$$p_1^{(N+1)}(t) = p_1^{(N)}(t) + \int_0^t \lambda_{p_1}(\xi)\big[\dot{p}_1^{(N)}(\xi) - \beta_1\tilde{p}_1^{(N)}(\xi)\tilde{x}_2^{(N)}(\xi) - \beta_5\tilde{p}_1^{(N)}(\xi)\tilde{x}_3^{(N)}(\xi) - \beta_6\tilde{p}_1^{(N)}(\xi)\tilde{x}_4^{(N)}(\xi) - k_2p_1^{(N)}(\xi) - \tilde{p}_1^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi)\left(\frac{1}{2A_2}\right)\left(\tilde{p}_1^{N}(\xi) - \tilde{p}_5^{(N)}(\xi)\right) + \beta_1\tilde{p}_2^{(N)}(\xi)\tilde{x}_3^{(N)}(\xi) + \beta_6\tilde{p}_2^{(N)}(\xi)\tilde{x}_4^{(N)}(\xi) + \tilde{p}_5^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi)\left(\frac{1}{2A_2}\right)\left(\tilde{p}_1^{N}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\big]d\xi$$

$$p_2^{(N+1)}(t) = p_2^{(N)}(t) + \int_0^t \lambda_{p_2}(\xi)\big[\dot{p}_2^{(N)}(\xi) - \beta_1\tilde{x}_1^{(N)}(\xi)\tilde{p}_1^{(N)}(\xi) + \beta_1\tilde{x}_1^{(N)}(\xi)\tilde{p}_2^{(N)}(\xi) - \beta_2p_2^{(N)}(\xi) - k_2p_2^{(N)}(\xi) + \beta_2\tilde{p}_3^{(N)}(\xi)\big]d\xi$$

$$p_3^{(N+1)}(t) = p_3^{(N)}(t) + \int_0^t \lambda_{p_3}(\xi)\big[\dot{p}_3^{(N)}(\xi) + A_2 - \beta_5\tilde{p}_1^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi) + \beta_1\tilde{p}_2^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi) - \beta_3p_3^{(N)} - (k_2+k_3)p_3^{(N)}(\xi) - \tilde{p}_3^{(N)}(\xi)\left(\frac{1}{2A_3}\right)\left(\tilde{p}_3^{(N)}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x}_3^{(N)}(\xi)$$

$$+\beta_3\tilde{p}_4^{(N)}(\xi)+\tilde{p}_5^{(N)}(\xi)\left(\frac{1}{2A_3}\right)\left(\tilde{p}_3^{(N)}(\xi)-\tilde{p}_5^{(N)}(\xi)\right)\tilde{x}_3^{(N)}(\xi)\big]d\xi$$

$$p_4^{(N+1)}(t)=p_4^{(N)}(t)+\int_0^t\lambda_{p_4}(\xi)\big[\dot{p}_4^{(N)}(\xi)-\beta_6\tilde{p}_1^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi)+\beta_6\tilde{p}_2^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi)$$
$$-\beta_4p_4^{(N)}(\xi)-k_2\tilde{p}_4^{(N)}(\xi)+\beta_4p_5^{(N)}(\xi)\big]d\xi$$

$$p_5^{(N+1)}(t)=p_5^{(N)}(t)+\int_0^t\lambda_{p_5}(\xi)\big[\dot{p}_5^{(N)}(\xi)+\beta_7\tilde{p}_1^{(N)}(\xi)-k_2p_5^{(N)}(\xi)-\beta_7\tilde{p}_5^{(N)}(\xi)\big]d\xi$$

where λ_{x_i} and λ_{p_i}, $i=1,2\cdots,5$ are the general Lagrange multipliers and $\tilde{x}_i^{(N)}$ and $\tilde{p}_i^{(N)}$,$i=1,2\cdots,5$ denote the restricted variations, i.e.,

$$\delta\tilde{x}_i^{(N)}=\delta\tilde{p}_i^{(N)}=0 \text{ for } i=1,2\cdots,5$$

Making the above correction functional stationary, we can obtain following stationary conditions:

$$\dot{\lambda}_{x_1}(\xi)-k_2\lambda_{x_1}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{x_1}(t)=0$$
$$\dot{\lambda}_{x_2}(\xi)-(\beta_2+k_2)\lambda_{x_2}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{x_2}(t)=0$$
$$\dot{\lambda}_{x_3}(\xi)-(\beta_3+k_2+k_3)\lambda_{x_3}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{x_3}(t)=0$$
$$\dot{\lambda}_{x_4}(\xi)-(\beta_4+k_2)\lambda_{x_4}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{x_4}(t)=0$$
$$\dot{\lambda}_{x_5}(\xi)-(\beta_7+k_2)\lambda_{x_5}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{x_5}(t)=0$$
$$\dot{\lambda}_{p_1}(\xi)+k_2\lambda_{p_1}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{p_1}(t)=0$$
$$\dot{\lambda}_{p_2}(\xi)-(\beta_2+k_2)\lambda_{p_2}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{p_2}(t)=0$$
$$\dot{\lambda}_{p_3}(\xi)-(\beta_3+k_2+k_3)\lambda_{p_3}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{p_3}(t)=0$$

$$\dot{\lambda}_{p_4}(\xi)-(\beta_4+k_2)\lambda_{p_4}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{p_4}(t)=0$$
$$\dot{\lambda}_{p_5}(\xi)-(\beta_7+k_2)\lambda_{p_5}(\xi)=0,\ \ \xi\in[0,t]$$
$$1+\lambda_{p_5}(t)=0$$

The Lagrange multipliers, therefore, can be identified as

$$\lambda_{x_1}(\xi) = -e^{k_2(\xi-t)};\ \lambda_{x_2}(\xi) = -e^{(\beta_2+k_2)(\xi-t)};\ \lambda_{x_3}(\xi) = -e^{(\beta_3+k_2+k_3)(\xi-t)};$$
$$\lambda_{x_4}(\xi) = -e^{(\beta_4+k_2)(\xi-t)};\ \lambda_{x_5}(\xi) = -e^{(\beta_7+k_2)(\xi-t)};$$
$$\lambda_{p_1}(\xi) = -e^{k_2(t-\xi)};\ \lambda_{p_2}(\xi) = -e^{(\beta_2+k_2)(t-\xi)};\ \lambda_{p_3}(\xi) = -e^{(\beta_3+k_2+k_3)(t-\xi)};$$
$$\lambda_{p_4}(\xi) = -e^{(\beta_4+k_2)(t-\xi)};\ \lambda_{p_5}(\xi) = -e^{(\beta_7+k_2)(t-\xi)}$$

Substituting the above multipliers into the correction functionals results in the following iteration formulae:

$$x_1^{(N+1)}(t) = x_1^{(N)}(t) - \int_0^t e^{k_2(\xi-t)}\big[\dot{x}_1^{(N)}(\xi) - k_1 - \beta_7\tilde{x}_5^{(N)}(\xi) + \beta_1\tilde{x}_1^{(N)}(\xi)\tilde{x}_2^{(N)}(\xi) + \beta_5\tilde{x}_1^{(N)}(\xi)\tilde{x}_3^{(N)}(\xi) + \beta_6\tilde{x}_1^{(N)}(\xi)\tilde{x}_4^{(N)}(\xi) + k_2x_1^{(N)}(\xi) - \frac{1}{2A_2}\left(\tilde{p}_1^{N}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x_1}^{(N)}(\xi)\big]d\xi$$

$$x_2^{(N+1)}(t) = x_2^{(N)}(t)\int_0^t e^{(\beta_2+k_2)(\xi-t)}\big[\dot{x}_2^{(N)}(\xi) - \beta_1\tilde{x}_1^{(N)}(\xi)\tilde{x}_2^{(N)}(\xi) - \beta_5\tilde{x}_1^{(N)}(\xi)\tilde{x}_3^{(N)}(\xi) - \beta_6\tilde{x}_1^{(N)}(\xi)\tilde{x}_4^{(N)}(\xi) + \beta_2x_2^{(N)}(\xi) + k_2x_2^{(N)}(\xi)\big]d\xi$$

