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ORIGINAL ARTICLE

Optimal Control Strategy of *Plasmodium vivax* Malaria Transmission in Korea

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Abstract
Objective: To investigate the optimal control strategy for *Plasmodium vivax* malaria transmission in Korea.
Methods: A *Plasmodium vivax* malaria transmission model with optimal control terms using a deterministic system of differential equations is presented, and analyzed mathematically and numerically.
Results: If the cost of reducing the reproduction rate of the mosquito population is more than that of prevention measures to minimize mosquito-human contacts, the control of mosquito-human contacts needs to be taken for a longer time, comparing the other situations. More knowledge about the actual effectiveness and costs of control intervention measures would give more realistic control strategies.
Conclusion: Mathematical model and numerical simulations suggest that the use of mosquito-reduction strategies is more effective than personal protection in some cases but not always.

1. Introduction

Malaria is a mosquito-borne infectious disease caused by a eukaryotic protist of the genus *Plasmodium*. Malaria is naturally transmitted by the bite of a female *Anopheles* mosquito. The primary vector in Korea is reported to be *A sinensis*. Since the re-emergence of *Plasmodium vivax* malaria in 1993[1,2], it has been endemic and continues to cause extensive morbidity in Korea, despite the huge efforts invested to control it.

The first mathematical malaria model proposed by Ross [3], was subsequently modified by MacDonald, which has influenced both the modeling and the application of control strategies to malaria [4]. Recently, the optimal control theory has been applied to malaria Okosun et al [5], and to vector-borne disease Lashari

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Table 1. The description of parameters for the model

Parameter	Description
b_m	Per capita rate of newly emerging adult mosquitoes
β_{mh}	Infected mosquito to human transmission efficiency
β_{hm}	Infected human to mosquito transmission efficiency
σ	Average number of contact made to host by a single mosquito
r	Per capita rate of progression of humans from the infectious state to the susceptible state
p	Probability of exposed humans going through short-term incubation periods
T_h^s	Per capita rate of progression of humans from the short term of exposed state to the infectious state
T_h^l	Per capita rate of progression of humans from the long term of exposed state to the infectious state

et al [6], who modified the model of Blayneh et al [7], but introduced some awkward terms.

Models for *Plasmodium flaciparum* malaria or vector-borne diseases have been studied by many researchers [8−10]. In contrast, models for *P vivax* malaria are rare. Recently, Nah et al [11] proposed a model of *P vivax* malaria transmission. In this paper, by combining the ideas of Blayneh et al [7] and Nah et al [11], we propose the deterministic model of *P vivax* malaria transmission with optimal control terms. Using the optimal control theory, we sought optimal control strategies of *P vivax* malaria transmission in Korea.

2. Materials and Methods

2.1. Model description: optimal control

To construct a deterministic model for *P vivax* malaria transmission with control terms, the model of Nah et al [11] was modified and optimal control terms inspired by the model of Blayneh et al [7] were added as follows:

$$\begin{cases} \dfrac{dS_H}{dt} = -\beta_{mh}\sigma(1-u_2(t))\dfrac{S_H(t)}{H}I_M(t) + rI_H(t) \\ \dfrac{dE_H^s}{dt} = p\beta_{mh}\sigma(1-u_2(t))\dfrac{S_H(t)}{H}I_M(t) - T_h^sE_H^s(t) \\ \dfrac{dE_H^l}{dt} = (1-p)\beta_{mh}\sigma(1-u_2(t))\dfrac{S_H(t)}{H}I_M(t) - T_h^lE_H^l(t) \\ \dfrac{dI_H}{dt} = T_h^sE_H^s(t) + T_h^lE_H^l(t) - rI_H(t) \\ \dfrac{dS_M}{dt} = b_m(1-u_1(t))(S_M(t)+I_M(t)) - \beta_{hm}\sigma(1-u_2(t))\dfrac{I_H(t)}{H}S_M(t) - b_mS_M(t) - \rho u_1(t)S_M(t) \\ \dfrac{dI_M}{dt} = \beta_{hm}\sigma(1-u_2(t))\dfrac{I_H(t)}{H}S_M(t) - b_mI_M(t) - \rho u_1(t)I_M(t) \end{cases} \quad (1)$$

In the model, human population $H(t)$ is divided into four classes: susceptible (S_H), short term exposed (E_H^s), long term exposed (E_H^l), and infectious (I_H). Mosquito population $M(t)$ is also divided into two classes: susceptible (S_M), and infectious (I_M). Note that the mosquito population $M(t)$ is not constant while human population $H(t)$ is constant.

The factor of $1-u_1(t)$ reduces the reproduction rate of the mosquito population. It is assumed that the mortality rate of mosquitoes (susceptible and infected) increases at a rate proportional to $u_1(t)$, where $\rho > 0$ is a rate constant. In the human population, the associated force of infection is reduced by a factor of $1-u_2(t)$, where $u_2(t)$ measures the level of successful prevention efforts. In fact, the control $u_2(t)$ represents the use of prevention measures to minimize mosquito-human contacts. Table 1 lists detailed descriptions of the parameters. The system (1) has a unique solution set. (See Appendix A for detail.)

