International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2014): 5.611

A Study of Malaria Epidemic Model Using the Effect of Lost Immunity

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Abstract: ***The model is developed to apply malaria data for both human population (hosts) and vector (mosquito) population. The hosts are divided into four compartments, susceptible $S_h(t)$, infected $I_h(t)$infectious $Z_h(t)$ and removed $R_h(t)$ at time t and vectors are divided into three compartments susceptible mosquitoes $S_m(t)$, infected mosquitoes $I_m(t)$ and infectious mosquitoes $Z_m(t)$ at time t. Recovered group for mosquitoes is not considered, because mosquitoes are assumed to remain infectious until death. As the model has two different populations (hosts and vectors), the expected basic reproduction number reflects the infection transmitted from human to vector and vice-versa. In the present study, we have considered the effect of lost immunity and the partially recovered rate as a function of infection dependent. We have studied the application of optimal control theory to the model. Numerical illustration of the model is also given.***

Keywords: recurrent epidemic, basic reproduction number, immunity and optimal control.

1. Introduction

According to the latest WHO estimates, released in September 2015, there were 214 million cases of malaria in 2015 and 438 000 deaths. Between 2000 and 2015, malaria incidence fell by 37% globally; during the same period, malaria mortality rates decreased by 60%. An estimated 6.2 million malaria deaths have been averted globally since 2000. Sub-Saharan Africa continues to carry a disproportionately high share of the global malaria burden. In 2015, the region was home to 89% of malaria cases and 91% of malaria deaths. In 2013, an estimated 437 000 African children died before their fifth birthday due to malaria. Globally, the disease caused an estimated 453 000 under-five deaths in 2013.

Malaria is caused by four members of the genus Plasmodium; Plasmodium vivax (P. vivax), Plasmodium falciparum (P. falciparum), Plasmodium malariae (P. malariae) and Plasmodium ovale (P. ovale). Plasmodium falciparum (malignant tertian malaria) and P. malariae (quartan malaria) are the most common species of malarial parasite in Asia and Africa. Plasmodium vivax (benign tertian malaria) predominates in Latin America, India and Pakistan. Plasmodium ovale (ovale tertian malaria) is almost exclusively found in Africa.

In most cases, malaria is transmitted through the bites of female *Anopheles* mosquitoes. The intensity of transmission depends on factors related to the parasite, the vector, the human host, and the environment. Transmission is more intense in places where the mosquito lifespan is longer (so that the parasite has time to complete its development inside the mosquito) and where it prefers to bite humans rather than other animals. Transmission also depends on climatic conditions that may affect the number and survival of mosquitoes, such as rainfall patterns, temperature and humidity (Talawar and Pujar, 2011). In many places, transmission is seasonal, with the peak during and just after the rainy season. Malaria epidemics can occur when climate and other conditions suddenly favour transmission in areas where people have little or no immunity to malaria. They can also occur when people with low immunity move into areas with intense malaria transmission, for instance to find work, or as refugees. Human immunity is another important factor, especially among adults in areas of moderate or intense transmission conditions. Partial immunity is developed over years of exposure, and while it never provides complete protection, it does reduce the risk that malaria infection will cause severe disease. For this reason, in areas with less transmission and low immunity, all age groups are at risk.

