MANAGEMENT STRATEGIES IN A MALARIA MODEL COMBINING HUMAN AND TRANSMISSION-BLOCKING VACCINES

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Abstract. We propose a new mathematical model studying control strategies of malaria transmission. The control is a combination of human and transmission-blocking vaccines and vector control (larvicide). When the disease induced death rate is large enough, we show the existence of a backward bifurcation analytically if vaccination control is not used, and numerically if vaccination is used. The basic reproduction number is a decreasing function of the vaccination controls as well as the vector control parameters, which means that any effort on these controls will reduce the burden of the disease. Numerical simulation suggests that the combination of the vaccinations and vector control may help to eradicate the disease. We investigate optimal strategies using the vaccinations and vector controls to gain qualitative understanding on how the combinations of these controls should be used to reduce disease prevalence in malaria endemic setting. Our results show that the combination of the two vaccination controls integrated with vector control has the highest impact on reducing the number of infected humans and mosquitoes.

1. Introduction. Malaria is a mosquito-borne disease that currently affects over 100 countries worldwide and the highest incidence and mortality rates are reported in sub-Saharan Africa. The World Health Organization (WHO) estimates that 438,000 people died in 2015 from malaria, approximately 90% of the deaths occurred in the African region, followed by the South-East Asia region 7% [33]. In an effort to reduce malaria transmission, control strategies such as indoor and outdoor spray of insecticide, insecticide treated bed-nets, drug treatment, and intermittent preventive treatment in pregnant women and infants are widely used.

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Concurrent use of multiple malaria control interventions have been recommended as an effective strategy to reduce malaria and its burden [6]; and the strategy has shown encouraging results in reducing malaria burden worldwide [21, 33]. Scientists have developed several candidates of malaria vaccines and recent clinical trials have shown promising results [18, 22, 24, 30, 31, 34]. These vaccines target malaria parasite at different stages of its life cycle. Malaria parasite develops both in humans and in the female mosquitoes and has three main stages: sporozoites are the stage transmitted from mosquito to humans, merozoites are the stage responsible for malaria disease, and gametocytes are the infective stage for mosquitoes. The candidate vaccines can be classified in three categories [14, 30]: (i) sporozoite (pre-erythrocytic) vaccines (human vaccine, HV) which prevent (or reduce) susceptibility of humans to malaria, (ii) merozoite (blood-stage) vaccines (diseases-modifying) that increase recovery rate of infected humans by limiting spread of merozoites to red blood cells, and (iii) gametic vaccines (transmission-blocking vaccine, TBV) that stop transmission from infected person to susceptible mosquitoes by inhibiting parasite development in the mosquito [2]. None of these three types of malaria vaccines is yet available on the market.

Most malaria vaccine candidates are not expected to provide perfect immunity. These vaccines may not completely prevent infection but could reduce the probability of being infected or reduce the consequences of being infected. Such vaccines can be classified as imperfect vaccines [12, 30]. For example, a human vaccine candidate, RTS,S/AS01, completed Phase III human trials in 2012 [23, 27] and the results of the trial show that RTS,S reduces the risk of developing severe malaria by 26%-58%, and the time to first infection by 45%, and protection does not wane after 15 months [23]. The current industry’s interest is in sporozoite vaccines, with a secondary interest in merozoite vaccines. Both vaccines, especially the merozoite vaccines, are of interest for travelers and military. Gametic vaccines (or transmission-blocking vaccines) would not directly stop malaria from infected individuals [5, 34], but prevent the development of malarial parasites in the mosquito mid-gut and hence the mosquito will not transmit the parasite when the mosquito takes next bite. Moreover, since sexual stages do not multiply, the chances of resistant mutants emerging from transmission-blocking vaccines would be minimal. Such a vaccine would have the potential to reduce the disease burden in poor areas in Africa, Asia, and Latin America where malaria is endemic [2, 32]. Since malaria infections are transmitted within a few hundred meters from an infectious human, transmission-blocking vaccines would protect the immediate neighborhood of the vaccinated individuals in a community. Several transmission-blocking vaccines including: Pfs 48/45, Pfs 230, Pfs 25, and Pfs 28 of *P. falciparum*, (and some of their *P. vivax* analogs) have undergone pre-clinical development, some proving highly immunogenic; however, none has yet passed early stages of clinical testing [24, 34]. For transmission-blocking vaccines, mosquitoes will be indirectly vaccinated through biting vaccinated humans; the vaccine is not yet tested on humans, however, it has a potential to be used in conjunction with traditional types human vaccines and other interventions [4, 15].

Mathematical models have been developed to explore the impact of vaccinations on prevalence of infection and disease, and to guide the process of malaria vaccine development [2, 12, 14, 18, 24, 27, 29, 30, 31, 34 and references therein]. Such models will help us have a better understanding of the potential impact of malaria vaccines in different settings and the ways in which they integrate with the traditional malaria-control interventions (such as treatment, mosquito-control,
bed nets). Optimal human vaccination integrated with bed nets control program has been studied in [20]. In [30], imperfect HV was incorporated in a model to explore the role of gametocytes density on disease spread. Some mathematical models have suggested that all the three-stage vaccines could contribute to elimination of transmission under certain settings [14]. Smith et al. computed the basic reproduction number with a Ross-MacDonald model incorporating TBV, and their model showed that efficacy and coverage of TBV are important [28]. Zhao et al. developed a compartmental deterministic model to explore the impact of TBV [34]; the model incorporates vaccinated human and mosquito compartments, and their results suggested that increasing vaccination coverage could reduce disease burden.

In this study, we develop a mathematical model to investigate the impact of the combined human and transmission-blocking vaccines integrated with mosquito control on reducing malaria transmission and spread. We use techniques of optimal control theory [16, 19] to illustrate control strategies using the three control actions. In section 2, methods and model derivations are presented; in section 3, the basic reproduction number is calculated, stability analysis is performed and simulation results are presented; in section 4, the optimal control problem is formulated, existence and uniqueness of the optimal control are proved; in section 5, optimal control strategies are presented numerically by solving optimality system, consisting of the state and adjoint systems and control characterization; finally, in section 6, conclusive remarks are provided.

2. Methods and model derivation. We consider two malaria vaccines, transmission-blocking vaccine (TBV) and human vaccine (HV). We assume that TBV is perfect and effective lifetime long, however, HV gives only temporary protection and wanes through time. Even though TBV is still under development, we assume that it is effective lifetime long as long as it is available and we assume that it is perfect due to the promising high immunogenicity of TBV [24, 26]. We assume that individuals receive a combination of both TBV and HV for the first time. Thus, individuals who have been vaccinated before will receive only HV after the vaccine wanes. Unvaccinated individuals are those who never received a vaccine against malaria.

Initially, humans are susceptible ($S_h$). These susceptible individuals either receive the two dose vaccines and become vaccinated at rate $\xi_h$ and enter the vaccinated and protected class, $V_h$, or they become infected at rate $\lambda_v$, where $\lambda_v$ is described in 1. Once infected, $S_h$-individuals move to the un-vaccinated infectious class, $I_h$, and infectious individuals die due to the disease at rate $\delta_h$. Infectious individuals recover at rate $\eta_h$ and progress to infected class, $R_h$. These recovered individuals are not infectious and are temporarily immune; they lose the temporary immunity at rate $\rho_h$ and return to the vaccinated but un-protected class, $V_B$.

Human vaccine wanes at rate $\omega_h$ and vaccinated individuals in $V_h$ class lose protection and progress to the vaccinated (with TBV), but un-protected class, $V_B$. Individuals in the $V_B$ class either receive human vaccine, become protected at rate $\nu_h$ and return to $V_h$ class, or they become infected at rate $\lambda_v$. Once infected, $V_B$ individuals progress to infected class, $J_h$. Infected $J_h$-individuals recover at rate $\eta_h$ and enter the recovered class, $M_h$; these recovered individuals are temporarily immune and lose the temporary immunity at rate $\rho_h$ and return to the vaccinated but un-protected class, $V_B$. 
The size of the human population increases as a result of recruitment at constant rate $\Lambda_h$. The natural mortality rate for all humans is $\mu_h$. The total population of humans at time $t$ is: $N_h(t) = S_h(t) + I_h(t) + R_h(t) + V_h(t) + V_B(t) + J_h(t) + M_h(t)$.

All mosquitoes are susceptible initially ($S_v$). If these susceptible mosquitoes bite vaccinated (with TBV) humans, they enter the removed (or indirectly vaccinated) class ($V_v$) at rate $\lambda_{h2}$. We assume that once mosquitoes enter the removed class, they will not transmit the disease for the rest of their lifetime. If susceptible mosquitoes bite an un-vaccinated (with TBV) infectious human, $I_h$, they progress to infectious mosquito class ($I_v$) at rate $\lambda_{h1}$. Both $\lambda_{h1}$ and $\lambda_{h2}$ are described in [1]. The natural mortality rate for mosquitoes is $\mu_v$, and the total population of mosquitoes at time $t$ is: $N_v(t) = S_v(t) + I_v(t) + V_v(t)$.