An optimal control problem can now be formulated for the transmission dynamics of *P vivax* malaria transmission in Korea. The goal is to show that it is possible to implement time dependent anti-malaria control techniques while minimizing the cost of implementation of such control measures.

Table 2. The parameter values for the model

Parameter	Value
b_m	0.7949 [0.1,1.5]
β_{mh}	0.5
β_{hm}	0.5
σ	0.3 [0.25,0.5]
r	0.07 [0.01,0.5]
p	0.25
T_h^s	1/25.9
T_h^l	1/360.3

An optimal control problem with the objective cost functional can be given by

$$J(u_1, u_2) = \int_0^T \left(AI_H(t) + \frac{B_1}{2} u_1^2(t) + \frac{B_2}{2} u_2^2(t)\right)dt, \qquad (2)$$

subject to the state system given by (1).

The goal is to minimize the infected human populations and the cost of implementing the control. In the objective cost functional, the quantities A, B_1 and B_2 represent the weight constants of infected human, for mosquito control and prevention of mosquito-human contacts, respectively. The costs associated with mosquito control and prevention of mosquito-human contacts are described in the terms $B_1u_1^2$ and $B_2u_2^2$, respectively.

Optimal control functions (u_1^*, u_2^*) need to be found such that

$J(u_1^*, u_2^*) = \min\{J(u_1, u_2) | (u_1, u_2) \in U\}$,

subject to the system of equations given by (1), where $U = \{(u_1, u_2) | u_i(t)$ is piecewise continuous on $[0, T], 0 \le u_i(t) \le 1, i = 1,2\}$ is the control set.

Such optimal control functions (u_1^*, u_2^*) exist, and the optimality system can be derived. (See Appendix B for detail.)

2.2. Numerical simulation

Using the forward-backward sweep method, the optimality system was solved numerically. This consists of 12 ordinary differential equations from the state and adjoint equations, coupled with the two controls. In choosing upper bounds for the controls, it was supposed that the two controls would not be 100% effective, so the upper bounds of u_1 and u_2 were chosen to be 0.8. The weight in the objective functional is $A_1 = 1000$. The parameters in Table 2 were adopted from other articles [11] and used for our simulation.

We simulate the model in different scenarios. Figure 1 depicts scenarios for the state variables of the model for the case when the cost is the same for the two controls. Figure 2 depicts scenarios for the state variables of the model for the case when the cost of prevention measures to minimize mosquito-human contact is more expensive than the cost of reducing the reproduction rate of the mosquito population. Figure 3 depicts scenarios for the state variables of the model for the case when the cost of reducing the reproduction rate of the mosquito population are more expensive than the cost of prevention measures to minimize mosquito-human contacts.

It is also worth noting that different initial mosquitoes populations do not have effect on the optimal strategies (Figures 4 − 6).

2.3. Results

If the cost of reducing the reproduction rate of the mosquito population is more than that of prevention measures to minimize mosquito-human contacts, the u_2 control needs to be taken for a longer time, comparing the other situations (Figures 1 to 3). In that situation, full effort for u_2 is needed after the high peak of infected human population.

On the other hand, Figures 4 to 6 suggest that even though the mosquito population is not so high in initial point, full efforts for u_1 and u_2 are needed for at least some of the time.

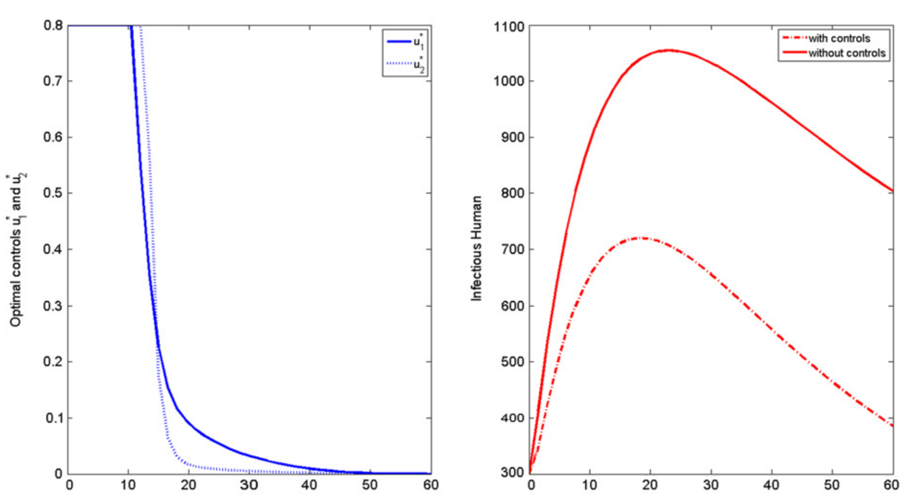

Figure 1. Optimal controls when $B_1 = B_2 = 1000$ with high mosquito population.