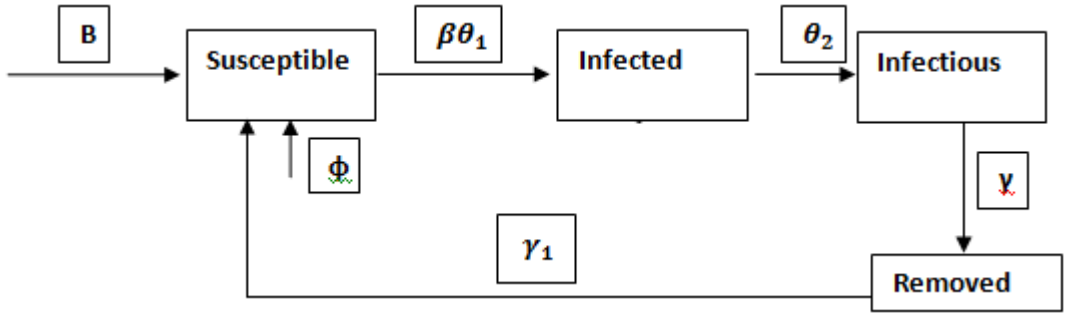
The first deterministic compartmental model was developed by Ross (1915), where host and vector populations are modeled as susceptible-infected-susceptible (SIS) and susceptible-infected (SI) respectively. Macdonald (1957) developed the malaria model by modifying the Ross model adding an exposed class. Smith et al.,(2012), based on a model of Ross and Macdonald , concluded that there is a relationship between the ratio of mosquitoes to humans and the number of infected humans, hence it is not necessary to kill every mosquito to end disease transmission. Mwanga et al (2014a) developed SIR malaria model for human population and SI model for mosquito population and used different parameter values estimated by Agusto et al (2012), Chitnis et al (2006) and Mukandavire et al (2010) for malaria transmission model. They studied the effect of infective immigrants in the presence drug resistance strains. Mwanga et al (2014b) also studied the malaria model in the presence parameter uncertainty using MCMC method. A person infected with malaria may be reinfected before recovering completely if bitten again by an infectious mosquito (Nedelman, 1985). Therefore, in the present paper we consider partially recovered humans (removals) with temporary immunity and lost immunity. We develop SEIR for human (hosts) population and SEI for mosquito (vector) population. We study the effect of lost immunity on state variables.

2. Formulation of the Model

The model divides the human population into four groups or compartments; those who are susceptible to the disease,

those who are infected but not infectious, those who are infectious and those who are in some form of recovery.

Following is the transfer diagram of the malaria disease



The system of differential equations is

$$S' = B - \left(\beta\theta_1\left(\frac{f}{f+v}\right) - \phi\right)S + \gamma_1 R$$

$$I' = \left(\beta\theta_1\left(\frac{f}{f+v}\right)\right)S - (\theta_2 + \mu)I \quad (1)$$

$$Z' = (\theta_2 + \mu)I - \gamma Z$$

$$R' = \gamma Z - \gamma_1 R$$

Where $N = S + I + Z + R$, B is the recruitment of susceptible, β is the contact rate between bacterial and susceptible hosts, θ_1 is the proportion of infected individuals who are infectious, θ_2 is the proportion of infected mosquitoes who are also infectious, μ is immigration of infectious individuals, ϕ rate at which susceptible remain uninfected even after contract, γ rate at which individuals acquired immunity and γ_1 rate at which removed individuals lose their immunity.

Due to biological reasons, only non-negative solutions of the system (1) are acceptable. It is necessary to study the solution properties of the system (1) in the closed set,

$$\Gamma = \{(S, I, Z, R) \in R^4; S + I + Z + R \leq N\} \quad (2)$$

A vector (four tuple), $E = (S, I, Z, R)$ is said to be an equilibrium point for the system (1) if it satisfies the following conditions,

S'=0, I'=0, Z'=0 and R'=0 (3)

An equilibrium point E is meaningful iff E $\in$ Γ. The equilibrium points are said to be disease free or endemic depending on I and Z. If there is no disease ($I = 0$ and $Z = 0$), then the equilibrium point is said to be a disease-free equilibrium (DFE) point, otherwise if $I \neq 0$ or $Z \neq 0$ (in other words $I > 0$ or $Z > 0$), then the equilibrium point is called endemic.

