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A MATHEMATICAL MODEL STUDYING MOSQUITO-STAGE TRANSMISSION-BLOCKING VACCINES

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Abstract. A compartmental deterministic model is proposed to evaluate the effectiveness of transmission-blocking vaccines of malaria, which targets at the parasite stage in the mosquito. The model is rigorously analyzed and numerical simulations are performed. The results and implications are discussed.

1. **Introduction.** Malaria is a life-threatening disease caused by *Plasmodium* parasites that are transmitted to people through the bites of infected mosquitoes. There are four types of human malaria: *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*, among which *P. falciparum* and *P. vivax* are the most common and *P. falciparum* is the most deadly. According to the *World malaria report 2011*, there are 3.3 billion people in 106 countries and territories living in areas at risk of malaria transmission; and there were about 216 million cases of malaria infection and 655,000 deaths due to malaria in 2010. Malaria is the most prevalent tropical and subtropical parasitic disease and the leading cause of mortality and morbidity in some Africa countries. For a mosquito to feed on a human, it must actively seek the human host. This mosquito can systematically target and identify human beings [10, 22] and once attracted, it may seek and bite humans as many times as possible until it takes a blood meal. 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). For example, the long lifespan and strong human-biting habit of the African mosquito species is the main reason why more than 85% of the world's malaria deaths are in Africa. Transmission also depends on climatic conditions that may affect the number and survival of mosquitoes, such as rainfall patterns, temperature and humidity. In many places, transmission is seasonal, with the peak during and just after the rainy season.

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Uncomplicated malaria may be treated with oral medications such as artemisinins in combination with other antimalarials (known as artemisinin-combination therapy, or ACT.) The success of treatment varies, depending on what strain of malaria the patient has, whether or not the parasites are drug-resistant [15, 21, 34], and whether or not the patient is able to complete the course of drugs needed. Malaria has been successfully eliminated from many countries of the world. However, the elimination process slowed down after the effort to eradicate malaria worldwide was abandoned some 40 years ago. Since Australia and Singapore were certificated as malaria-free by WHO in the 1980s, the United Arab Emirates was the first to be certificated until 2007 [26]. During the process of the elimination, vector control using chemicals such as dichlorodiphenyltrichloroethane (DDT) played an essential role. However, this strategy has been gradually abandoned because it caused ecological impact of chemical use [36]. Currently, an "integrated vector management" (IVM) [36] is employed, which reinforces between health and environment, optimizing benefits to both. These interventions include vector control (such as indoor residual sprays (IRS), space spraying, and chemical larvicides and adulticides) and personal protection/prevention (such as insecticide-treated nets (ITNs) and antimalaria drugs.)

Recent international commitments to malaria elimination and eradication have drawn attention of the development of new tools. One important piece is vaccination development. There are mainly two types of vaccines of malaria including those targeting the parasite stage that are exposed only in the mosquito, referred to as transmission-blocking vaccines (TBVs) and those targeting at the parasite stage that are exposed only in the human. The first effective human-stage vaccine against malaria, known as RTS, S has been developed by GlaxoSmithKline and PATH Malaria Vaccine Initiative, which receives fundings from the Bill and Melinda Gates Foundation. A study in a recent phase 3 clinical trial of the vaccine in Africa showed roughly 50% reduction in malaria cases in a 12 month period following vaccination [24, 29, 35]. In addition, several mosquito-stage antigens, 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 [30]. However, none have yet passed early stages of clinical testing. In the rest of the paper, TBVs are referred to the vaccine targeting the parasites at the mosquito stage.

Mathematical models and simulations have been used to provide an explicit framework for understanding the malaria transmission and make predictions by analyzing the modeling results whence giving recommendations to policy makers for over 100 years. Grassi and Ross discovered the mosquito's role in the parasite life cycle and transmission in 1897, and Ross was one among the first to use mathematical models to study transmission of malaria in early 1900. Malaria transmission models originated with Ronald Ross during a trip to organize malaria control in Mauritius (1907-1908) [28], but the models of George Macdonald [19] were applied more systematically during the Global Malaria Eradication Program (GMEP) from 1955 to 1969. Over the past 100 years, many mathematical models were proposed to address different issues from different perspectives, among which the most popular is epidemiological compartment models which are predominantly deterministic and differential equations based [20]. In particular, several mathematical models have been developed to study the impacts of drug resistance and insecticide resistance on the disease [2, 11, 14, 15]; impact of immunity [3, 12, 15, 16]; impact of transmission