$$x_3^{(N+1)}(t) = x_3^{(N)}(t) - \int_0^t e^{(\beta_3+k_2+k_3)(\xi-t)}\big[\dot{x}_3^{(N)}(\xi) - \beta_2\tilde{x}_2^{(N)}(\xi) + \beta_3x_3^{(N)}(\xi) + (k_2+k_3)x_3^{(N)}(\xi) + \frac{1}{2A_3}\left(\tilde{p}_3^{(N)}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x}_3^{(N)}(\xi)\big]d\xi$$

$$x_4^{(N+1)}(t) = x_4^{(N)}(t) - \int_0^t e^{(\beta_4+k_2)(\xi-t)}\big[\dot{x}_4^{(N)}(\xi) - \beta_3\tilde{x}_3^{(N)}(\xi) + \beta_4x_4^{(N)}(\xi) + k_2x_4^{(N)}(\xi)\big]d\xi$$

$$x_5^{(N+1)}(t) = x_5^{(N)}(t) - \int_0^t e^{(\beta_7+k_2)(\xi-t)}\big[\dot{x}_5^{(N)}(\xi) - \beta_4\tilde{x}_4^{(N)}(\xi) + k_2x_5^{(N)}(\xi) + \beta_7x_5^{(N)}(\xi) - \frac{1}{2A_2}\left(\tilde{p}_1^{N}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x_1}^{(N)}(\xi) - \frac{1}{2A_3}\left(\tilde{p}_3^{(N)}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x}_3^{(N)}(\xi)\big]d\xi$$

$$p_1^{(N+1)}(t) = p_1^{(N)}(t) - \int_0^t e^{k_2(t-\xi)}\big[\dot{p}_1^{(N)}(\xi) - \beta_1\tilde{p}_1^{(N)}(\xi)\tilde{x}_2^{(N)}(\xi) - \beta_5\tilde{p}_1^{(N)}(\xi)\tilde{x}_3^{(N)}(\xi) - \beta_6\tilde{p}_1^{(N)}(\xi)\tilde{x}_4^{(N)}(\xi) - k_2p_1^{(N)}(\xi) - \tilde{p}_1^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi)\left(\frac{1}{2A_2}\right)\left(\tilde{p}_1^{N}(\xi) - \tilde{p}_5^{(N)}(\xi)\right) + \beta_1\tilde{p}_2^{(N)}(\xi)\tilde{x}_3^{(N)}(\xi) + \beta_6\tilde{p}_2^{(N)}(\xi)\tilde{x}_4^{(N)}(\xi) + \tilde{p}_5^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi)\left(\frac{1}{2A_2}\right)\left(\tilde{p}_1^{N}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\big]d\xi$$

$$p_2^{(N+1)}(t) = p_2^{(N)}(t) - \int_0^t e^{(\beta_2+k_2)(t-\xi)}\big[\dot{p}_2^{(N)}(\xi) - \beta_1\tilde{x}_1^{(N)}(\xi)\tilde{p}_1^{(N)}(\xi) + \beta_1\tilde{x}_1^{(N)}(\xi)\tilde{p}_2^{(N)}(\xi) - \beta_2p_2^{(N)}(\xi) - k_2p_2^{(N)}(\xi) + \beta_2\tilde{p}_3^{(N)}(\xi)\big]d\xi$$