Theorem: The system (1) admits at most two equilibrium points; one disease free equilibrium point (P_0) and one endemic equilibrium point (P^*), where $P_0 = \left(\frac{B}{\phi}, 0,0,0\right)$ and $P^* = (S^*, I^*, Z^*, R^*)$. The state variables at endemic equilibrium point P^* are

$$S^* = \frac{\frac{B}{\phi}}{\left(\frac{1}{\theta_2+\mu} + \frac{1}{\gamma} + \frac{1}{\gamma_1} + 1\right)},$$

$$I^* = \frac{\frac{1}{\theta_2+\mu}}{\left(\frac{1}{\theta_2+\mu} + \frac{1}{\gamma} + \frac{1}{\gamma_1} + 1\right)},$$

$$Z^* = \frac{\frac{1}{\gamma}}{\left(\frac{1}{\theta_2+\mu} + \frac{1}{\gamma} + \frac{1}{\gamma_1} + 1\right)},$$

$$R^* = \frac{1/\gamma_1}{\left(\frac{1}{\theta_2+\mu} + \frac{1}{\gamma} + \frac{1}{\gamma_1} + 1\right)} \quad (4)$$

Threshold values: There are three commonly used threshold values in epidemiology the basic reproduction number(R_0), the contact number (σ) and the replacement number (R). The basic reproduction number is defined as the average number of secondary infections that occurs when one infective is introduced into a completely susceptible population. These are all at the beginning of the spreading of an infection disease; the entire population (except the infective invader) is susceptible. The R_0 is defined at the time of invasion, where as σ and R are defined at all times.

Due to differences in demographic rates, rural-urban gradients and contact structure, different human populations may be associated with different values of R_0 for the same disease (Hethcote, 2000 ; Anderson and May, 2005).

Proposition: The Γ is positively invariant under the flow reduced by the system of differential equations (1).

Proof : The system of differential equations (1) can be written in the following way;

$$\frac{dX}{dt} = M(X)X + F \quad (5)$$

Where E=(S, I, Z, R), F=$(B, 0,0,0)$' and

$$M(X) = \begin{bmatrix} \beta\theta_1\left(\frac{f}{f+v}\right) - \phi & 0 & 0\,\gamma_1 \\ \beta\theta_1\left(\frac{f}{f+v}\right) & -(\theta_2+\mu) & 0\,0 \\ 0 & (\theta_2+\mu) & -\gamma\,0 \\ 0\,0\,\gamma & -\gamma_1 & \end{bmatrix}$$

As M(X) has all off-diagonal entries non-negative, M(X) is Metzler matrix. Using the fact that F≥ 0, the system (1) is positively invariant in R_+^4. Which means that any trajectory of the system of differential equations starting from an initial state in the positive orthant R_+^4 remains forever in R_+^4.

3. Time dependent immunity (TDI)

We consider time dependent immunity acquisition rate, $\gamma = \gamma(t)$. Assume that immunity is initially nil and that immunity tends asymptotically to a limiting value, say Λ. The rate of immunity (γ) is replaced by $\Lambda(1\text{-}e^{-vt^2})$. Then the last two equations of the system (1) of differential equations can be written as,

$$Z' = (\theta_2 + \mu)I - \Lambda(1 - e^{-vt^2})Z$$
$$R' = \Lambda(1 - e^{-vt^2})Z - \gamma_1 R \quad (6)$$

The modification has no effect on stationary values, since $\gamma \to \Lambda$ as t$\to \infty$. So the stationary point remains the same only with Λ replacing γ in system (1).

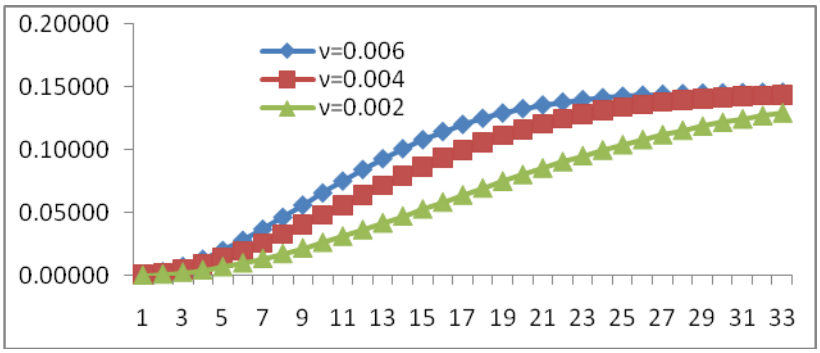


Figure 1: Effect of vaccination on time dependent immunity v/s Age

Note that this time-dependent model preserves the crossover phenomenon and the urban versus rural phenomenon.