intensity [13, 15]; impact of human interventions such as ITNs [1], combination of IRS and ITNs [6]; impact of environmental and climate changes [2, 4]; and impact of intermittent prophylactic treatment (IPT) [4, 25, 27]. However, there are few mathematical models studying the impact of vaccination on the disease control [7, 31], in particular rare for TBVs. Smith et al proposed a simple mathematical model to study the impact of TBVs and their simulation indicates that TBVs will reduce risks of reestablishment of transmission when vector control is withdrawn [32]. Their model showed that efficacy and coverage are equally important, implying that a vaccine that requires a small number of doses is preferable to one that is difficult to deliver, even if this entails accepting a lower efficacy. The results demonstrate that transmission-blocking vaccine has merits that make it worth further investigation.

In this paper, we will propose a deterministic compartmental model of malaria focusing on the impact of TBVs on the disease transmission. For TBVs, mosquitoes will be indirectly vaccinated through biting vaccinated humans. However, the vaccine does not protect humans from infection. We will assume that the vaccine is perfect in preventing the disease transmission from mosquitoes and the vaccine will be effective lifetime long as long as human is vaccinated. This condition can be easily released allowing the vaccinated class moving back into susceptible class due to loss of efficacy of the vaccine. A mosquito can live up to 30 days but the average life span of mosquitoes is about 2 to 3 weeks. Thus, as long as mosquitoes become infectious, they will remain infected throughout their life time no matter whether they bite people who are vaccinated or not. However, we assume that the vaccine takes effect immediately after mosquitoes in exposed class bite humans who are vaccinated no matter whether the human is infected or not. This assumption is reasonable given the mechanism of vaccination targeting at mosquito stage. The model shows that the additional death due to infection causes the backward bifurcation, which agrees with findings in other disease models, such as for syphilis [23], dengue fever [9] and AIDS/HIV [8]. The results of the model suggest that introducing TBVs helps reduce the basic reproduction number, i.e., reduce the disease burden.

The structure of the paper is as follows: In section 2, a mathematical model incorporating TBVs is formulated; In section 3, mathematical analysis of the model is carried out; In section 4, the transmission-blocking vaccines are accessed and numerical simulations are performed; In section 5, sensitivity analysis is performed to identity the critical control parameters; Finally in section 6, we make discussions and draw conclusions.

2. **Formulation of model.**

A TBVs program is aimed to either prevent or merely reduce transmission. The vaccine works in the way that humans who receive vaccines serve only as a media to pass the vaccines to mosquitoes where the disease transmission can be stopped. The total population of humans at time t ($N_h(t)$) are divided into susceptible but not vaccinated ($S_h(t)$), susceptible and vaccinated ($V_h(t)$), exposed but not vaccinated ($E_h(t)$), exposed and vaccinated ($F_h(t)$), infected but not vaccinated ($I_h(t)$), infected and vaccinated ($J_h(t)$), temporarily-immune but not vaccinated $R_h(t)$, and temporarily-immune and vaccinated class ($M_h(t)$). Thus,

$$N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t) + V_h(t) + F_h(t) + J_h(t) + M_h(t). \tag{1}$$

The total population of mosquitoes are divided into susceptible ($S_v(t)$), exposed ($E_v(t)$), infectious ($I_v(t)$), and vaccinated class ($V_v(t)$). Mosquitoes which are not

in infectious stage will not transmit the disease after they bite vaccinated human individuals, but the vaccine does not prevent infectious mosquitoes from transmitting the disease. A descriptive diagram of disease transmission is illustrated in Figure 4.