Susceptible humans (both $S_h$ and $V_B$) are infected at rate $\lambda_v$, susceptible mosquitoes are infected at rate of $\lambda_{h1}$, and susceptible mosquitoes are removed (or indirectly vaccinated) at rate of $\lambda_{h2}$, where

$$\lambda_v = \frac{C_{vh}I_v}{N_h}, \quad \lambda_{h1} = \frac{C_{hv}I_h}{N_h}, \quad \lambda_{h2} = \frac{C_{hv}(V_h + V_B + J_h + M_h)}{N_h}. \quad (1)$$

$C_{vh}$ is the effective transmission rate from vectors to humans (that is, the mosquito biting rate times the probability that an individual becomes infected through a bite from an infected mosquito) and $C_{hv}$ is the effective transmission rate from humans to vectors (that is, the mosquito biting rate times the probability that a susceptible mosquito becomes infected when it takes a bite on infected humans). It is assumed that TBV does not take effect when a mosquito takes a blood meal from a vaccinated person if the mosquito is already infected. For the mosquito population, we choose the Verhulst-Pearl logistic birth function [17], $B$, defined by:

$$B(N_v) = r_v \left(1 - \frac{N_v}{L}\right) \quad (2)$$

where $r_v$ is a positive growth constant, $L > 0$ is the environmental carrying capacity [17].

To incorporate a mosquito control intervention at the early stage of mosquito life-cycle, such as larvicide, we multiply $B(N_v)$ by $(1-u)$ where $0 \leq u < 1$; $u = 0$ when there is no mosquito control, and when $u > 0$, the mosquito growth reduces due to the intervention.

The descriptions of parameters and its values are listed in Table 1 and the detailed reference for each value can be found in [7] [34]. A complete schematic diagram is provided in Figure 1.

The complete model is given by the system of differential equations in (3).

$$\begin{align*}
    \dot{S}_h &= \Lambda_h + \rho_h R_h - \lambda_v S_h - (\xi_h + \mu_h) S_h, \\
    \dot{I}_h &= \lambda_v S_h - (\eta_h + \mu_h + \delta_h) I_h, \\
    \dot{R}_h &= \eta_h I_h - (\rho_h + \mu_h) R_h, \\
    \dot{V}_h &= \xi_h S_h + \nu_h V_B - (\omega_h + \mu_h) V_h, \\
    \dot{V}_B &= \omega_h V_h + \rho_h M_h - \lambda_v V_B - (\nu_h + \mu_h) V_B, \\
    \dot{J}_h &= \lambda_v V_B - (\eta_h + \mu_h + \delta_h) J_h, \\
    \dot{M}_h &= \eta_h J_h - (\rho_h + \mu_h) M_h, \\
    \dot{S}_v &= (1-u) B(N_v) N_v - \lambda_{h1} S_v - \lambda_{h2} S_v - \mu_v S_v, \\
    \dot{I}_v &= \lambda_{h1} S_v - \mu_v I_v, \\
    \dot{V}_v &= \lambda_{h2} S_v - \mu_v V_v.
\end{align*} \quad (3)$$
### Table 1. Description of parameters of the basic malaria model, the detailed reference for each value can be found in [7, 34].

| Parameter | Description                                      | Baseline values and range                      |
|-----------|--------------------------------------------------|------------------------------------------------|
| $\Lambda_h$ | Recruitment rate of humans per year             | $10^4/55 \in [10^4/72, 10^4/35]$              |
| $L$       | Environmental carrying capacity per year         | $10^5 \in [10^4/72, 10^4/35] \times \frac{40}{3}$ |
| $r_v$     | Mosquito growth constant per year               | $4 \times 365/21$                              |
| $\mu_h$   | Natural death rate of host per year             | $1/55 \in [1/72, 1/35]$                       |
| $\mu_v$   | Natural death rate of vector per year           | $365/21 \in [365/28, 365/14]$                 |
| $C_{hv}$  | The effective transmission rate from humans to mosquitoes per year per bite | $9 \in [2.6, 32 \times 365]$                   |
| $C_{vh}$  | The effective transmission rate from mosquitoes to humans per year per bite | $0.8 \in [0.001 \times 365, 0.27 \times 365]$ |
| $\xi_h$   | Vaccination rate of humans with mixture vaccine dose per year | $0.01 \in [0, \ln 5]$                         |
| $\rho_h$  | Rate of loss of immunity per year               | $2 \in [1/50, 4]$                              |
| $\eta_h$  | Rate of development of temporal immunity per year | $1 \in [1/2, 6]$                               |
| $\delta_h$ | Disease-induced death rate per year            | $0.1/55 \in [0, 4.1 \times 10^{-4}] \times 365$ |
| $\nu_h$   | Vaccination rate of humans per year with HV dose only | $0.1 \in [0, \ln 5]$                         |
| $\omega_h$ | Rate of loss of HV acquired-immunity per year in vaccinated group of humans | $1/4 \in [1/5, 1]$                             |
| $u$       | 1 – $u$ represents reduction factor of mosquitoes birth due to control such as larvacide | $0 \in [0, 0.72]$                             |

![Figure 1. The schematic diagram of the mathematical model.](image-url)
3. Model analysis. All the variables in model (3) are non-negative since they represent human and female mosquito populations. It can be easily verified that model (3) has non-negative solutions for non-negative initial conditions.

**Theorem 3.1.** If \( N_h(0) > 0 \) then the total population, \( N_h(t) \), is bounded:

\[
0 < (N_h)_{\min} \leq N_h(t) \leq (N_h)_{\max}
\]

where \((N_h)_{\min} = \min\left( N_h(0), \frac{\Lambda_h}{\mu_h + \delta_h} \right)\) and \((N_h)_{\max} = \max\left( N_h(0), \frac{\Lambda_h}{\mu_h} \right)\).

**Proof.** Assume all components are non-negative. Adding all equations related to human population, we have

\[
\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \delta_h (I_h + J_h).
\]

Adding \(\mu_h N_h\) on both sides, multiplying the integration factor \(e^{\mu_h t}\), and integrating the resulting equation from 0 to \(t\), we have

\[
N_h(t) = e^{-\mu_h t} N_h(0) + \int_0^t e^{\mu_h (s-t)} (\Lambda_h - \delta_h (I_h(s) + J_h(s))) ds
\]

\[
\leq e^{-\mu_h t} N_h(0) + \int_0^t e^{\mu_h (s-t)} \Lambda_h ds
\]

\[
= e^{-\mu_h t} N_h(0) + \frac{\Lambda_h}{\mu_h} (1 - e^{-\mu_h t}).
\]

Note that the derivative of the right-hand side is \(\mu_h e^{-\mu_h t} \left( \frac{\Lambda_h}{\mu_h} - N_h(0) \right)\). Thus, it is a monotone function and its absolute maximum is \(\max(N_h(0), \frac{\Lambda_h}{\mu_h})\).

Rewriting Eq. (4) we have

\[
\frac{dN_h}{dt} = \Lambda_h - (\mu_h + \delta_h) N_h + \delta_h (N_h - I_h - J_h).
\]

Similarly, we have

\[
N_h(t) = e^{-\mu_h + \delta_h} t N_h(0) + \int_0^t e^{(\mu_h + \delta_h) (s-t)} (\Lambda_h + \delta_h (N_h(s) - I_h(s) - J_h(s))) ds
\]

\[
\geq e^{-\mu_h + \delta_h} t N_h(0) + \frac{\Lambda_h}{\mu_h + \delta_h} (1 - e^{-(\mu_h + \delta_h) t}).
\]

Thus, its absolute minimum is \(\min(N_h(0), \frac{\Lambda_h}{\mu_h + \delta_h})\). \(\square\)

Also, it can be easily established that the biologically feasible region \(\mathbb{D} \subset \mathbb{R}^4_+\) defined by

\[
\mathbb{D} = \{ (I_h, J_h, I_v, S_h, V_h, V_B, S_v, L, M_h, V_v) \in \mathbb{R}^4_+: 0 < (N_h)_{\min} \leq N_h \leq (N_h)_{\max}, \text{ and } 0 \leq N_v \leq N_v^0 \}
\]

is a positively-invariant and attracting set to the system (3), where \(N_v^0 = (L((1-u) r_v - \mu_v))/((1-u) r_v)\) is the positive equilibrium of the total mosquito population which exists if \((1-u) r_v / \mu_v > 1\). Its derivation is explained in section 3.1.
3.1. Basic reproduction number in the presence of malaria. For simplicity, let us denote
\[ K_1 = \xi_h + \mu_h, K_2 = \omega_h + \mu_h, K_3 = \nu_h + \mu_h, K_4 = \eta_h + \delta_h + \mu_h, \text{ and } K_5 = \rho_h + \mu_h. \]

Also, let us denote the state variables in the order by
\[ X = (I_h, J_h, I_v, S_h, V_h, V_B, S_v, R_h, M_h, V_v). \]

Under the disease free environment, mosquito population dynamics follows:
\[ \dot{N}_v = ((1 - u)\gamma_v - \mu_v) \left(1 - \frac{N_v}{L(1 - u)\gamma_v - \mu_v}/((1 - u)\gamma_v)\right)N_v. \]

It is easy to see that there is a threshold parameter \( R_v \equiv (1 - u)\gamma_v/\mu_v \) such that mosquitoes die out if \( R_v < 1 \), otherwise mosquitoes persist. With this, the notation \( N_v^0 = \frac{\mu_v(R_v-1)L}{(1-u)\gamma_v} \).