4. Application of the Model

The model (1) is reformulated to apply to malaria data for both human population (hosts) as well as to vector population. The hosts are divided into four compartments as before, susceptible,$S_h(t)$, infected,$I_h(t)$, infectious ,$Z_h(t)$ and removed,$R_h(t)$ at time t and vectors are divided into three compartments susceptible mosquitoes, $S_m(t)$, infected mosquitoes, $I_m(t)$ and infectious mosquitoes, $Z_m(t)$ at time t. Recovered group for mosquitoes is not considered, because mosquitoes are assumed to remain infectious until death. The system differential equations for human population is

$$S_h' = B_h - (\beta_{hm}\theta_1 I_m - \phi_h)S_h + \gamma_1 R_h$$
$$I_h' = (\beta_{hm}\theta_1 I_m)S_h - (\theta_2 + \mu_h)I_h \quad (7)$$
$$Z_h' = (\theta_2 + \mu_h)I_h - \gamma_h Z_h$$
$$R_h' = \gamma_h Z_h - \gamma_{1h} R_h$$

The system differential equations for mosquito population is

$$S_m' = B_m - (\beta_{mh}\theta_1 I_h)S_m$$
$$I_m' = (\beta_{mh}\theta_1 I_h)S_m - (\theta_2)I_m \quad (8)$$
$$Z_m' = (\theta_2)I_m - \gamma_m Z_m$$

The model has two different populations (hosts and vectors) and therefore the expected basic reproduction number reflects the infection transmitted from human population to vector and vice-versa. Thus the basic reproduction number, R_0 can be taken as $\sqrt{R_{hm}XR_{mh}}$. Where R_{hm} basic reproduction number for the infection from hosts to vectors, $R_{hm} = \frac{B_h\beta_{hm}\theta_1}{\phi_h(\theta_2+\mu_h)}$ and basic reproduction number for the infection from vectors to hosts, $R_{mh}=\frac{B_m\beta_{mh}\theta_1}{(\theta_2)}$.

Thus, $R_0=\sqrt{\frac{B_h\beta_{hm}\theta_1}{\phi_h(\theta_2+\mu_h)}\frac{B_m\beta_{mh}}{(\theta_2)}}$ (9)

4 (a). Effect of lost immunity

The quantity $\gamma_1 R$ in system (1) allows for a return path from the partially recovered or losing immunity, back to the susceptible compartment. Furthermore, γ_1 is taken as a function of $\beta_{hm}\theta_1$ (that is infection dependent recovery rate) in difference to the observation by many that the greater the endemicity of the disease, the greater the immunity among population. Thus γ_1 should decrease with increasing$\beta_{hm}\theta_1$. The exact relationship is in terms of a parameter τ and takes the form $\gamma_1(\beta_{hm}\theta_1) = \frac{\beta_{hm}\theta_1 e^{-\beta_{hm}\theta_1\tau}}{1-e^{-\beta_{hm}\theta_1\tau}}$ (Aron and May,1982)