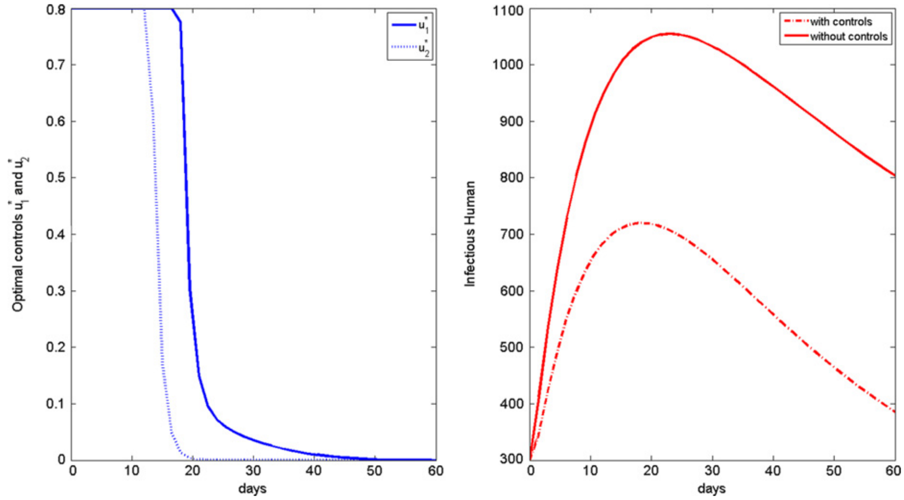

Figure 2. Optimal controls when $B_1 = 10$, $B_2 = 1000$ with high mosquito population.

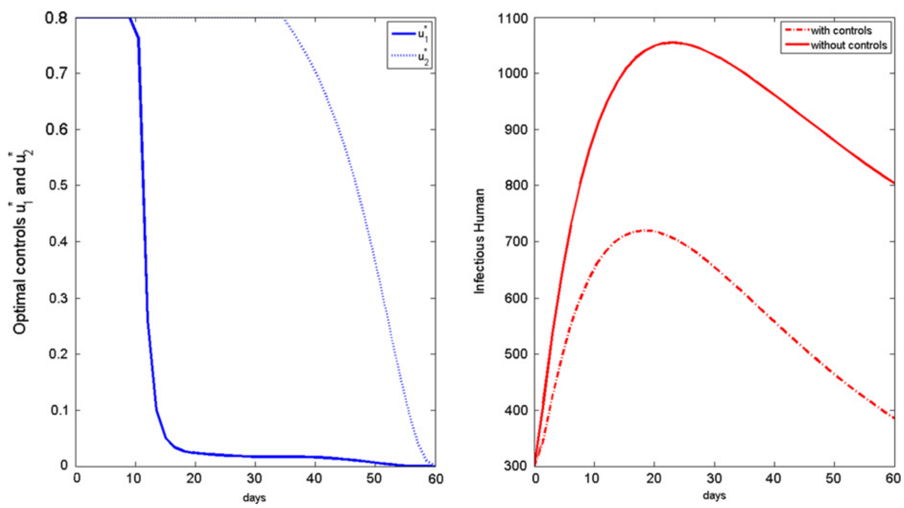

Figure 3. Optimal controls when $B_1 = 1000$, $B_2 = 10$ with high mosquito population.

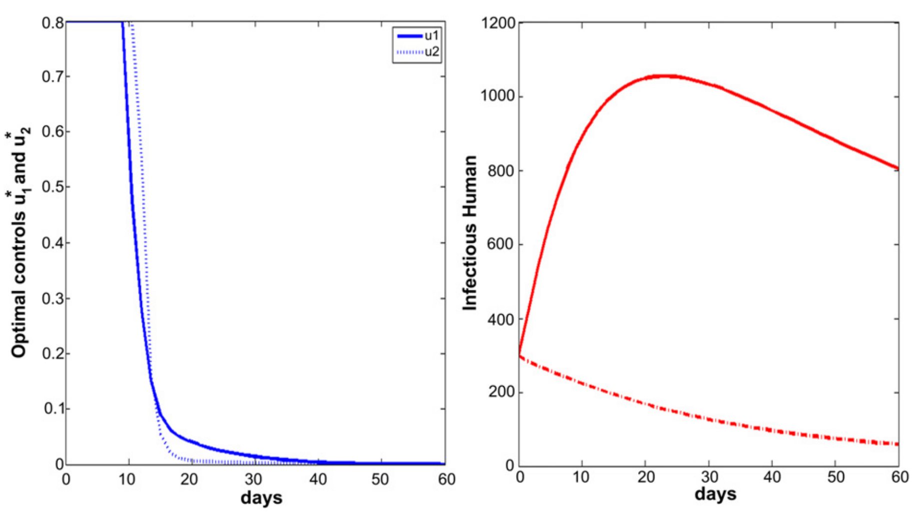

Figure 4. Optimal controls when $B_1 = B_2 = 1000$ with low mosquito population.