The system \( (3) \) monitors human and female mosquito populations in the presence of the disease. The disease-free equilibrium of model \( (3) \) is given by:
\[ E_{vac}^0 = (I^*_h, J^*_h, I^*_v, S^*_h, V^*_h, V^*_B, S^*_v, R^*_h, M^*_h, V^*_v) \]
where
\[ I^*_h = 0, J^*_h = 0, I^*_v = 0, S^*_h = \frac{\Lambda_h}{K_1}, V^*_h = \frac{\xi_h\Lambda_hK_3}{K_1\mu_h(K_3 + \omega_h)}, V^*_B = \frac{\xi_h\Lambda_h\omega_h}{K_1\mu_h(K_3 + \omega_h)}, \]
\[ S^*_v = \frac{K_1\mu_vN_v^0}{(\chi_h\xi_h + K_1\mu_v)}, R^*_h = 0, M^*_h = 0, \text{ and } V^*_v = \frac{\xi_h\Lambda_h\omega_v}{K_1\mu_v(\chi_v + \xi_h\Lambda_h)}. \]

The basic reproduction number, \( R_{vac} \), of model \( (3) \) is calculated using the next generation approach where \( R_{vac} \) is the spectral radius of the next generation matrix \( [8] \):
\[ R_{vac} = \mu_h \sqrt{\frac{\mu_vC_{vh}C_vh(\gamma_v - 1)L}{(1 - u)\gamma_vK_1\lambda_h(\psi_hC_{hv} + \psi_vK_1)}}. \]

The above basic reproduction number can be further explained by
\[ R_{vac} = \sqrt{R_{vh}R_{hv}} \]
where
\[ R_{vh} = C_{vh} \left( \frac{S^*_h}{N^*_h} \right) \times \frac{1}{\mu_v} \]
is the number of susceptible humans infected by one infectious mosquito, in its life time, introduced to a disease free human environment, and
\[ R_{hv} = C_{hv} \left( \frac{S^*_v}{N^*_h} \right) \times \frac{1}{\mu_h + \delta_h + \eta_h} \]
is the number of mosquitoes infected by one infectious human \( (I^*_h) \), in the mean infectious period, introduced to a disease free mosquitoes environment. It is worth noting that introducing infectious mosquitoes also infect vaccinated but unprotected individuals \( (V^*_v) \). However, infected and vaccinated \( (J^*_v) \) individuals will not produce any new infections to the mosquitoes population. This is in agreement with the observation that \( \nu_h \) does not appear in the basic reproduction number.

The local stability of the disease-free equilibrium is summarized in Theorem 3.2 as in [9].
By making appropriate substitutions, the equation 3.2. Special case: \( \delta_h = 0 \). For the case where there is no disease induced morality, \( \delta_h = 0 \), we have:

\[
N_h^* = \frac{\Lambda_h}{\mu_h}, \quad S_h^* = \frac{\Lambda_h K_4 K_5}{K_1 K_4 K_5 + \mu_h (K_5 + \eta_h) \lambda_h^*}, \quad \lambda_{h1}^* = \frac{C_{hv} \lambda_v^* S_h^*}{K_4 N_h^*}, \quad \lambda_{h2}^* = \frac{\xi_h S_h^*}{\mu_h N_h^*},
\]

\[
I_v^* = \frac{\lambda_{h1}^* N_v^0}{\lambda_{h1}^* + \lambda_{h2}^* + \mu_v}, \quad \text{and} \quad \lambda_v^* = \frac{C_{vh} I_v^*}{N_h^*}.
\]

By making appropriate substitutions, the equation \( \lambda_v^* = \frac{C_{vh} I_v^*}{N_h^*} \) is reduced to:

\[
\lambda_v^* = \frac{N_v^0 \mu_h^2 K_5 \lambda_v^* C_{hv} C_{vh}}{\Lambda_h [\mu_h (\mu_v (K_5 + \eta_h) + C_{hv} K_5) \lambda_v^* + K_4 K_5 (\mu_v K_1 + \xi_h C_{hv})]}
\] (6)

Equation (6) has the following two solutions:

\[
\lambda_v^* = 0, \quad \text{and} \quad \lambda_v^* = \frac{K_5 K_4 (\mu_v K_1 + \xi_h C_{hv}) (R_{vac}^2 - 1)}{\mu_v (K_5 + \eta_h) + C_{hv} K_5}
\]

The following results are established.

**Theorem 3.3.** If \( \delta_h = 0 \) (i.e. \( K_4 = \eta_h + \mu_h \)) in the system 3, the following two properties hold.

(a) There is exactly one malaria endemic equilibrium and it exists only if \( R_{vac} > 1 \).

(b) If \( R_{vac} < 1 \), the disease-free equilibrium, \( E_0^{vac} \), is the only feasible equilibrium and it is locally asymptotically stable.

3.3. Special case: \( \xi_h = 0 \). When \( \xi_h = 0 \) in system 3, the basic reproduction number, denoted by \( R_0 \), is given by:

\[
R_0 = \sqrt{\frac{C_{vh} C_{hv} \mu_h L (R_v - 1)}{(1 - u) r_v K_4 \Lambda_h}}.
\] (7)

In this case, we have, \( V_h^* = V_B^* = J_1^* = M_h^* = V_v^* = 0 \) and hence \( \lambda_{h2}^* = 0 \). Also,

\[
S_h^* = \frac{\Lambda_h}{K_1 + (1 - \frac{\mu_v}{K_4 K_5}) \lambda_v^*}; \quad I_v^* = \frac{\lambda_v^* S_h^*}{K_4 K_5}; \quad R_h^* = \frac{\eta_h \lambda_v^*}{K_4 K_5} S_h^*;
\]

\[
N_h^* = \left( 1 + \frac{K_5 + \eta_h}{K_4 K_5} \lambda_v^* \right) S_h^*, \quad \lambda_{h1}^* = \frac{K_5 C_{hv} \lambda_v^*}{K_4 K_5 + (K_5 + \eta_h) \lambda_v^*}, \quad I_v^* = \frac{\lambda_{h1}^* N_v^0}{\lambda_{h1}^* + \mu_v}, \quad \text{and} \quad \lambda_v^* = \frac{C_{vh} I_v^*}{N_h^*}.
\]

All the state variables and \( \lambda_{h1}^* \) are expressed in terms of \( \lambda_v^* \); and the equation \( \lambda_v^* = \frac{C_{vh} I_v^*}{N_h^*} \) is reduced to:

\[
\lambda_v^* (a(\lambda_v^*)^2 + b\lambda_v^* + c) = 0
\]

where \( a = \Lambda_h (\frac{1}{K_4} + \frac{\eta_h}{K_4 K_5}) (\mu_v K_5 + \mu_v \eta_h + C_{hv} K_5), \quad b = \Lambda_h (2 \mu_v K_5 + 2 \mu_v \eta_h + C_{hv} K_5) - \lambda_v^0 C_{vh} C_{hv} K_5 (1 - \frac{\rho_v \eta_h}{K_4 K_5}), \quad c = \Lambda_h \mu_v K_4 K_5 (1 - R_0^2). \)
Notice that $a > 0$ and $b$ can be re-written as:

$$b = \Lambda_h (2\mu_v K_5 + 2\mu_v \eta_h + C_{hv} K_5) - \frac{\Lambda_h R_0^2 \mu_v K_4 K_5}{\mu_h} (1 - \frac{\rho_h \eta_h}{K_4 K_5}).$$

Then there is a backward bifurcation, when $R_0 = 1$, if and only if

$$b = \Lambda_h (2\mu_v K_5 + 2\mu_v \eta_h + C_{hv} K_5) - \frac{\Lambda_h \mu_v K_4 K_5}{\mu_h} (1 - \frac{\rho_h \eta_h}{K_4 K_5}) < 0.$$  

This can be further represented in terms of $\delta_h$ as

$$\delta_h > \mu_h \left(1 + \eta_h K_5 + C_{hv} \mu_v \right).$$

This result is summarized in the following Theorem.