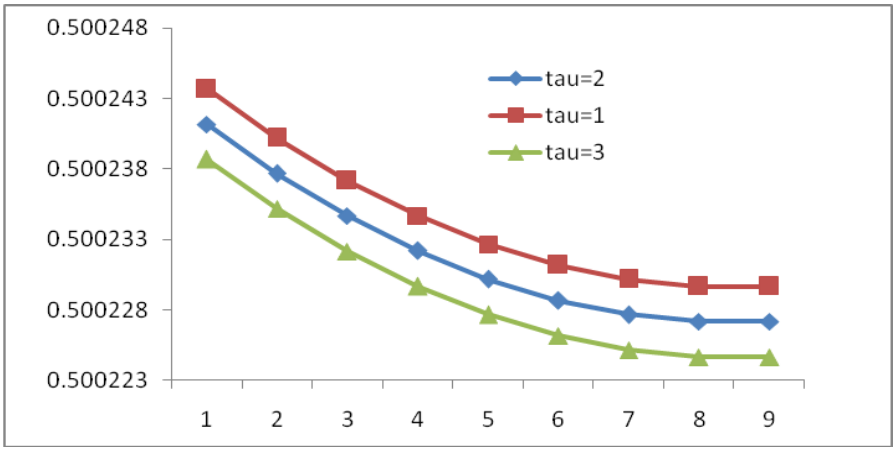


Figure 2: Effect of lost immunity as a function of infection rate for various τ ($\tau = 1, \tau = 2, \tau = 3$)

5. Application of Optimal Control Theory

For analysis of the optimal level of effort required to control the spread of malaria, two control measures are taken into consideration. Screening and treatment of asymptomatic infective individuals (u_1) and treatment of symptomatic individuals with antimalarial drugs (u_2). The optimal control problem is stated as follows;

Minimize the number of infected (both asymptomatic, I and symptomatic, Z) within the time horizon T, that is $t \in [0, T]$ given by the function

$$J = \min_{u \in U} \int_0^T F(t, u, q) + h(t, u)\, dt \quad (10)$$

Subject to the state system of equations (7-8),

$$\begin{aligned} S_h' &= B_h - (\beta_{hm}\theta_1 I_m - \phi_h)S_h + \gamma_{1h}R_h \\ I_h' &= (\beta_{hm}\theta_1 I_m)S_h - (\theta_2 + \mu_h + u_1)I_h \\ Z_h' &= (\theta_2 + \mu_h)I_h - (\gamma_h + u_2)Z_h \\ R_h' &= \gamma_h Z_h - \gamma_{1h}R_h + u_1 I_h + u_2 Z_h \quad (11) \\ S_m' &= B_m - (\beta_{mh}\theta_1 I_h)S_m \\ I_m' &= (\beta_{mh}\theta_1 I_h)S_m - (\theta_2)I_m \\ Z_m' &= (\theta_2)I_m - \gamma_m Z_m \end{aligned}$$

and the control constraint

$$U = \{u_j \text{ given that } u_j(t) \text{ is Lebesgue measurable}, 0 \le u_j(t) \le 1, \text{for } j = 1,2, t \in [0,t]\} \quad (12)$$

Where

$$F(t, u, q) = A_{12} I_h + A_2 Z_h + c_1 u_1 (I_h) + c_2 u_2 (Z_h) \quad (13)$$

$$h(t, u) = \tfrac{1}{2} w_1 {u_1}^2(t) + \tfrac{1}{2} w_2 {u_2}^2(t) \quad (14)$$

and q is the solution of the state system (7). c_1 and c_2 are the individual costs for screening and treatment of asymptomatic individuals and for the treatment of symptomatic individuals respectively, A_1, A_2, w_1 and w_2 are the relative weights. $F(t, u, q)$ defines actual costs while $h(t, u)$ defines the background costs (such as ordering, shipment and distribution, and storage).

Therefore the optimal control problem (10) is to minimize the cost function

$$J = \int_0^T [A_1 I_h + A_2 Z_h + c_1 u_1 (I_h) + c_2 u_2 (Z_h) + \frac{1}{2} w_1 {u_1}^2(t) + \frac{1}{2} w_2 {u_2}^2(t)]dt \quad (15)$$

This performance specification involves the number of asymptomatic and symptomatic individuals as well as effect of implementing the asymptomatic control (u_1) and symptomatic control (u_2).