$$p_3^{(N+1)}(t) = p_3^{(N)}(t) - \int_0^t e^{(\beta_3+k_2+k_3)(t-\xi)}\big[\dot{p}_3^{(N)}(\xi) + A_2 - \beta_5\tilde{p}_1^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi) + \beta_1\tilde{p}_2^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi) - \beta_3 p_3^{(N)} - (k_2+k_3)p_3^{(N)}(\xi) - \tilde{p}_3^{(N)}(\xi)\left(\frac{1}{2A_3}\right)\left(\tilde{p}_3^{(N)}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x}_3^{(N)}(\xi) + \beta_3\tilde{p}_4^{(N)}(\xi) + \tilde{p}_5^{(N)}(\xi)\left(\frac{1}{2A_3}\right)\left(\tilde{p}_3^{(N)}(\xi) - \tilde{p}_5^{(N)}(\xi)\right)\tilde{x}_3^{(N)}(\xi)\big]d\xi$$

$$p_4^{(N+1)}(t) = p_4^{(N)}(t) - \int_0^t e^{(\beta_4+k_2)(t-\xi)}\big[\dot{p}_4^{(N)}(\xi) - \beta_6\tilde{p}_1^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi) + \beta_6\tilde{p}_2^{(N)}(\xi)\tilde{x}_1^{(N)}(\xi) - \beta_4 p_4^{(N)}(\xi) - k_2\tilde{p}_4^{(N)}(\xi) + \beta_4 p_5^{(N)}(\xi)\big]d\xi$$

$$p_5^{(N+1)}(t) = p_5^{(N)}(t) - \int_0^t e^{(\beta_7+k_2)(t-\xi)}\big[\dot{p}_5^{(N)}(\xi) + \beta_7\tilde{p}_1^{(N)}(\xi) - k_2 p_5^{(N)}(\xi) - \beta_7\tilde{p}_5^{(N)}(\xi)\big]d\xi$$

5. Numerical results and discussion

The optimality system has been solved numerically and the results have been interpreted graphically using Maple. The optimality system is a nonlinear two-point boundary value problem, with separated boundary conditions at times $t = 0$ and $t = T$. Let the simulation be done for the terminal value $T = 20$.
Let the values of the parameters be [4]:
$k_1 = 2.923 \times 10^{-4}, k_2 = 1.077 \times 10^{-4}, k_3 = 1.731 \times 10^{-5}, \beta_1 = 3.000 \times 10^{-5}$,
$\beta_2 = 5.500.\beta_3 = 1.000, \beta_4 = 1.000, \beta_5 = 1.500 \times 10^{-4}, \beta_6 = 6.000 \times 10_{-5}$,
$\beta_7 = 7.000 \times 10^{-2}$.
Let us choose the weight constants $A_1 = 1000, A_2 = 100, A_3 = 10$.
The initial costates values of $p_1(0), p_2(0), p_3(0), p_4(0), p_5(0)$ are unknown constants to be determined by imposing transversality conditions $p_1(T) = 0, p_2(T) = 0, p_3(T) = 0, p_4(T) = 0, p_5(T) = 0$.

In figure 1, the effect of optimal control in the susceptible population is analyzed. We observe a decline in the population of susceptible with and without control. With control that is when the susceptibles are vaccinated we infer a steady decrease in their population compared to without control. For instance, by 10^{th} day, the susceptible population is below 6000 whereas it is close to 10000 without control. Also the vaccination does not work to the children who are exposed to the disease , so they move to the exposed and infected compartments.

In figure 2, the number of individuals who are exposed to HFMD is presented. The increase in curve is observed denoting that the susceptible move to the exposed compartment because they may gain disease when they are in contact with infected patients or with those carrying post-infection virus or with those who are already exposed. However, the number of exposed children with control is comparatively lesser than without control.

In figure 3, the effect of optimal control in infected population is discussed. The figure shows that in the presence of control the number of infected population moves close zero. The treatment given to the infected helped to minimize the