**Theorem 3.4.** If $\xi_h = 0$ in the system (3), the following two properties hold.

(a) If $R_0 > 1$, there is exactly one malaria endemic equilibrium.
(b) If $R_0 = 1$, a backward bifurcation occurs if and only if the following inequality holds:

$$\delta_h > \mu_h \left(1 + \frac{\eta_h}{K_5} + \frac{C_{hv}}{\mu_v} \right).$$

The above inequality shows that no backward bifurcation can occur when the disease induced mortality rate is less than natural mortality rate. Figure 2 shows that a backward bifurcation occurs when $\delta_h = 4\mu_h$ (see (a) and (b)), but a forward bifurcation occurs when $\delta_h = \mu_h$ (see (c) and (d)). The existence of a backward bifurcation for malaria models has been reported in several research work, which arises often by introducing more mosquito stages (such as the exposed mosquito stage) or in the presence of a loss of immunity. A necessary condition for a backward bifurcation to occur in these models is that the disease-induced death rate is high enough, compared with the natural death rate. In the context of epidemic transmission, high disease-induced death rate will indirectly increase the susceptible pool, which makes the model behaves more like an SI type model, which is often accused for causing backward bifurcation. This result corroborates with the result in for a dengue transmission model. This further suggests that there is a potential danger of backward bifurcation for a severe and deadly malaria strain, thus more efforts are needed to eradicate the disease in this situation. When there is a backward bifurcation, in order to eradicate the disease, we need to further bring the basic reproduction number below the following threshold:

$$R_c = \sqrt{1 - \frac{b^2}{4a\Lambda_h \mu_v K_4 K_5}}.$$  

Notice that

$$R_{vac} = \sqrt{\frac{\mu_h \mu_v}{\xi_h C_{hv} + \mu_v \mu_h + \mu_h \xi_h}} R_0 \leq R_0.$$  

This implies that any effort in vaccination will reduce the basic reproduction number.
Figure 2. The bifurcation diagram for the special case where \( \xi_h = 0 \). The basic reproduction number is calculated with \( u \) varying. The two panels in the first row show a backward bifurcation for \( \delta_h = 4 \mu_h \), which might represent severe malaria version. The two panels in the second row show a forward bifurcation for \( \delta_h = \mu_h \), which might represent a mild version of malaria. The other parameters are listed in Table 1. On the graphs, solid red lines represent the stable endemic equilibrium, dashed blue lines represent the unstable endemic equilibrium, solid green lines represent the stable disease-free equilibrium and dashed green lines represent the unstable disease-free equilibrium.

3.4. Endemic equilibrium. Let \( D_0 = \frac{1}{K_3}, D_1 = \frac{\eta_h}{K_4 K_5}, D_2 = 1 - \rho_h D_1, D_3 = \mu_h (K_4 + \omega_h) \), and \( D_4 = \xi_h \omega_h \). The endemic equilibrium of the system (3) is given by

\[
E_{vac}^* = (I_h^*, J_h^*, I_v^*, S_h^*, V_h^*, V_B^*, S_v^*, R_h^*, M_h^*, V_v^*)
\]

where

\[
S_h^* = \frac{\lambda_h}{K_1 + D_2 \lambda_v}, \quad I_h^* = \lambda_h^* D_0 S_h^*, \quad R_h^* = \lambda_h^* D_1 S_h^*, \quad V_B^* = \frac{D_4 S_h^*}{D_3 + K_2 D_2 \lambda_v},
\]

\[
V_h^* = \frac{(K_3 + D_2 \lambda_v) \xi_h S_h^*}{D_3 + K_2 D_2 \lambda_v^*}, \quad J_h^* = \lambda_v^* D_0 V_B^*, \quad M_h^* = \lambda_v^* D_1 V_B^*,
\]

\[
S_v^* = \frac{\mu_v N_v^0}{\lambda_{h1} + \lambda_{h2} + \mu_v}, \quad I_v^* = \lambda_{h1} S_v^*, \quad V_v^* = \frac{\lambda_{h2} S_v^*}{\mu_v},
\]

Here, \( \lambda_{h1}^* = \frac{C_h I_h^*}{N_h^*} \), \( \lambda_{h2}^* = \frac{C_h (V_v^* + V_B^* + J_h^* + M_h^*)}{N_h^*} \), \( \lambda_v^* = \frac{C_v h I_v^*}{N_h^*} \), and \( N_v^* = S_h^* + I_h^* + R_h^* + V_h^* + V_B^* + J_h^* + M_h^* \). Since \( D_2 > 0 \), \( S_h^* > 0 \) and \( S_h^* \) is expressed in terms of \( \lambda_v^* \), all the remaining components of \( E_{vac}^* \) as well as \( \lambda_{h1}^* \) and \( \lambda_{h2}^* \) are positive and are expressed in terms of \( \lambda_v^* \).

After appropriate substitution and simplification, the equation \( \lambda_v^* = \frac{C_v h I_v^*}{N_h^*} \) is reduced to:

\[
a_4 (\lambda_v^*)^4 + a_3 (\lambda_v^*)^3 + a_2 (\lambda_v^*)^2 + a_1 \lambda_v^* + a_0 = 0
\]

where

\[
D_0 = \xi_h K_3 + D_3 + D_4,
\]
\[ D_1 = \xi_h D_2 + D_0 D_3 + D_0 D_4 + D_1 D_3 + D_1 D_4 + D_2 K_2, \]
\[ D_2 = D_2 K_2 (D_0 + D_1), \]
\[ a_4 = \Lambda_h (\mu_v D_2 + D_0 D_2 C_{hv} K_2) D_2, \]
\[ a_3 = \Lambda_h (C_{hv} \xi_h D_2 + C_{hv} D_0 D_3 + C_{hv} D_0 D_4 + C_{hv} D_1 D_4 + 2 \mu_v D_1) D_2 + \Lambda_h D_0 D_2 C_{hv} K_2 D_1 - D_0 D_2^2 C_{hv} C_{ch} K_2^2 N_v^0, \]
\[ a_2 = \Lambda_h (\xi_h C_{hv} K_3 + 2 \mu_v D_0 + D_4 C_{hv}) D_2 + \Lambda_h (\xi_h D_2 C_{hv} + D_0 D_3 C_{hv} + D_0 D_3 C_{hv} + D_1 D_4 + \mu_v D_3) D_1 + \Lambda_h D_0 D_2 C_{hv} K_2 D_0 - D_0 D_2^2 C_{hv} C_{ch} K_2 (K_1 K_2 + 2 D_3) N_v^0, \]
\[ a_1 = \Lambda_h (C_{hv} \xi_h K_3 + C_{hv} D_4 + 2 \mu_v D_0) D_1 + \Lambda_h C_{hv} (\xi_h D_2 + D_0 D_3 + D_0 D_4 + D_1 D_4) D_0 - D_0 D_2 D_3 C_{hv} C_{ch} (2 K_1 K_2 + D_3) N_v^0, \]
\[ a_0 = \Lambda_h K_1 (\mu_v K_1 + \xi_h C_{hv}) (K_3 + w_h)^2 (1 - R_vac^2). \]

Obviously, \( a_4 > 0 \) and \( a_0 < 0 \) if \( R_vac > 1 \); thus, the polynomial equation in \( [3] \) has at least one positive root, which implies that the system \( [3] \) has at least one endemic equilibrium. Thus, the following result is established.

**Theorem 3.5.** If \( R_vac > 1 \) there is at least one endemic equilibrium to system \( [3] \).

It is easy to see that the basic reproduction number \( R_vac \) is a monotonously decreasing function in terms of \( \xi_h \) and \( u \). This means that any effort in mosquito larvae control or vaccination will reduce the disease burden; however, like in the case of \( \xi_h = 0 \), a backward bifurcation might also occur for the complete model and additional effort is needed in order to eradicate the disease. Figure 3 shows that a backward bifurcation occurs when \( \delta_h = 4 \mu_h \), but a forward bifurcation occurs when \( \delta_h = 0.5 \mu_h \). Here, the basic reproduction number \( R_vac \) and infection prevalence \( I_h \) and \( I_v \) are calculated by varying the value of \( \xi_h \) from 0 to 0.2, while the other parameter values are the same as in Table 1. This is further confirmed from Figure 4, in which the top three panels indicate the disease persists and approaches a fixed level for some initial data when \( \delta_h = 4 \mu_h \) and the bottom three panels indicate the disease almost dies out in 40 years for some other initial data. This clearly indicates that a backward bifurcation occurs when \( \delta_h = 4 \mu_h \). It is worthy to point out that the numerical simulation indicates that a backward bifurcation will occur even when \( \delta_h = \mu_h \). In addition, as the vaccination effort increases, the number of infected individuals decreases but the number of infected individuals with vaccination increases. Figure 5 shows the simulation for parameter values outside of range of backward bifurcation. The top three panels show the simulation for \( \xi_h = 0.001 \), in which \( R_vac = 1.62127 \) and the disease persists and converges to the endemic equilibrium. The bottom three panels show the simulation for \( \xi_h = 0.1 \), in which \( R_vac = 0.45893 \), and the disease asymptotically dies out. Numerical simulations indicate that, when \( \delta_h = 4 \mu_h \) and \( u = 0 \), it requires a minimum value of vaccination effort \( \xi_h = 0.10248 \) to eradicate the disease.