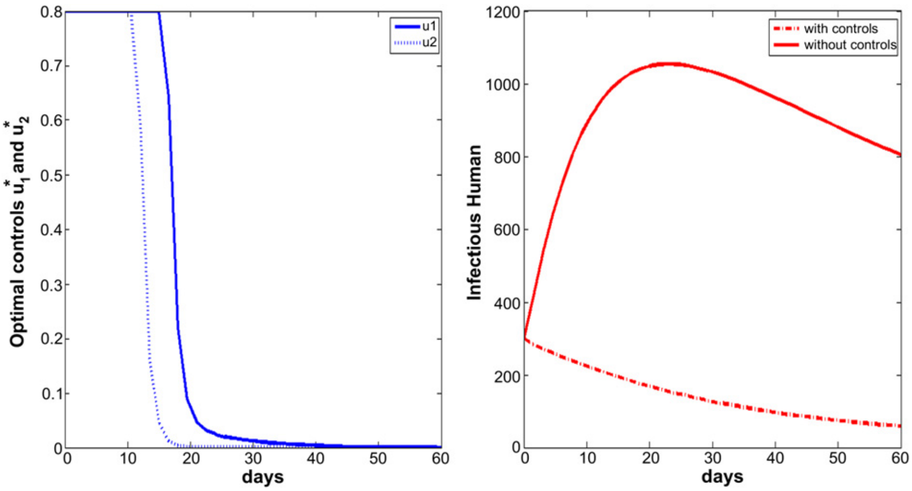

Figure 5. Optimal controls when $B_1 = 10$, $B_2 = 1000$ with low mosquito population.

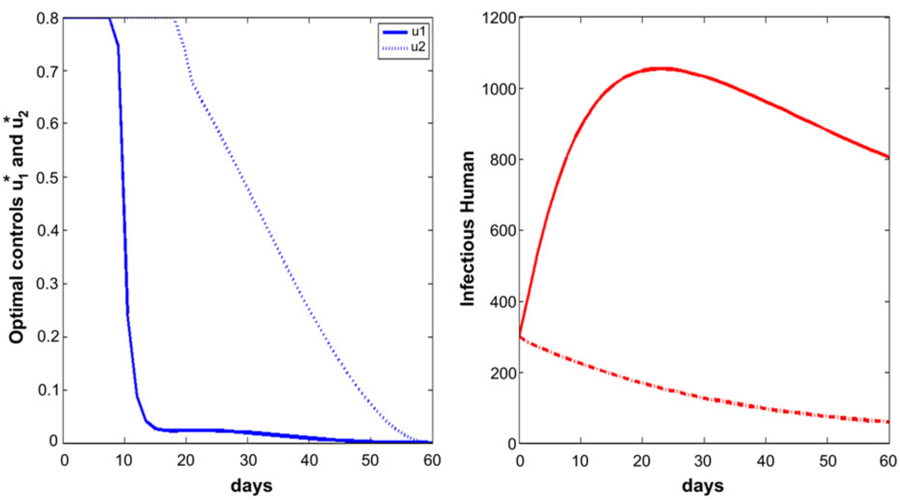

Figure 6. Optimal controls when $B_1 = 1000$, $B_2 = 10$ with low mosquito population.

3. Discussion and Conclusions

After 1993's reemergence of malaria, the endemicity of *P vivax* malaria is becoming a growing concern in South Korea. Public health advisories were subsequently issued to apply community mosquito control and personal protection.

The purpose of this work is to suggest optimal control strategies of *P vivax* malaria in different scenarios. In all cases, optimal control programs lead effectively reduce the number of infectious individuals. We have used a deterministic model with time-dependent parameters to develop the transmission dynamics of *P vivax* malaria in Korea. For numerical simulations, most parameters were adopted from other articles [11].

Mathematical model and numerical simulations suggest that the use of mosquito-reduction strategies is more effective than personal protection in some cases but not always. Public health authorities should choose the proper control strategy where their situation lies in the scenarios discussed in the Results section.

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Appendix A. The existence and uniqueness of solution

We consider system (1). We obtain the existence and uniqueness of solution. In here we are given a suitable control set.

Theorem 1. The system (1) with any initial condition has a unique solution.