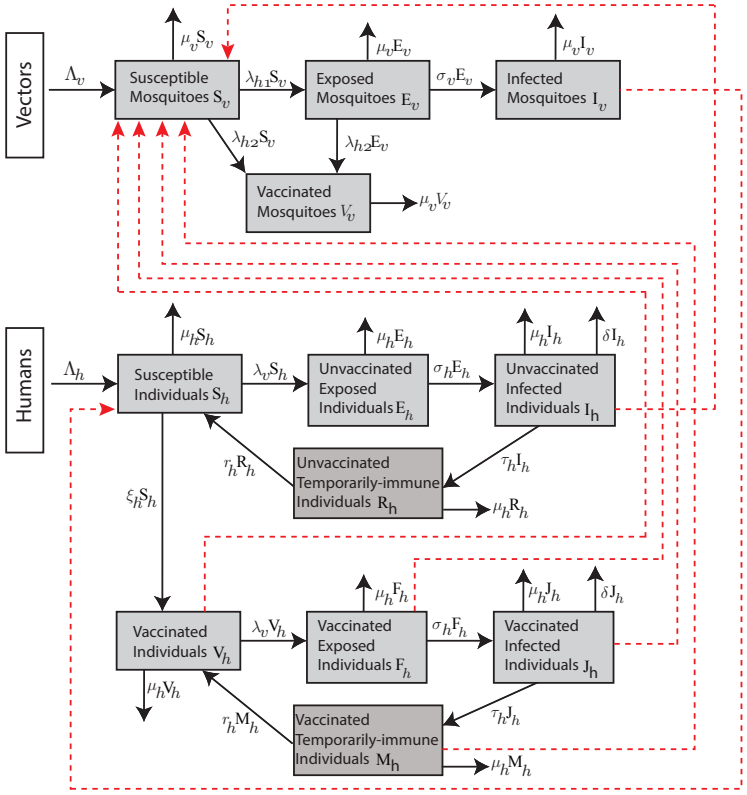

FIGURE 1. The schematic diagram of a mathematical model with TBVs.

The infection of human hosts is acquired following effective contact with an infectious female mosquito at a rate of λ_v, where

$$\lambda_v = \frac{C_{vh} I_v}{N_h}. \tag{2}$$

The parameter C_{vh} is the effective contact rate of vectors, and is defined as the product of the biting rate of mosquitoes and the probability of transmission per bite (from an infectious mosquito to susceptible human) [31].

The infection of mosquitoes is acquired when susceptible mosquitoes take a blood meal from infectious humans at a rate of λ_{h1}, where

$$\lambda_{h1} = \frac{C_{hv} I_h}{N_h}. \tag{3}$$

The parameter C_{hv} is the effective contact rate of humans, and is defined as the product of the average number of mosquito bites received by humans and the probability of transmission (from an infectious human to a susceptible mosquito).

Both hosts are assumed to grow logistically with constant recruitment rate Λ_h and Λ_v for humans and mosquitoes respectively and those newly recruited individuals are susceptible. The transmission-blocking vaccines are given to humans at rate ξ_h. Human hosts die with death rate μ_h and additional death rate δ due to infection by malaria. The individuals in exposed class progress to the infection stage at rate σ_h; infected individuals recovered with partial immunity at rate τ_h; and the temporary immunity will lose at rate r_h. Due to the short life span of mosquitoes, we assume that mosquitoes die at their natural death rate μ_v only; exposed mosquitoes progress to the infectious class at rate σ_v. The description of parameters and its values are listed in Table 1, and the detailed reference for each value can be found in [31].

TABLE 1. Description of parameters of the basic malaria model

Param.	Description	Baseline values
Λ_h	Recruitment rate of humans	$[10^5$-$10^6]$ /year
Λ_v	Recruitment rate of vectors	$10^4 \times 365$ /year
μ_h	Natural death rate of host	$1/55 \in [1/45, 1/60]$ /year
μ_v	Natural death rate of vector	$[365/28, 365/21]$ /year
C_{hv}	Contact rate from host to vector	Variable
C_{vh}	Contact rate from vector to host	Variable
ξ_h	Vaccination rate of humans	Variable
r_h	Rate of loss of immunity	365/68.5
τ_h	Rate of development of temporal immunity	Variable
δ	Disease-induced death rate	$[0\text{-}4.1 \times 10^{-4}] \times 365$ /year
σ_h	Progression rate to symptoms development for the host	365/14 /year
σ_v	Progression rate to symptoms development for the vector	365/12 /year

A susceptible mosquito becomes vaccinated hence stops transmitting the disease when it takes a blood meal from a vaccinated person, no matter whether the person is infected or not. Therefore, the rate of change of the susceptible mosquitoes are described by

$$S_v' = \Lambda_v - \lambda_{h1} S_v - \lambda_{h2} S_v - \mu_v S_v$$

where

$$\lambda_{h2} = \frac{C_{hv}(V_h + F_h + J_h + M_h)}{N_h}. \tag{4}$$

The vaccine does not take effect if a mosquito takes a blood meal from a vaccinated person if the mosquito has already become infectious. Moreover, the person who received the transmission-blocking vaccine can be infected. The rate of change of the exposed and infected mosquitoes are described by

$$\begin{aligned} E_v' &= \lambda_{h1} S_v - \lambda_{h2} E_v - \sigma_v E_v - \mu_v E_v, \\ I_v' &= \sigma_v E_v - \mu_v I_v. \end{aligned}$$

The rate of change of the vaccinated mosquitoes are described by

$$V_v' = \lambda_{h2} S_v + \lambda_{h2} E_v - \mu_v V_v.$$

The mosquitoes in vaccinated class do not directly involve in disease transmission. However, they still make contribution to the spread of disease because they keep

producing their offsprings. An ideal recipe should be that the vaccine not only prevents the development of malaria in the mosquito body but also restrains the reproduction of mosquitoes.