We find optimal control pair (u_1^*, u_2^*) such that

$$J(u_1^*, u_2^*) = Min\{J(u_1, u_2);\ (u_1, u_2) \in U\} \quad (16)$$

Now applying the necessary condition from Pontryagin's Maximum Principle (PMP), we have the problem minimizing a Hamiltonian, H pointwisely with respect to u_1 and u_2

Theorem: Given an optimal control pair $U^*(t) = (u_1^*(t), u_2^*(t))$ and a solution of the system (11) there exists adjoint variables $\lambda_{S_h}(t), \lambda_{I_h}(t), \lambda_{Z_h}(t), \lambda_{R_h}(t), \lambda_{S_m}(t), \lambda_{I_m}(t)$ and $\lambda_{Z_m}(t)$ such that, the Hamiltonian is given by

$$H(S_h, I_h, Z_h, R_h, S_m, I_m, Z_m) = [\left[A_1 I_h + A_2 Z_h + c_1 u_1(I_h) + c_2 u_2(Z_h) + \frac{1}{2} w_1 {u_1}^2(t) + \frac{1}{2} w_2 {u_2}^2(t)\right] + \lambda_{S_h}(B_h - (\beta_{hm}\theta_1 I_m - \phi_h)S_h + \gamma_{1h} R_h) + \lambda_{I_h}\left((\beta_{hm}\theta_1 I_m)S_h - (\theta_2 + \mu_h + u_1)I_h\right) + \lambda_{Z_h}\left((\theta_2 + \mu_h)I_h - (\gamma_h + u_2)Z_h\right) + \lambda_{R_h}(\gamma_h Z_h - \gamma_{1h} R_h + u_1 I_h + u_2 Z_h) + \lambda_{S_m}(B_m - (\beta_{mh}\theta_1 I_h)S_m) + \lambda_{I_h}\left((\beta_{hm}\theta_1 I_h)S_m - (\theta_2)I_m\right) + \lambda_{Z_m}\left((\theta_2)I_h - (\gamma_m)Z_h\right)]$$ (17)

And $\lambda'_{S_h} = -[\lambda_{S_h}\left(-(\beta_{hm}\theta_1 I_m - \phi_h) + \lambda_{I_h}\beta_{hm}\theta_1 I_m\right)]$

λ'_{I_h} =-

$[A_1 + c_1 u_1 + \lambda_{S_h}(-(\beta_{hm}\theta_1)S_h +$

$\lambda_{I_h}\left((\beta_{hm}\theta_1)S_h - (\theta_2 + \mu_h + u_1)\right)$

$+\lambda_{Z_h}(\theta_2 + \mu_h) + \lambda_{R_h}(u_1)]$

λ'_{Z_h}=-$[A_2 + c_2 u_2 + \lambda_{Z_h}(-(\gamma_h + u_2)) + \lambda_{R_h}(\gamma_h + u_2)]$

and

λ'_{R_h}=-$[\lambda_{S_h}\gamma_{1h} + \lambda_{R_h}(-\gamma_{1h})]$

$\lambda'_{S_m} = -[\lambda_{S_m}\left(-(\beta_{mh}\theta_1 I_h) + \lambda_{I_m}\beta_{mh}\theta_1 I_h\right)]$

λ'_{I_m} =-$[\lambda_{S_m}(-(\beta_{mh}\theta_1)S_m + \lambda_{I_m}\left((\beta_{mh}\theta_1)S_m - (\theta_2)\right)$

$+\lambda_{Z_m}(\theta_2)]$

λ'_{Z_h}=-$[\lambda_{Z_h}(-\gamma_h)]$ (18)

With transversality conditions

$$\lambda_{S_h}(T) = \lambda_{I_h}(T) = \lambda_{Z_h}(T) = \lambda_{R_h}(T) = \lambda_{S_m}(T) = \lambda_{I_m}(T) = \lambda_{Z_m}(T) = 0$$ (19)

The optimal control u_1^* *and* u_2^* is given by

$$u_1^* = \min\left\{\max\left(0, \frac{1}{w_1}(\lambda_I - \lambda_R - c_1)I, 1\right\}\right.$$

$$u_2^* = \min\left\{\max\left(0, \frac{1}{w_2}(\lambda_Z - \lambda_R - c_2)Z, 1\right\}\right.$$ (20)