Similar results have been observed when the basic reproduction number \( R_vac \), and the infection prevalence \( I_h \) and \( I_v \) are calculated by varying the value of \( u \). Numerical simulations indicate that, when \( \delta_h = 4 \mu_h \) and \( \xi_h = 0.01 \), it requires a minimum value of mosquito larvae control effort \( u = 0.63845 \) to eradicate the disease.
4. Optimal control formulation and analysis. We formulate an optimal control problem to find an optimal combination of the vaccinations and mosquito control that will minimize the cost of implementing the two vaccinations as well as the number of infected humans and the total mosquito population. The control function $\xi_h(t)$ represents time dependent effort of providing the combined dose of vaccination to un-vaccinated individuals; the control function $\nu_h(t)$ represents time dependent effort of providing the human vaccine dose to vaccinated individuals who lost immunity to the disease; and the control function $u(t)$ represents the control effort that minimizes mosquito breeding such as larvicide; the efforts are practiced on the time interval $[0, T]$, where $T$ is the time (in years) that the control is implemented. To include control, model (3) is modified to:

$$\begin{cases}
\dot{S}_h &= \lambda_h + \rho_h R_h - \lambda_v S_h - (\xi_h(t) + \mu_h) S_h, \\
\dot{I}_h &= \lambda_v S_h - (\eta_h + \mu_h + \delta_h) I_h, \\
\dot{R}_h &= \eta_h I_h - (\rho_h + \mu_h) R_h, \\
\dot{V}_h &= \xi_h(t) S_h + \nu_h(t) V_B - (\omega_h + \mu_h) V_h, \\
\dot{V}_B &= \omega_h V_h + \rho_h M_h - \lambda_v V_B - (\nu_h(t) + \mu_h) V_B, \\
\dot{J}_h &= \lambda_v V_B - (\eta_h + \mu_h + \delta_h) J_h, \\
\dot{M}_h &= \eta_h J_h - (\rho_h + \mu_h) M_h, \\
\dot{S}_v &= (1 - u(t)) B(N_v) N_v - \lambda_h S_v - \lambda_{h2} S_v - \mu_v S_v, \\
\dot{I}_v &= \lambda_{h1} S_v - \mu_v I_v, \\
\dot{V}_v &= \lambda_{h2} S_v - \mu_v V_v.
\end{cases} \tag{10}$$

Figure 3. The bifurcation diagram for the complete model. The basic reproduction number is calculated with $u = 0$ and $\xi_h$ varying from 0 to 0.2. The three panels in the first row show a backward bifurcation when $\delta_h = 4\mu_h$, which might represent severe malaria version. The three panels in the second row show a forward bifurcation when $\delta_h = 0.5\mu_h$, which might represent a mild version of malaria. On the graphs, solid red lines represent the stable endemic equilibrium, dashed blue lines represent the unstable endemic equilibrium, solid green lines represent the stable disease-free equilibrium and dashed green lines represent the unstable disease-free equilibrium.
Figure 4. Simulation for different initial data when $\delta_h = 4\mu_h$, $u = 0$, and $\xi_h = 0.03$. The basic reproduction number is $R_{vac} = 0.95907$. The three panels in the first row show the disease persists for some initial data. The three panels in the second row show the disease asymptotically dies out for some other initial data.

Figure 5. Simulation for different vaccination effort when $\delta_h = 4\mu_h$ and $u = 0$. The three panels in the first row are generated when $\xi_h = 0.001$, in which $R_{vac} = 1.62127$, and the disease persists. The three panels in the second row are generated when $\xi_h = 0.1$, in which $R_{vac} = 0.45893$, and the disease asymptotically dies out.
with initial conditions

\[ S_h(0) = S_h^0, I_h(0) = I_h^0, R_h(0) = R_h^0, V_h(0) = V_h^0, V_B(0) = V_B^0, \]
\[ J_h(0) = J_h^0, M_h(0) = M_h^0, S_v(0) = S_v^0, I_v(0) = I_v^0, V_v(0) = V_v^0. \]  

(11)

The objective functional corresponding to the model described by the equation system (10) is given by:

\[ J(\xi_h, \nu_h, u) = \int_0^T (A_1 I_h(t) + A_2 J_h(t)) dt + \int_0^T A_3 I_v(t) dt \]
\[ + \int_0^T (B_1 \xi_h(t) S_h(t) + B_2 \nu_h(t) V_B(t) + C_1 \xi_h^2(t) + C_2 \nu_h^2(t)) dt \]
\[ + \int_0^T (B_3 u(t) N_v(t) + C_3 u^2(t)) dt \]  

(12)

where \( A_i, i = 1 \cdots 3, B_j, j = 1, 2 \) and \( C_k, k = 1 \cdots 3 \) are positive constants that balance the relative importance for the terms in \( J \).

In the objective functional, \( J \), the first term \( \int_0^T (A_1 I_h(t) + A_2 J_h(t)) dt \) represents the total number of infected humans over the time period \( T \) to be minimized; the term \( \int_0^T A_3 I_v(t) dt \) represents the total number of infected mosquitoes to be minimized; \( \int_0^T (B_1 \xi_h(t) S_h(t) + B_2 \nu_h(t) V_B(t) + C_1 \xi_h^2(t) + C_2 \nu_h^2(t)) dt \) represents the cost of implementing both the human and transmission-blocking vaccines; and \( \int_0^T (B_3 u(t) N_v(t) + C_3 u^2(t)) dt \) represents the cost of implementing larvacide control.

We seek an optimal control \((\xi_h^*, \nu_h^*, u^*) \in U\) such that

\[ J(\xi_h^*, \nu_h^*, u^*) = \min_{(\xi_h, \nu_h, u) \in U} J(\xi_h, \nu_h, u) \]

subject to system (10), where the control set, \( U \), is:

\[ U = \{ (\xi_h, \nu_h, u) \in (L^\infty(0,T))^3 \mid 0 \leq \xi_h \leq \xi_h^{max}, 0 \leq \nu_h \leq \nu_h^{max}, 0 \leq u \leq u^{max} \} \],

where the inequalities in \( U \) hold a.e. in \((0,T)\), and \( \xi_h^{max}, \nu_h^{max} \) and \( u^{max} \) are upper bounds of the control parameters \( \xi_h, \nu_h \) and \( u \), respectively.

4.1. Existence of an optimal control.

**Theorem 4.1.** There exist optimal controls \( \xi_h^*, \nu_h^* \) and \( u^* \) which minimize the objective functional \( J \) subject to system (10).

**Proof.** Assume that the state solutions of system (10) are bounded in finite time. Due to uniform \( L^\infty \) bounds on the controls and states, there exists a minimizing sequence \( \{ \xi_h^n(\cdot), \nu_h^n(\cdot), u^n(\cdot) \}_{n \geq 1} \). That is,

\[ \lim_{n \to \infty} J(\xi_h^n, \nu_h^n, u^n) = \inf_{(\xi_h, \nu_h, u) \in U} J(\xi_h, \nu_h, u). \]

Let \( S_h^n, I_h^n, R_h^n, V_h^n, V_B^n, J_h^n, M_h^n, S_v^n, I_v^n, V_v^n \) be state trajectories corresponding to \( \xi_h^n(\cdot), \nu_h^n(\cdot), u^n(\cdot) \). Due to uniform boundedness of state sequences, their derivatives are uniformly bounded, and the state sequences are equicontinuous. By the Arzelà-Ascoli Theorem, there exist \( S_h^*, I_h^*, R_h^*, V_h^*, V_B^*, J_h^*, M_h^*, S_v^*, I_v^*, V_v^* \) such that on a subsequence,

\( (S_h^n, I_h^n, R_h^n, V_h^n, V_B^n, J_h^n, M_h^n, S_v^n, I_v^n, V_v^n) \to (S_h^*, I_h^*, R_h^*, V_h^*, V_B^*, J_h^*, M_h^*, S_v^*, I_v^*, V_v^*) \)

uniformly on \([0,T]\). The sequences of controls are uniformly bounded, so there exist subsequences \( \{ \xi_h^n\}, \{ \nu_h^n\}, \{ u^n\} \) and controls \( \xi_h^*, \nu_h^* \) and \( u^* \) such that

\[ \xi_h^n \to \xi_h^*, \ \nu_h^n \to \nu_h^*, \ \ u^n \to u^* \text{ weakly in } L^2([0,T]). \]
Using the lower-semicontinuity of $L^2$-norm with respect to weak convergence, we have

\[
J(\xi_h^*, \nu_h^*, u^*) \leq \liminf_{n \to \infty} \int_0^T \left[ A_1 I_h^n(t) + A_2 J_h^n(t) + A_3 I_v^n(t) + B_1 \xi_h^n(t) S_h^n(t) + B_2 \nu_h^n(t) V_B^n(t) + B_3 u^n(t) N_v^n(t) + C_1 (\xi_h^n(t))^2 + C_2 (\nu_h^n(t))^2 + C_3 (u^n(t))^2 \right] dt
\]

\[
= \lim_{n \to \infty} J(\xi_h^n, \nu_h^n, u^n)
\]

\[
= \inf_{(\xi_h, \nu_h, u) \in U} J(\xi_h, \nu_h, u).
\]

Using the convergence of the state sequences, and passing to the limit in the ODE system, we have that $S_h^*, I_h^*, R_h^*, V_B^*, J_{h}^*, M_{h}^*, S_v^*, I_v^*$ and $V_v^*$ are the states corresponding to the optimal control $(\xi_h^*, \nu_h^*, u^*)$.