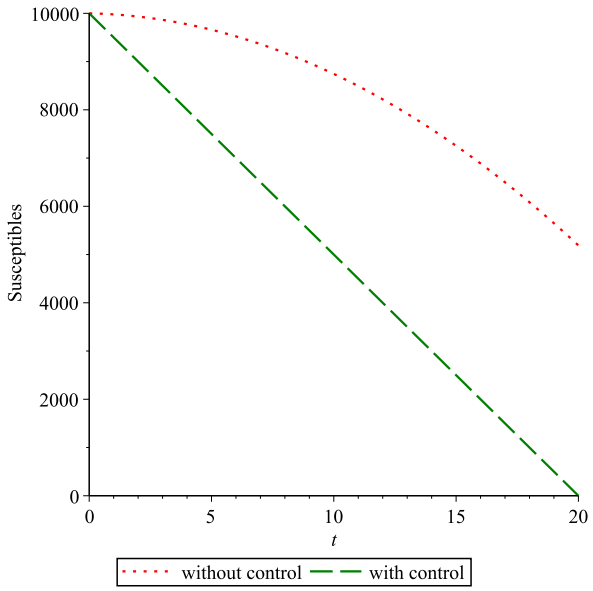

Figure 1. The effect of optimal control in the susceptible population.

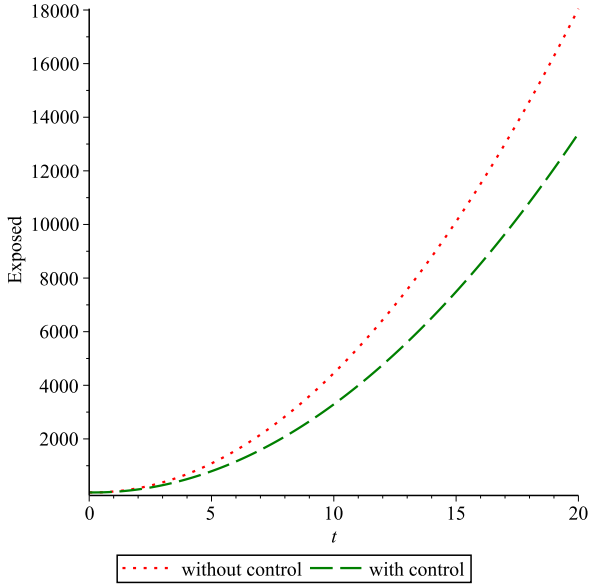

Figure 2. The effect of optimal control in the Exposed population.

infected population. The infected population move to the clinically recovered or post-infection virus shedding group compartment when they get treated. They move to the post-infection virus shedding group because their symptoms are only reduced but they are not fully recovered. On the other hand, we infer a rapid increase in the number of infected individuals in the absence of control.

In figure 4, the number of individuals in the post-infection virus shedding group is shown. We assumed that initially only 4 children were clinically recovered. There is no increase in the clinically recovered graph due to the effectiveness of the control in the infected individuals. Whereas in the absence of control, we observe a rapid increase in the clinically recovered group as symptoms may subside over a period of time but they act as carrier of the viruses.

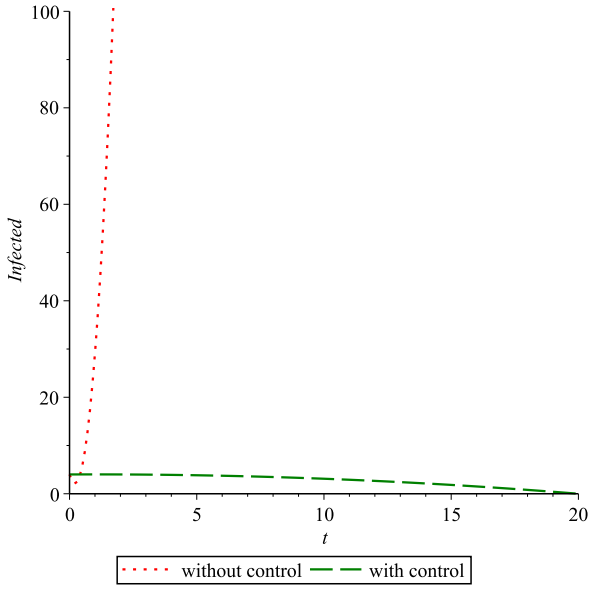

Figure 3. The effect of optimal control in the Infected population.