Proof. We can rewrite (1) as :

$$\frac{dX}{dt} = AX + F(X,U),$$

where $X = \left[S_H, E_H^s, E_H^l, I_H, S_M, I_M\right]^T$,

$$A = \begin{pmatrix} 0 & 0 & 0 & r & 0 & 0 \\ 0 & -T_h^s & 0 & 0 & 0 & 0 \\ 0 & 0 & -T_h^s & 0 & 0 & 0 \\ 0 & T_h^s & T_h^l & -r & 0 & 0 \\ 0 & 0 & 0 & 0 & -b_m & 0 \\ 0 & 0 & 0 & 0 & 0 & -b_m \end{pmatrix}$$

$U = [u_1, u_2]^T$ and $F(X,U) = \Big[-\beta_{mh}\sigma(1-u_2(t))\frac{S_H(t)}{H}I_M(t),$ $p\beta_{mh}\sigma(1-u_2(t))\frac{S_H(t)}{H}\ I_M(t),(1-p)\beta_{mh}\sigma\ \ (1-u_2(t))\frac{S_H(t)}{H}$ $I_M(t), 0, b_m(1-u_1(t))(S_M(t)+I_M(t))-\beta_{hm}\sigma(1-u_2(t))$ $S_M\frac{I_H(t)}{H}-\rho u_1(t)S_M(t), \beta_{hm}\sigma(1-u_2(t))S_M\ \ \frac{I_H(t)}{H}-\rho u_1(t)$ $I_M(t)\Big]^T$. So let $G(X,U) = AX + F(X,U)$. Defined matrix A is a linear. So A is a bounded operator. Define a matrix norm and a vector norm as follows $\|A\| = \Sigma_{i,j}|a_{ij}|, \|X\| = \|(x_i)\| = \Sigma_i|x_i|$, respectively. To show the existence of solution of the system (1), we have to prove that $F(X,U)$ satisfy a Lipschitz condition. Let

$$H(t) := S_H(t) + E_H^s(t) + E_H^l(t) + I_H(t).$$

and

$$M(t) := S_M(t) + I_M(t).$$

But

$$\frac{d}{dt}H'(t) = 0. \quad \text{So, } H(t) \equiv H\left(\text{a constant}\right) < \infty,$$

$$\frac{d}{dt}M(t) = -u_1(t)(b_m+\rho)M(t) \le 0. \quad \text{Hence,}$$

$$M(t) \le M(0) < \infty.$$

For any given pairs $(X_1, U), (X_2, V)$,

$$X_j = \left[S_{Hj}, E_{Hj}^s, E_{Hj}^l, I_{Hj}, S_{Mj}, I_{Mj}\right]^T, j = 1, 2,$$

$$U = (u_1, u_2)^T, V = (v_1, v_2)^T,$$

we obtain,

$$\begin{aligned} &\|F(X_1,U) - F(X_2,V)\| \\ &\le \beta_{mh}\sigma/H|(1-u_2)S_{H1}I_{M1} - (1-v_2)S_{H2}I_{M2}| \\ &+p\beta_{mh}\sigma/H|(1-u_2)S_{H1}I_{M1} - (1-v_2)S_{H2}I_{M2}| \\ &+(1-p)\beta_{mh}\sigma/H|(1-u_2)S_{H1}I_{M1} - (1-v_2)S_{H2}I_{M2}| \\ &+b_m|(1-u_1)(S_{M1}+I_{M1}) - (1-v_1)(S_{M2}+I_{M2})| \\ &+\beta_{hm}\sigma/H|(1-u_2)S_{M1}I_{H1} - (1-v_2)S_{M2}I_{H2}| \\ &+\rho|u_1S_{M1} - v_1S_{M2}| + \beta_{hm}\sigma/H|(1-u_2)S_{M1}I_{H1} \\ &-(1-v_2)S_{M2}I_{H2}| + \rho|u_1I_{M1} - v_1I_{M2}| \\ &= 2\beta_{mh}\sigma/H|(1-u_2)S_{H1}I_{M1} - (1-v_2)S_{H2}I_{M2}| \\ &+b_m|(1-u_1)(S_{M1}+I_{M1}) - (1-v_1)(S_{M2}+I_{M2})| \\ &+2\beta_{hm}\sigma/H|(1-u_2)S_{M1}I_{H1} - (1-v_2)S_{M2}I_{M2}| \\ &+\rho|u_1S_{M1} - v_1S_{M2}| + \rho|u_1I_{M1} - v_1I_{M2}| \end{aligned} \tag{i}$$

We estimate the 4 terms in the right side of (i):

$$\begin{aligned} &2\beta_{mh}\sigma/H|(1-u_2)S_{H1}I_{M1} - (1-v_2)S_{H2}I_{M2}| \\ &\le 2\beta_{mh}\sigma/H[2M(0)|S_{H1} - S_{H2}| + 2H|I_{M1} - I_{M2}| \\ &+HM(0)|u_2 - v_2|], \end{aligned} \tag{ii}$$

$$\begin{aligned} &b_m|(1-u_1)(S_{M1}+I_{M1}) - (1-v_1)(S_{M2}+I_{M2})| \\ &\le 2b_m[|S_{M1} - S_{M2}| + |I_{M1} - I_{M2}| + M(0)|u_1 - v_1|], \end{aligned} \tag{iii}$$