We use Pontryagin’s Maximum principle [19] to derive necessary conditions that an optimal control must satisfy. This principle converts the problem of minimizing the objective functional [12] subject to the state system [10] into a problem of minimizing a Hamiltonian $H$, defined below, with respect to $(\xi_h, \nu_h, u)$. We form the Hamiltonian $H$:

\[
H = A_1 I_h + A_2 J_h + A_3 I_v + B_1 \xi_h S_h + B_2 \nu_h V_B + B_3 u N_v + C_1 (\xi_h)^2 + C_2 (\nu_h)^2 + C_3 u^2
\]

\[
+ \lambda_1 (\lambda_h + \rho_h R_h - \lambda_v S_h - (\xi_h(t) + \mu_h) S_h) + \lambda_2 (\lambda_v S_h - (\eta_h + \mu_h + \delta_h) I_h) + \lambda_3 (\eta_h I_h - (\rho_h + \mu_h) R_h)
\]

\[
+ \lambda_4 (\xi_h(t)) S_h + \nu_h(t) V_B - (\omega_h + \mu_h) V_h) + \lambda_5 (\omega_h V_h + \rho_h M_h - \lambda_v V_B - (\nu_h(t) + \mu_h) V_B)
\]

\[
+ \lambda_6 (\lambda_v V_B - (\eta_h + \mu_h + \delta_h) J_h) + \lambda_7 (\eta_h J_h - (\rho_h + \mu_h) M_h)
\]

\[
+ \lambda_8 (1 - u(t)) B(N_v) N_v - \lambda_{h1} S_v - \lambda_{h2} S_v - \mu_v S_v)
\]

\[
+ \lambda_9 (\lambda_{h1} S_v - \mu_v I_v) + \lambda_{10} (\lambda_{h2} S_v - \mu_v V_v).
\]

By differentiating the Hamiltonian function with respect to each state variable, we obtain the differential equations governing the adjoint variables:

\[
\dot{\lambda}_1 = -\frac{\partial H}{\partial S_h}, \quad \dot{\lambda}_2 = -\frac{\partial H}{\partial I_h}, \quad \dot{\lambda}_3 = -\frac{\partial H}{\partial R_h}, \quad \dot{\lambda}_4 = -\frac{\partial H}{\partial V_h}, \quad \dot{\lambda}_5 = -\frac{\partial H}{\partial V_B},
\]

\[
\dot{\lambda}_6 = -\frac{\partial H}{\partial J_h}, \quad \dot{\lambda}_7 = -\frac{\partial H}{\partial M_h}, \quad \dot{\lambda}_8 = -\frac{\partial H}{\partial S_v}, \quad \dot{\lambda}_9 = -\frac{\partial H}{\partial I_v}, \quad \text{and} \quad \dot{\lambda}_{10} = -\frac{\partial H}{\partial V_v}.
\]

This gives the adjoint system:

\[
\dot{\lambda}_1 = -\lambda_1 (-\lambda_v + \lambda_v \frac{S_h}{N_h} - \xi_h - \mu_h) - \lambda_2 (\lambda_v - \lambda_v \frac{S_h}{N_h}) - \lambda_4 \xi_h - \lambda_5 \lambda_v \frac{V_B}{N_h}
\]

\[
+ \lambda_6 \lambda_v \frac{V_B}{N_h} - \lambda_8 (\mu_{h1} \frac{S_v}{N_h} + \mu_{h2} \frac{S_v}{N_h}) + \lambda_9 \lambda_{h1} \frac{S_v}{N_h} + \lambda_{10} \lambda_{h2} \frac{S_v}{N_h} - B_1 \xi_h,
\]

\[
\dot{\lambda}_2 = -\lambda_1 \lambda_v \frac{S_h}{N_h} + \lambda_2 (\lambda_v \frac{S_h}{N_h} + K_4) - \lambda_3 \eta_h - \lambda_5 \lambda_v \frac{V_B}{N_h} + \lambda_6 \lambda_v \frac{V_B}{N_h}
\]

\[
- \lambda_8 \frac{S_v}{N_h} (-C_h v + \lambda_{h1} + \lambda_{h2}) - \lambda_9 \frac{S_v}{N_h} (C_h v - \lambda_{h1}) + \lambda_{10} \lambda_{h2} \frac{S_v}{N_h} - A_1,
\]
\[ \dot{\lambda}_3 = -\lambda_1 (\rho_h + \lambda_v \frac{S_h}{N_h}) + \lambda_2 \lambda_v \frac{S_h}{N_h} + \lambda_3 K_5 - \lambda_5 \lambda_v \frac{V_B}{N_h} + \lambda_6 \lambda_v \frac{V_B}{N_h} - \lambda_8 \frac{S_v}{N_h} (\lambda_{h1} + \lambda_{h2}) + \lambda_9 \lambda_{h1} \frac{S_v}{N_h} + \lambda_{10} \lambda_{h2} \frac{S_v}{N_h} \]

\[ \dot{\lambda}_4 = -\lambda_1 \lambda_v \frac{S_h}{N_h} + \lambda_2 \lambda_v \frac{S_h}{N_h} + \lambda_4 K_2 - \lambda_5 (\omega_h + \lambda_v \frac{V_B}{N_h}) + \lambda_6 \lambda_v \frac{V_B}{N_h} - \lambda_8 \frac{S_v}{N_h} (\lambda_{h1} - C_{hv} + \lambda_{h2}) + \lambda_9 \lambda_{h1} \frac{S_v}{N_h} - \lambda_{10} \frac{S_v}{N_h} (C_{hv} - \lambda_{h2}) \]

\[ \dot{\lambda}_5 = -\lambda_1 \lambda_v \frac{S_h}{N_h} + \lambda_2 \lambda_v \frac{S_h}{N_h} - \lambda_4 \nu_h - \lambda_5 (\lambda_v (\frac{V_B}{N_h} - 1) - \nu_h - \mu_h) - \lambda_6 \lambda_v (1 - \frac{V_B}{N_h}) - \lambda_8 \frac{S_v}{N_h} (\lambda_{h1} - C_{hv} + \lambda_{h2}) + \lambda_9 \lambda_{h1} \frac{S_v}{N_h} - \lambda_{10} \frac{S_v}{N_h} (C_{hv} - \lambda_{h2}) \]

\[ \dot{\lambda}_6 = -\lambda_1 \lambda_v \frac{S_h}{N_h} + \lambda_2 \lambda_v \frac{S_h}{N_h} - \lambda_5 \lambda_v \frac{V_B}{N_h} + \lambda_6 (\lambda_v \frac{V_B}{N_h} + K_4) - \lambda_7 \eta_h - \lambda_8 \frac{S_v}{N_h} (\lambda_{h1} - C_{hv} + \lambda_{h2}) + \lambda_9 \lambda_{h1} \frac{S_v}{N_h} - \lambda_{10} \frac{S_v}{N_h} (C_{hv} - \lambda_{h2}) - A_2 \]

\[ \dot{\lambda}_7 = -\lambda_1 \lambda_v \frac{S_h}{N_h} + \lambda_2 \lambda_v \frac{S_h}{N_h} - \lambda_5 (\rho_h + \lambda_v \frac{V_B}{N_h}) + \lambda_6 \lambda_v \frac{V_B}{N_h} + \lambda_7 K_5 - \lambda_8 \frac{S_v}{N_h} (\lambda_{h1} - C_{hv} + \lambda_{h2}) + \lambda_9 \lambda_{h1} \frac{S_v}{N_h} - \lambda_{10} \frac{S_v}{N_h} (C_{hv} - \lambda_{h2}) \]

\[ \dot{\lambda}_8 = -\lambda_8 \left( (1 - u) \frac{r_v}{L} \left( 1 - \frac{2N_v}{L} \right) - \lambda_{h2} - \lambda_{h1} \right) - \lambda_9 \lambda_{h1} - \lambda_{10} \lambda_{h2} - A_3 u \]

\[ \dot{\lambda}_9 = \lambda_1 C_{vh} \frac{S_h}{N_h} - \lambda_2 C_{vh} \frac{S_h}{N_h} + \lambda_5 C_{vh} \frac{V_B}{N_h} - \lambda_6 C_{vh} \frac{V_B}{N_h} - \lambda_8 (1 - u) \frac{r_v}{L} \left( 1 - \frac{2N_v}{L} \right) + \lambda_9 \mu_v - A_3 - B_3 u \]

\[ \dot{\lambda}_{10} = -\lambda_8 (1 - u) \left( 1 - \frac{2N_v}{L} \right) + \lambda_{10} \mu_v - B_3 u \]

together with the transversality conditions [19]:

\[ \lambda_i (T) = 0, \text{ for } i = 1, 2, 3, ..., 10. \]