The complete model for the transmission dynamics of malaria with TBVs is given by the following system of differential equations:

$$\begin{cases} S_h' &= \Lambda_h + r_h R_h - \xi_h S_h - \lambda_v S_h - \mu_h S_h, \\ E_h' &= \lambda_v S_h - \sigma_h E_h - \mu_h E_h, \\ I_h' &= \sigma_h E_h - \tau_h I_h - \mu_h I_h - \delta I_h, \\ R_h' &= \tau_h I_h - r_h R_h - \mu_h R_h, \\ V_h' &= \xi_h S_h + r_h M_h - \lambda_v V_h - \mu_h V_h, \\ F_h' &= \lambda_v V_h - \sigma_h F_h - \mu_h F_h, \\ J_h' &= \sigma_h F_h - \tau_h J_h - \mu_h J_h - \delta J_h, \\ M_h' &= \tau_h J_h - r_h M_h - \mu_h M_h, \\ S_v' &= \Lambda_v - \lambda_{h1} S_v - \lambda_{h2} S_v - \mu_v S_v, \\ E_v' &= \lambda_{h1} S_v - \lambda_{h2} E_v - \sigma_v E_v - \mu_v E_v, \\ I_v' &= \sigma_v E_v - \mu_v I_v, \\ V_v' &= \lambda_{h2} S_v + \lambda_{h2} E_v - \mu_v V_v. \end{cases} \tag{5}$$

3. **Analysis.** The model (5) monitors human and female mosquito populations, and consequently, all its associated parameters are non-negative. It is easy to show that the following positivity results hold.

Theorem 3.1. *Solutions of the model system (5) with positive initial data are positive for all time $t > 0$. In addition, the solution enters the boundary in finite time if and only if $E_h(0) = I_h(0) = F_h(0) = J_h(0) = E_v(0) = I_v(0) = 0$.*

Following the van den Driessche and Watmough's paper in 2002 [33], denote

$$\mathbf{x} = (E_h, F_h, E_v, I_h, J_h, I_v, S_h, V_h, S_v, R_h, M_h, V_v)^{\mathsf{T}}.$$

For simplicity, let us also denote

$$K_1 = \sigma_h + \mu_h,\ K_2 = \tau_h + \mu_h + \delta,\ K_3 = r_h + \mu_h,\ K_4 = \sigma_v + \mu_v,\ K_5 = \xi_h + \mu_h. \tag{6}$$

It is easy to compute the disease free equilibrium (DFE) of the model (5):

$$E_{TBV} = (0, 0, 0, 0, 0, 0, S_h^*, V_h^*, S_v^*, 0, 0, V_v^*)^{\mathsf{T}} \tag{7}$$

where

$$S_h^* = \frac{\Lambda_h}{K_5}, \quad V_h^* = \frac{\xi_h \Lambda_h}{\mu_h K_5}, \quad S_v^* = \frac{\Lambda_v K_5}{\mu_v K_5 + C_{hv}\xi_h}, \quad V_v^* = \frac{C_{hv}\xi_h \Lambda_v}{\mu_v[K_5\mu_v + C_{hv}\xi_h]}.$$

Moreover, the basic reproduction number of the model can be computed as the spectral radius of the second generation matrix:

$$\mathcal{R}_{TBV} = \mu_h \sqrt{\frac{\sigma_h \sigma_v C_{hv} C_{vh} \Lambda_v K_5}{K_1 K_2 \mu_v \Lambda_h (\mu_v K_5 + C_{hv}\xi_h)(C_{hv}\xi_h + K_4 K_5)}}. \tag{8}$$

3.1. **Stability of disease free equilibrium.** Let's first introduce the following lemma and we will use the lemma, in Theorem 3.3, to prove the stability of DFE. The lemma can be easily proved with elementary Calculus argument.