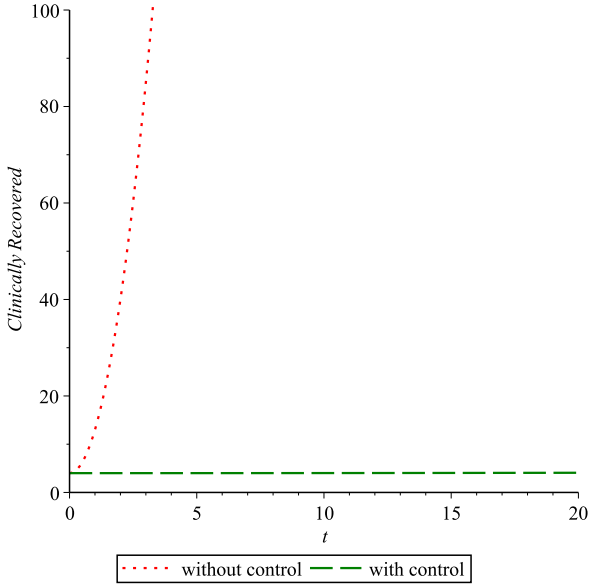

Figure 4. The effect of optimal control in the Clinically Recovered population.

In figure 5, the effect of optimal control in the fully recovered population is discussed. In the presence of control, we infer that there is an increase in the curve which is because as the clinically recovered population move to the fully recovered compartment, the susceptible population after the vaccination and also the infected population after the treatment move to fully recovered population. But after a certain interval of time there is a decrease in the fully recovered population as they may lose their immunity and move to susceptible class or they may get exposed to other strains of HFMD virus. On the other hand, without control initially there was a slight increase in the recovered population and there after it reduces. The slight increase in curve may be due to the children's own immunity. The figure clearly depicts the increase in recovered population with and without control.

At convergence, the value of the costate vector at $t = 0$ are
$[p_1(0) = 0.003304428876; p_2(0) = 23.76573493; p_3(0) = 22.47392574;$

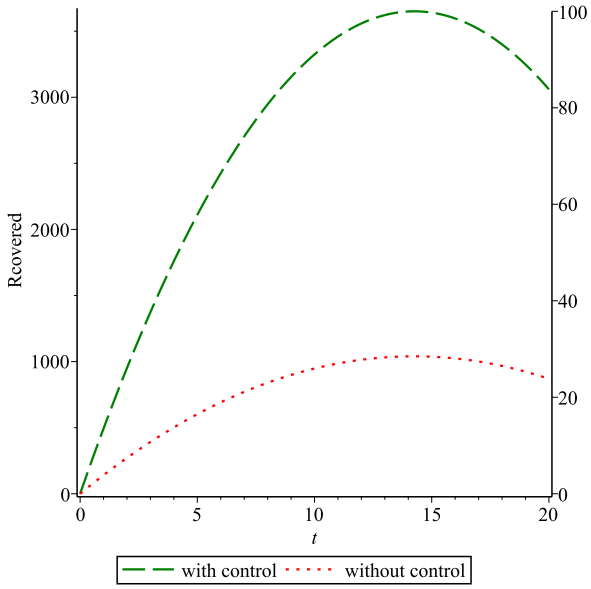

Figure 5. The effect of optimal control in the Fully Recovered population.

$p_4(0) = 0.0003412521205; p_5(0) = 0.002324704130]$

6. Conclusion

In this paper, a controlled SEIPR model of Hand Foot and Mouth Diseases was formulated by considering two controls as treatment for infected population and vaccination for susceptible population. An attempt was made to study the optimal combination of vaccination and treatment strategies with cure and vaccine towards eradication within a specified period. Pontryagin's maximum principle was used to characterize the optimal controls, and the optimality system was derived.The optimality system is two point boundary value problem. The solution for this optimal system is obtained by applying He's variational iteration method, which gives approximate solutions with high accuracy and the result is represented graphically. The numerical results show that the optimal strategy becomes more effective when we combined the vaccination and treatment strategies together.

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