In characterizing the optimal control, we differentiate the Hamiltonian $H$ in equation [13] to have:

\[ \frac{\partial H}{\partial \xi_h} = 0, \quad \frac{\partial H}{\partial \nu_h} = 0, \text{ and } \frac{\partial H}{\partial u} = 0, \]

on the interior of the control set, where

\[ \frac{\partial H}{\partial \xi_h} = B_1 S_h + 2C_1 \xi_h - S_h \lambda_1 + S_h \lambda_4, \]

\[ \frac{\partial H}{\partial \nu_h} = B_2 V_B + 2C_2 \nu_h + V_B \lambda_4 - V_B \lambda_5, \]

\[ \frac{\partial H}{\partial u} = B_3 N_v + 2C_3 u - B(N_v) \lambda_8. \]
From Pontryagin’s principle [19], we establish the following theorem:

**Theorem 4.2.** Given an optimal, \((\xi_h^*, \nu_h^*, u^*)\), and solutions, \(S_h, I_h, R_h, V_h, V_B, J_h, M_h, S_v, I_v,\) and \(V_v\) of the corresponding state system [10], then there exist adjoint variables \(\lambda_i\) for \(i = 1, 2, 3, ..., 10\), which satisfy the adjoint system in [14] and transversality conditions [15]. Furthermore, we characterize this optimal control \((\xi_h^*, \nu_h^*, u^*)\) as

\[
\begin{align*}
\xi_h^* &= \max \left\{ 0, \min \left\{ \xi_{\max}, \frac{S_h (\lambda_1 - \lambda_4 - B_1)}{2C_1} \right\} \right\}, \\
\nu_h^* &= \max \left\{ 0, \min \left\{ \nu_{\max}, \frac{V_B (\lambda_5 - \lambda_4 - B_2)}{2C_2} \right\} \right\}, \\
u^* &= \max \left\{ u_{\min}, \min \left\{ u_{\max}, \frac{N_v \left( \nu_s r_v \left( 1 - \frac{N_v}{L_v} \right) - B_3 \right)}{2C_3} \right\} \right\}.
\end{align*}
\]

The adjoint system in equation [14] is linear in \(\lambda_j\), \(j = 1, 2, ..., 10\). Since we have a linear system in finite time with bounded coefficients, it follows that \(\lambda_j\), \(j = 1, 2, ..., 10\) are uniformly bounded. Using the boundedness of the state and adjoint functions, we can show that the solution of the optimality system is unique for small time \(T\), which gives the uniqueness of the optimal control. This type of “small time” uniqueness result is standard in nonlinear systems with opposite orientations [11].

**Theorem 4.3.** For \(T\) sufficiently small, the optimal control is unique.

5. **Numerical results.** The optimal control is obtained numerically by solving the optimality system, consisting of the state system, adjoint system and control characterization. First, we solve system [10] with a guess for the controls forward in time, over interval \([0, T]\), using MATLAB function ode45 and the initial conditions in equation [11]. Then, the system [14] is solved by an ode45 backward in time using solutions from the previous step and the transversality conditions in equation [15]. The controls are updated by using a convex combination of the previous controls and the values from the characterizations [16]. This process ends when the values of the approximations at the previous iterations are very close to the ones at the previous iteration, for details see [16].

We investigate and compare numerical results using various combinations of three controls in the following scenarios:

**Case 0.** without control, (i.e., \(\xi_h = 0, \nu_h = 0,\) and \(u = 0\));

**Case 1.** optimize mixed transmission-blocking & human vaccination \(\xi_h\) while human vaccination \(\nu_h\) and vector control \(u\) are set to zero, (i.e., \(\xi_h \geq 0, \nu_h = 0,\) and \(u = 0\));

**Case 2.** optimize vector control \(u\) while mixed transmission-blocking & human vaccination \(\xi_h\) and human vaccination \(\nu_h\) are set to zero, (i.e., \(u \geq 0, \xi_h = 0,\) and \(\nu_h = 0\));

**Case 3.** optimize mixed transmission-blocking & human vaccination \(\xi_h\) and vector control \(u\) while human vaccination \(\nu_h\) is set to zero, (i.e., \(\xi_h \geq 0, u \geq 0,\) and \(\nu_h = 0\));

**Case 4.** optimize mixed transmission-blocking & human vaccination \(\xi_h\) and human vaccination \(\nu_h\) while vector control \(u\) is set to zero, (i.e., \(\xi_h \geq 0, \nu_h \geq 0,\) and \(u = 0\));
Case 5. optimize mixed transmission-blocking & human vaccination $\xi_h$, human vaccination $\nu_h$ and vector control $u$, (i.e., $\xi_h \geq 0$, $\nu_h \geq 0$, and $u \geq 0$).

Since the first dose of vaccine is the mixed human and transmission-blocking (i.e. $\xi_h$) vaccine, the case where the human vaccination is optimized in the absence of the mixed transmission and human vaccination (i.e. $\nu_h \geq 0$ and $\xi_h = 0$) is untenable.

In [25], vaccination cost was estimated at $7 per dose and distribution cost was estimated at $0.35 per dose; using this estimation, we set $B_1 = 7.3$. We assume that $B_1 \geq B_2 > B_3$, which is based on the assumption that the cost of implementing the mixed TBV & HV vaccination program is more expensive than the cost of implementing the HV vaccination program alone; and implementing vector control program is cheaper than vaccination program. Table 2 gives a list of values of weight constants used in our numerical simulations to solve the optimal control problem; other parameter values are listed in Table 1, for which the basic reproduction number of the autonomous system is $R_{vac} = 3.0459$.

Table 2. Values for the parameters for our numerical scenarios.

| Parameter | Value | Parameter | Value | Parameter | Value | Parameter | Value |
|-----------|-------|-----------|-------|-----------|-------|-----------|-------|
| $A_1$     | 7.3   | $B_1$     | $A_1$ | $C_1$     | 100   | $\xi_h^{max}$ | $\ln(4)/4$ |
| $A_2$     | $A_1$ | $B_2$     | $B_1/2$ | $C_2$     | 100   | $\nu_h^{max}$ | $\ln(4)/4$ |
| $A_3$     | $A_1/10$ | $B_3$    | $B_1/100$ | $C_3$     | 100   | $u^{max}$ | 0.4 |

In Figures 6 – 9 we chose the upper bound of the controls $\xi_h$ and $\nu_h$, such that $\xi_h^{max} = \nu_h^{max} = \ln(4)/4$, which is equivalent to 75% of the population in a closed susceptible population vaccinated in 4 years, while the upper bound for the vector control, $u$, is $u^{max} = 0.4$. The optimal solution to the control problem is solved over a time period of 6 years. In Figures 6 – 8, we choose the initial value as the endemic equilibrium without control: $S_h^0 = 3522$, $I_h^0 = 3924$, $R_h^0 = 1944$, $V_h^0 = 0$, $V_B^0 = 0$, $J_h^0 = 0$, $M_h^0 = 0$, $S_v^0 = 6.1645 \times 10^4$, $I_v^0 = 1.3345 \times 10^4$, and $V_v^0 = 0$.

![Figure 6](image-url)

Figure 6. Optimal control solution for Case 5 in which the initial values are set to be the endemic equilibrium when no control is applied.

In Figure 6, we presented the optimal control solution for Case 5 strategy. In this figure, the optimal mixed vaccination control $\xi_h$ is at the upper bound for the first 3 years and 3 months, and then drops to zero and stay at zero until the end of six years; the human vaccine control, $\nu_h$, is initially zero, then increases to the upper bound slowly for one year, and then drops slowly to zero for the next one year and two months, and stays at zero until the end of the sixth year; and the
optimal vector control, \( u \), is at the upper bound for five years and 9 months, and then drops to zero. Also, in Figure 7 we presented the optimal solution for the state variables for Case 5 strategy and solution for the strategy without control. As it can be seen in the Figures 7 (a) – (j), the control strategy leads to reduce the number of infectious humans \( I_h \) and the number of infectious mosquitoes \( I_v \); at the end of the control period, the control diminishes the sizes of \( I_h \) by 75% and \( I_v \) by approximately 66% compared to the sizes in the absence of control.