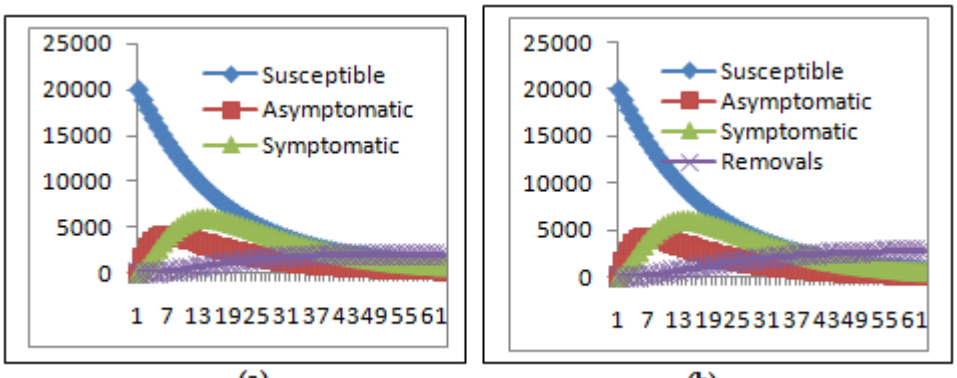
6. Numerical Illustration

In the simulation we consider various parameter values and some hypothetical values for state variables. First, we considered the model without any control measures and compared the state variables. Fig. 3 (a-d) gives a comparison of state variables when the loss of immunity is considered and the optimal controls are not in operation. Fig.3 (c-d) gives the effect of lost immunity on the state variables. The number of infectives (symptomatic) is more when lost immunity is considered ($\gamma_1 > 0$) as compared to that when lost immunity is not considered in the model ($\gamma_1 = 0$). Fig. 4 illustrates the comparison of the effect of lost immunity on removals (immunized or recovery).

We study the effect of controls on the number of individuals of asymptomatic and symptomatic considering effect of control on asymptomatic alone, symptomatic alone and both (Fig. 5 (a-c)). Fig.5(c) illustrates that treating asymptomatic individuals alone will be more than treating the symptomatic individuals.

Table: Model parameter values. Figures in parenthesis are the values used for estimating state variables.

Parameter	Description	Value	Reference
B_{hm}	Recruitment of susceptible	(1/60)X365	(10)
β_{hm}	Contact rate between bacterial and susceptible hosts	0.03-0.5 (**0.4**)	(1,7,13)
θ_1	Proportion of infected individuals who are infectious	0.15-0.6 (**0.6**)	(11)
θ_2	Proportion of infected mosquitoes who are also infectious	0.02-0.5 (**0.028**)	(11)
μ_h	Immigration of infectious individuals	0.00004	(4)
$\emptyset_h$	Rate at which susceptible remain uninfected even after contract	0.001-0.03(**0.028**)	Assumed
γ_h	Rate at which individuals acquired immunity	0.0146	(4)
γ_1	Rate at which removed individuals lose their immunity	0.001-0.01(**0.01**)	Assumed

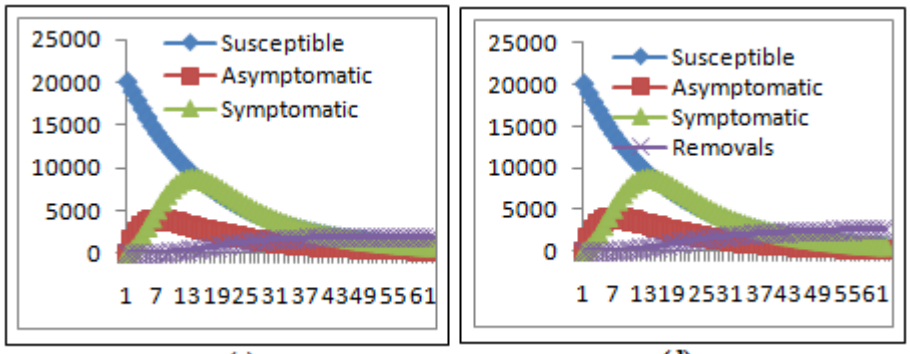


(*a*) ($\gamma_1 = 0$ *and Time independent immunity*)