$$\begin{aligned} &2\beta_{hm}\sigma/H|(1-u_2)S_{H1}I_{M1} - (1-v_2)S_{H2}I_{M2}| \\ &\le 2\beta_{hm}\sigma/H[2M(0)|I_{H1} - I_{H2}| + 2H|S_{M1} - S_{M2}| \\ &+M(0)H|u_2 - v_2|], \end{aligned} \tag{iv}$$

$$\rho|u_1S_{M1} - v_1S_{M2}| \le \rho[M(0)|u_1 - v_1| + |S_{M1} - S_{M2}|] \tag{v}$$

and

$$\rho|u_1I_{M1} - v_1I_{M2}| \le \rho[M(0)|u_1 - v_1| + |I_{M1} - I_{M2}|]. \tag{vi}$$

Since $0 \le u_i, v_i \le 1, 0 \le S_{Hi}, I_{Hi} \le H$ and $0 \le S_{Mi}, I_{Mi} \le M(0), i = 1, 2$, by (i)-(vi), we have

$$\begin{aligned} &\|F(X_1,U) - F(X_2,V)\| \\ &\le (4\beta_{mh}\sigma M(0)/H)|S_{H1} - S_{H2}| + (4\beta_{hm}\sigma M(0)/H)|I_{H1} - I_{H2}| \\ &+(2b_m + 4\beta_{hm}\sigma M(0) + \rho)|S_{M1} - S_{M2}| \\ &+(2b_m + 4\beta_{mh}\sigma M(0) + \rho)|I_{M1} - I_{M2}| \\ &+(2b_mM(0) + 2\rho M(0))|u_1 - v_1| \\ &+(2\beta_{mh} + 2\beta_{hm}\sigma M(0))|u_2 - v_2| \\ &\le K(|S_{H1} - S_{H2}| + |S_{M1} - S_{M2}| + |I_{H1} - I_{H2}| + |I_{M1} - I_{M2}| \\ &+|u_1 - v_1| + |u_2 - v_2|) \\ &\le K(\|X_1 - X_2\| + \|U - V\|), \end{aligned}$$

where $K = \max\{4\beta_{mh}\sigma M(0)/H, 4\beta_{hm}\sigma M(0)/H, 2b_m + 4\beta_{hm}\sigma M(0) + \rho, 4\beta_{mh}\sigma + 2b_m + \rho, 2M(0)(b_m+\rho), 2\beta_{mh} + 2\beta_{hm}\ \sigma M(0)\}$ Thus, we obtain $F(X,U)$ is uniformly Lipschitz continuous. Let $L = \|A\| < \infty$. Then,

$$\|G(X_1,U) - G(X_2,V)\| \le (K+L)(\|X_1 - X_2\| + \|U - V\|).$$

Hence, the system (1) satisfy all conditions of the Picard-Lindelof Theorem ([12,13]) and also the function $F(X,U)$ is continuously differentiable. Therefore, the system (1) have a unique solution.

Appendix B. Analysis of optimal control control problem

We are to prove the existence of optimal control pairs for the system (1). Firstly, We set control space

$$U=\{(u_1,u_2)|u_i \text{ is piecewise continuous on } [0,T], 0 \le u_i(t) \le 1, i=1,2\}.$$

We consider an optimal control problem to minimize the objective functional:

$$J(u_1,u_2)=\int_0^T \left(AI_H(t)+\frac{B_1}{2}u_1^2(t)+\frac{B_2}{2}u_2^2(t)\right)dt.$$

Theorem 2. There exist an optimal control u_1^* and u_2^* such that

$$J\left(u_1^*,u_2^*\right)=\min_{u_1,u_2\in U} J(u_1,u_2) \tag{3}$$

subject to the control system (1) with initial conditions.-Proof. To prove the existence of an optimal control pairs we use the result in [14]. The set of control and corresponding state variables is a nonempty. Because for each control pairs we have proved in the Theorem 1 that there exists corresponding state solutions. And also it is ok when the control $u_1=u_2=0$. Note that the control and the state variables are nonnegative values. The control space U is close and convex by definition. In the minimization problem, the convexity of the objective functional in u_1 and u_2 have to satisfy. The integrand in the functional, $AI_H(t)+\frac{B_1}{2}u_1^2(t)+\frac{B_2}{2}u_2^2(t)$ is convex function on the control u_1 and u_2. Also we can easily check that there exist a constant $\rho>1$, a numbers $\omega_1 \ge 0$ and $\omega_2>0$ such that

$$J(u_1,u_2)\ge \omega_1+\omega_2\left(|u_1|^2+|u_2|^2\right)^{\rho/2}$$

which completes the existence of an optimal control.To find the optimal solution we apply Pontryagin's Maximum Principle ([15–17]) to the constrained control problem, then the principle converts (1), (2) and (3) in to a problem of minimizing pointwise a Hamiltonian, $\mathscr{H}$, with respect to u_1 and u_2. The Hamiltonian for our problem is the integrand of the objective functional coupled with the six right hand sides of the state equations:

$$\mathscr{H}(\mathbf{x}(t),\mathbf{u}(t),\lambda(t)) = AI_H(t)+\frac{B_1}{2}u_1^2(t)+\frac{B_2}{2}u_2^2(t) + \Sigma_{i=1}^6\lambda_i(t)g_i \tag{4}$$

where g_i is the right hand side of the differential equation of the ith state variable and also $\mathbf{x}(t)=(S_H,E_H^s,E_H^l,I_H,S_M,I_M)$, $\mathbf{u}(t)=(u_1(t),u_2(t))$ and $\lambda(t)=(\lambda_1(t),\lambda_2(t),\lambda_3(t),\lambda_4(t),\lambda_5(t),\lambda_6(t))$.

By applying Pontryagin's Maximum Principle([18]) if $(\mathbf{x}^*(t),\mathbf{u}^*(t))$ is an optimal control, then there exists a non-trivial vector function $\lambda(t)$ satisfying the following equalities:

$$\frac{d\mathbf{x}}{dt}=\frac{\partial\mathscr{H}(\mathbf{x}(t),\mathbf{u}(t),\lambda(t))}{\partial\lambda},$$

$$0=\frac{\partial\mathscr{H}(\mathbf{x}^*(t),\mathbf{u}^*(t),\lambda(t))}{\partial\mathbf{u}},$$

$$\lambda'(t)=-\frac{\partial\mathscr{H}(\mathbf{x}^*(t),\mathbf{u}^*(t),\lambda(t))}{\partial\mathbf{x}}.$$

If follows from the derivation above

$$\begin{cases} u_i^*=0, \text{if } \frac{\partial\mathscr{H}}{\partial u_i}<0 \\ 0\le u_i^*\le 1, \text{if } \frac{\partial\mathscr{H}}{\partial u_i}=0 \\ u_i^*=1, \text{if } \frac{\partial\mathscr{H}}{\partial u_i}>0. \end{cases}$$

Now, we apply the necessary conditions to the Hamiltonian $\mathscr{H}$.

Theorem 3. Let $S_H^*(t), E_H^{s*}(t), E_H^{l*}(t), I_H^*(t), S_M^*(t)$ and $I_M^*(t)$ be optimal state solutions with associated optimal control variables u_1^* and u_2^* for the optimal control problem (1) and (2). Then, there exist adjoint variables $\lambda_1(t),\lambda_2(t),\lambda_3(t),\lambda_4(t),\lambda_5(t)$ and $\lambda_6(t)$ that satisfy

$$\lambda_1'(t)=\lambda_1(t)\beta_{mh}\sigma\left(1-u_2^*(t)\right) I_M^*\frac{1}{H}$$
$$-\lambda_2(t)p\beta_{mh}\sigma\left(1-u_2^*(t)\right) I_M^*\frac{1}{H}$$
$$-\lambda_3(t)(1-p)\beta_{mh}\sigma\left(1-u_2^*(t)\right) I_M\frac{1}{H}$$

$$\lambda_2'(t)=\lambda_2(t)T_h^s-\lambda_4(t)T_h^s$$

$$\lambda_3'(t)=\lambda_3(t)T_h^l-\lambda_4(t)T_h^l$$

$$\lambda_4'(t)=-A-\lambda_1(t)r+\lambda_4(t)r+\lambda_5(t)\beta_{hm}\sigma\left(1-u_2^*(t)\right) S_M^*\frac{1}{H}$$
$$-\lambda_6(t)\beta_{hm}\sigma\left(1-u_2^*(t)\right) S_M^*\frac{1}{H}$$

$$\lambda_5'(t)=-\lambda_5(t)\big(b_m\left(1-u_1^*(t)\right) - \beta_{hm}\sigma\left(1-u_2^*(t)\right) I_H^*\frac{1}{H}$$
$$-b_m-\rho u_1^*(t)\big)$$
$$-\lambda_6(t)\beta_{hm}\sigma\left(1-u_2^*(t)\right) I_H^*\frac{1}{H}$$

$$\begin{aligned}\lambda_6'(t)=&\lambda_1(t)\beta_{mh}\sigma\left(1-u_2^*(t)\right)\ S_H^*\frac{1}{H}\\ &-\lambda_2(t)p\beta_{mh}\sigma\left(1-u_2^*(t)\right)\ S_H^*\frac{1}{H}\\ &-\lambda_3(t)(1-p)\beta_{mh}\sigma\left(1-u_2^*(t)\right)\ S_H^*\frac{1}{H}\\ &-\lambda_5(t)b_m\left(1-u_1^*(t)\right)+\lambda_6\left(b_m+\rho u_1^*\right)\end{aligned}$$

with transversality conditions(or boundary conditions)