**Figure 7.** Optimal solution of human and mosquito population for Case 5.

In Figure 8, we presented the optimal control and optimal infectious state variable solutions for Case 4 control strategy and for the case without control. At the end of the control period, the control strategy reduces the number of infected humans by approximately 64.3% and the number of infected mosquitoes by approximately 65.3% compared to the case without control. The control profile is shown in Figures 8 (d) & (e), the optimal mixed vaccination control, \( \xi_h \), is at the upper bound for the first three years and ten months then drops to zero; and the human vaccine control, \( \nu_h \), is zero initially, then increases to the upper bound slowly for seven months, and then stays at the upper bound until the end of the third year, and then drops to zero and stayed at zero for three years (until the end of the sixth year). From Figures 7 and 8 we can conclude that the performance of the control strategy Case 5 is better than the control strategy Case 4 in reducing human infections.

Also, for comparison, in Figure 9 we choose initial value for the state variables with low level of infections: \( S_0^h = 4000 \), \( I_0^h = 10 \), \( R_0^h = 2 \), \( V_B^0 = 0 \), \( J_h^0 = 0 \), \( M_h^0 = 0 \), \( R_h^0 = 0 \), \( S_0^v = 10000 \), \( I_0^v = 10 \), and \( V_v^0 = 0 \). Optimal solution for the control variables and optimal solution for the state variables are presented for the control strategy Case 5 and for the case without control. Without control, the value of the state variables reaches equilibrium approximately after two years, and with control, the infectious human and mosquito populations increase at slow rates. By the end of the sixth year, the control strategy approximately reduces the number of infected
Figure 8. Optimal control solution for Case 4.

Figure 9. Optimal control solution for Case 5 control strategy with low level of infections as initial values for the state variables: \( S_0^h = 4000, I_0^h = 10, R_0^h = 2, V_0^h = 0, J_0^h = 0, M_0^h = 0, R_0^v = 0, S_0^v = 10000, I_0^v = 10, \) and \( V_0^v = 0. \)
humans by 61% and the number of infected mosquitoes by 77% compared to the case without control. The optimal mixed vaccination control $\xi_h$ is at the upper bound for the first four years and two months, then dropped to zero afterwards; the human vaccine control, $\nu_h$, is initially zero for the first year, then increases to the upper bound slowly for a year, and stayed at the upper bound for a year, followed by a decrease to zero afterwards; and the optimal vector control, $u$, is at the upper bound for five years and 9 months, and then drops to zero. With control, the number of infected humans and mosquitoes is low and increases at slow rate throughout the control period. By comparing this result with the number of infectious individuals with and without control at the end of the control period in Figure 7, we observe that, introducing the control program in an area with low initial infections is more effective than in areas with high initial number of infections in terms of keeping the infection at a low level throughout the control period.

In Table 3, all control strategies are compared based on the values of the objective functional at the optimal control solution (column two) and at constant maximum control (column three). The fourth column is the percentage cost decrease of each strategy at optimal control compared to strategy with constant maximum control. For the constant maximum control we set the controls $\xi_h$, $\nu_h$, and $u$ at their respective upper bound values. From the table, it can be observed that the cost values using the optimal controls are lower than the values using the constant controls for each case. In particular, in Case 5, the cost can be reduced by 10.23% using optimal control strategy compared with using the constant control strategy. The cost over the control period (six years) for the case without any control is 230,787, which is higher than the values of the cost functionals for all five cases we considered. In addition, the cost is ranked from high to low in in Case 2, 1, 4, 3, 5. In this regards, the best strategies are Cases 5 and 3. We also present, in Table 4, the percentage decrease in cost for each strategy at optimal control compared to the optimal cost with the strategy in Case 0 (third column) and the optimal cost with the strategy in Case 2 (fourth column). These results show the need to implement different strategies, and emphasizes the need for vaccination.

Table 3. Values of the objective functional at the optimal control solution (column two) and at the upper bound values of the non-zero controls (column three); the fourth column is the percentage decrease in cost for each strategy at optimal control compared to strategy with maximum control.

| Strategy/Control | Cost with optimal control | Cost with constant maximum control | Percentage decrease in cost at Optimal Control compared to maximum control |
|------------------|---------------------------|-----------------------------------|--------------------------------------------------------------------------|
| Case 1           | 181,345                   | 191,066                           | 5.99%                                                                    |
| Case 2           | 199,938                   | 199,943                           | 0.0025%                                                                  |
| Case 3           | 157,672                   | 171,830                           | 8.24%                                                                    |
| Case 4           | 181,129                   | 193,335                           | 6.31%                                                                    |
| Case 5           | 157,635                   | 175,596                           | 10.23%                                                                   |

Also, for all strategies we did a comparison based on minimum number of infected humans and mosquitoes, and the result is consistent with the above ranking (Figures 7–9). By the end of the sixth year, the control strategy in Case 5 has minimum number of infected humans and mosquitoes, and the case without any control has the highest number of infected humans and mosquitoes.
Table 4. Values of the cost functional at the optimal control solution (column two); percentage cost decrease of each strategy at optimal control compared to strategy without control, Case 0 (column three); and percentage decrease in cost for each strategy at optimal control compared to strategy in Case 2 at optimal control, (column four).

| Strategy/Control | Cost with optimal control | Percentage cost decrease compared with Case 0 | Percentage decrease in cost compared with Case 2 |
|------------------|---------------------------|-----------------------------------------------|--------------------------------------------------|
| Case 1           | 181,345                   | 27.26%                                        | 10.25%                                           |
| Case 2           | 199,938                   | 15.43%                                        | 0.0%                                             |
| Case 3           | 157,672                   | 46.37%                                        | 26.81%                                           |
| Case 4           | 181,129                   | 27.42%                                        | 10.38%                                           |
| Case 5           | 157,635                   | 46.41%                                        | 26.84%                                           |

Finally, we run several optimal control simulations for different values of $\xi_h^{max}$, $\nu_h^{max}$ and $u^{max}$. The results show that for all strategies, the number of infected humans and mosquitoes as well as the values of the objective functional (or cost) decrease as the values of the upper bounds, $\xi_h^{max}$, $\nu_h^{max}$ and $u^{max}$, increase.

6. Conclusion. We proposed a new mathematical model studying control strategies of malaria transmission, more specifically through vaccination and a larvae control on mosquitoes. We demonstrated analytically that a backward bifurcation occurs if the disease-induced death rate is large enough in the case where no vaccination is employed (i.e., $\xi_h = 0$). For the case where vaccination is employed, we demonstrated numerically that a backward bifurcation might still or even more likely occur when additional death rate due to infection is large enough. This is because the vaccines we considered are a combination of the lifetime long effective transmission-blocking vaccine and a temporarily protected human vaccine. When the disease-induced death rate is large, the proportion of susceptible pool will be larger, which will cause a backward bifurcation.

The basic reproduction number is a decreasing function of both vaccination effort $\xi_h$ and the mosquito larvae control $u$, which indicates that any effort on these controls will lower the burden of the disease. Numerical simulation suggests that employment of both control strategies will help eradicate the disease more efficiently.

We investigated optimal vaccination and vector control over a six-year period to gain qualitative understanding on how these three controls should be used to reduce disease prevalence in malaria endemic and non-endemic settings. Our results show that the combination of transmission-blocking and human vaccines integrated with vector control (or Case 5) has the highest impact in reducing the number of infected humans and mosquitoes as well as in minimizing cost. This is followed by the control with mixed vaccinations ($\xi_h \geq 0$) and vector control ($u \geq 0$), but without human vaccination ($\nu_h = 0$) or Case 3 strategy; and the strategy with vector control alone (or Case 2) has the least impact. From the comparison in Figures 6–9 as well as from Tables 3–4, we observe that there is no significant difference between the strategies with and without administering human vaccine in reducing number of infected humans and mosquitoes. From these results, in areas where resources are limited, the control strategy with the combination of the mixed vaccination ($\xi_h \geq 0$) and the vector control ($u \geq 0$) is recommended. Also, our results suggest
that, at optimal control, as the vaccination and vector control efforts increase (or the upper bounds of the control parameters increase) the disease prevalence and cost decreases. For the parameter values we used in the simulations, comparing with the case without control, the optimal control in Case 5 reduces infection in humans by 75%, infection in mosquitoes by 66%, and the direct cost by 46.41%; also, compared to the strategy with constant maximum control, the optimal control in Case 5 reduces the total cost by 10.23%. Finally, we compare simulation results when the initial values of state variables are at malaria endemic equilibrium without control (Figure 7) with the simulation results when the initial values are at low level of infections (Figure 9). We observe that, in keeping the infection at a low level throughout the control period, the implementation of the control program in an area with low initial infections is more effective than in areas with endemic malaria infections.

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