(b) ($\gamma_1 = 0$ *and Time dependent immunity*)

(c) $(\gamma_1 > 0$ *and Time independent immunity*$)$

(d) $(\gamma_1 > 0$ *and Time dependent immunity*$)$



(c) (d)

Figure 3: Effect of lost immunity on the state variables (a-d)

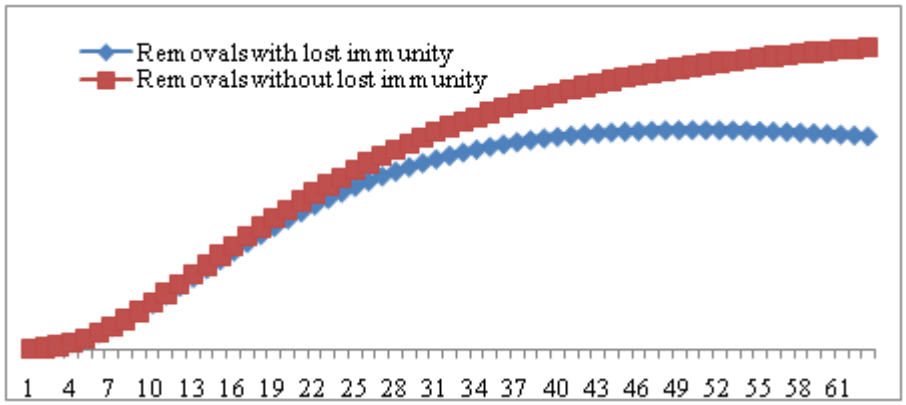
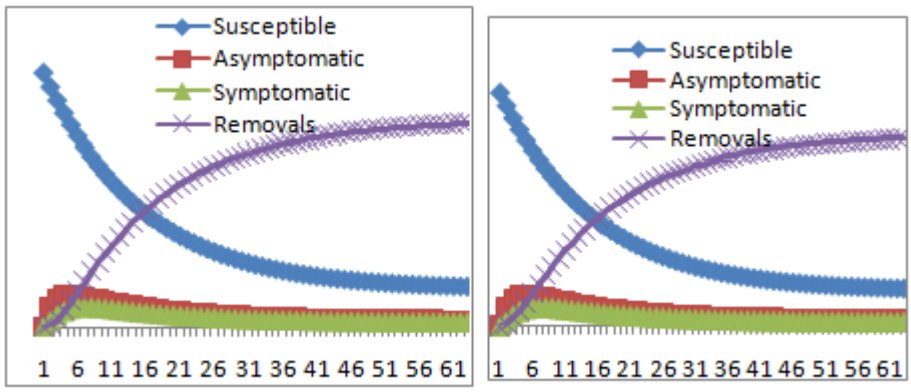
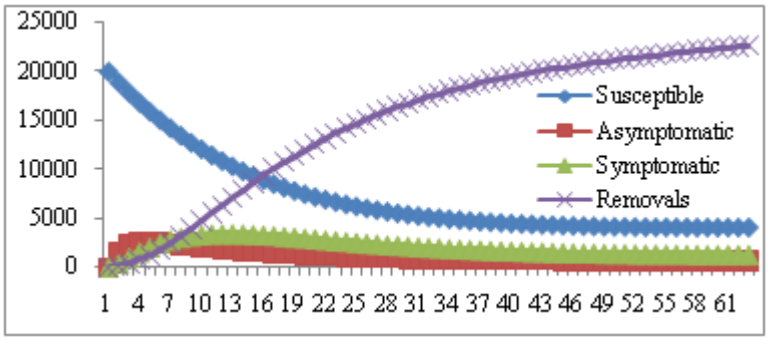


Figure 4: Comparison of removals with and without lost immunity



(a) $(u_1 \neq 0$ *and* $u_2 \neq 0)$ **(b)** $(u_1 = 0$ *and* $u_2 \neq 0)$



(c) $(u_1 \neq 0$ *and* $u_2 = 0)$

Figure 5: Optimal controls (a-c)

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