$$\lambda_j(T)=0, j=1,2,\ldots,6. \tag{5}$$

Furthermore, the optimal control u_1^* and u_2^* are given by

$$\begin{cases} u_1^*(t)=\min\left\{\max\left\{0,\frac{1}{B_1}\left((\rho+b_m)\lambda_5(t)S_M^*+(\rho\lambda_6(t)+b_m\lambda_5(t))I_M^*(t)\right)\right\},1\right\}\\ u_2^*(t)=\min\left\{\max\left\{0,\frac{1}{B_2}\left((-\lambda_1(t)+p\lambda_2(t)+(1-p)\lambda_3(t))\beta_{mh}\sigma S_H^*(t)I_M^*(t)\frac{1}{H}\right.\right.\right.\\ \qquad\left.\left.\left.+(\lambda_6(t)-\lambda_5(t))\ \beta_{hm}\sigma S_M^*(t)I_H^*(t)\frac{1}{H}\right)\right\},1\right\}\end{cases} \tag{6}$$

Proof. To determine the adjoint equations and the transversality conditions, we use the Hamiltonian (4). From setting $S_H(t)=S_H^*(t), E_H^s(t)=E_H^{s*}(t), E_H^l(t)=E_H^{l*}(t)$, $I_H(t)=I_H^*(t), S_M(t)=S_M^*(t)$ and $I_M(t)=I_M^*(t)$, and also differentiating the Hamiltonian (4) with respect to $S_H, E_H^s, E_H^l, I_H, S_M$ and I_M,we obtain

$$\begin{aligned}\lambda_1'=&-\frac{\partial\mathscr{H}}{\partial S_H}=\lambda_1\beta_{mh}\sigma\left(1-u_2^*\right)I_M^*\frac{1}{H}-\lambda_2p\beta_{mh}\sigma\left(1-u_2^*\right)I_M^*\frac{1}{H}-\lambda_3(1-p)\beta_{mh}\sigma\left(1-u_2^*\right)I_M^*\frac{1}{H}\\ \lambda_2'=&-\frac{\partial\mathscr{H}}{\partial E_H^s}=\lambda_2T_h^s-\lambda_4T_h^s\\ \lambda_3'=&-\frac{\partial\mathscr{H}}{\partial E_H^l}=\lambda_3T_h^l-\lambda_4T_h^l\\ \lambda_4'=&-\frac{\partial\mathscr{H}}{\partial I_H}=-A-\lambda_1r+\lambda_4r+\lambda_5\beta_{hm}\sigma\left(1-u_2^*\right)S_M^*\frac{1}{H}-\lambda_6\beta_{hm}\sigma\left(1-u_2^*\right)S_M\frac{1}{H}\\ \lambda_5'=&-\frac{\partial\mathscr{H}}{\partial s_M}=\lambda_5\left(b_m\left(1-u_1^*\right)-\beta_{hm}\sigma\left(1-u_2^*\right)I_H^*\frac{1}{H}-b_m-\rho u_1^*\right)\ -\lambda_6\beta_{hm}\sigma\left(1-u_2^*\right)I_H\frac{1}{H}\\ \lambda_6'=&-\frac{\partial\mathscr{H}}{\partial I_M}=\lambda_1\beta_{mh}\sigma\left(1-u_2^*\right)S_H^*\frac{1}{H}-\lambda_2p\beta_{mh}\sigma\left(1-u_2^*\right)S_H^*\frac{1}{H}-\lambda_3(1-p)\beta_{mh}\sigma\left(1-u_2^*\right)S_H\frac{1}{H}\\ &-\lambda_5b_m\left(1-u_1^*\right)+\lambda_6\left(b_m+\rho u_1^*\right).\end{aligned}$$

By the optimality conditions, we have

$$\begin{aligned}0=&\frac{\partial\mathscr{H}}{\partial u_1}=B_1u_1^*(t)-\lambda_5(t)\left(b_m\left(S_M^*+I_M^*\right)+\rho S_M^*\right)-\lambda_6(t)\rho I_M^*(t)\\ 0=&\frac{\partial\mathscr{H}}{\partial u_2}=B_2u_2^*(t)+\lambda_1(t)\beta_{mh}\sigma S_H^*(t)I_M^*(t)\frac{1}{H}-\lambda_2(t)p\beta_{mh}\sigma S_H^*(t)I_M^*(t)\frac{1}{H}\\ &-\lambda_3(t)(1-p)\beta_{mh}\sigma S_H^*(t)I_M^*(t)\frac{1}{H}+\lambda_5(t)\beta_{hm}\sigma I_H^*(t)S_M^*(t)\frac{1}{H}-\lambda_6(t)\beta_{hm}\sigma S_M^*(t)I_H^*(t)\frac{1}{H}.\end{aligned}$$

Using the property of the control space, we obtain the characterizations of $u_1^*(t)$ and $u_2^*(t)$ in (6). From the fixed of start time, we have transvesality conditions (5).

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