Lemma 3.2. *Consider a fourth order polynomial of the form*

$$p(x) = (x + a_1)(x + a_2)(x + a_3)(x + a_4) - c.$$

Suppose $c > 0$ *and* $a_i > 0$ *for all* $i = 1, 2, 3, 4$. *Denote* $a = a_1 a_2 a_3 a_4 - c$.

(i) If $a > 0$, *then either all roots are negative or two are negative and the real part of the complex roots is negative;*

(ii) If $a < 0$, *then at least one root is positive.*

Theorem 3.3. *The disease free equilibrium* E_{TBV} *is asymptotically stable if* $\mathcal{R}_{TBV} < 1$ *and unstable if* $\mathcal{R}_{TBV} > 1$.

Proof. The linearized system of the model (5) at E_{TBV} can be written as

$$\mathbf{x}' = A\mathbf{x}, \quad A = \begin{pmatrix} A_{11} & 0 \\ A_{21} & A_{22} \end{pmatrix}$$

where

$$A_{11} = \begin{pmatrix} -K_1 & 0 & 0 & 0 & 0 & \frac{C_{vh}S_h^*}{N_h^*} \\ 0 & -K_1 & 0 & 0 & 0 & \frac{C_{vh}S_h^*}{N_h^*} \\ 0 & 0 & -(\frac{C_{hv}V_h^*}{N_h^*} + K_4) & \frac{C_{hv}S_v^*}{N_h^*} & 0 & 0 \\ \sigma_h & 0 & 0 & -K_2 & 0 & 0 \\ 0 & \sigma_h & 0 & 0 & -K_2 & 0 \\ 0 & 0 & \sigma_v & 0 & 0 & -\mu_v \end{pmatrix}$$

and

$$A_{22} = \begin{pmatrix} -(\mu_h + \xi_h) & 0 & 0 & r_h & 0 & 0 \\ \xi_h & -\mu_h & 0 & 0 & r_h & 0 \\ \frac{C_{hv}V_h^*S_v^*}{(N_h^*)^2} & -\frac{C_{hv}S_v^*S_h^*}{(N_h^*)^2} & -(\mu_v + \frac{C_{hv}V_h^*}{N_h^*}) & \frac{C_{hv}V_h^*S_v^*}{(N_h^*)^2} & -\frac{C_{hv}S_v^*S_h^*}{(N_h^*)^2} & 0 \\ 0 & 0 & 0 & -K_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & -K_3 & 0 \\ -\frac{C_{hv}V_h^*S_v^*}{(N_h^*)^2} & \frac{C_{hv}S_v^*S_h^*}{(N_h^*)^2} & \frac{C_{hv}V_h^*}{N_h^*} & -\frac{C_{hv}V_h^*S_v^*}{(N_h^*)^2} & \frac{C_{hv}S_v^*S_h^*}{(N_h^*)^2} & -\mu_v \end{pmatrix}.$$

The characteristic equation of A_{22} is

$$\det(\lambda I - A_{22}) = (\lambda + K_3)^2(\lambda + K_5)(\lambda + \mu_h)(\lambda + \mu_v + \frac{C_{hv}V_h^*}{N_h^*})(\lambda + \mu_v).$$

Thus, the eigenvalues of A_{22} are all negative.

The characteristic equation of A_{11} is

$$\det(\lambda I - A_{11}) = (\lambda + K_1)(\lambda + K_2)\left[(\lambda + \frac{C_{hv}V_h^*}{N_h^*} + K_4)(\lambda + K_1)(\lambda + K_2)(\lambda + \mu_v) - \sigma_h \frac{C_{vh}S_h^*}{N_h^*}\sigma_v \frac{C_{hv}S_v^*}{N_h^*}\right].$$

The eigenvalues of the matrix A_{11} are $\lambda_1 = -K_1$, $\lambda_2 = -K_2$ and the roots of the forth order polynomial

$$p_A(\lambda) = (\lambda + \frac{C_{hv}V_h^*}{N_h^*} + K_4)(\lambda + K_1)(\lambda + K_2)(\lambda + \mu_v) - \sigma_h \frac{C_{vh}S_h^*}{N_h^*}\sigma_v \frac{C_{hv}S_v^*}{N_h^*}$$

By Lemma 3.2 , one root of the polynomial $p_A(\lambda)$ is positive if

$$(\frac{C_{hv}V_h^*}{N_h^*} + K_4)K_1K_2\mu_v < \sigma_h \frac{C_{vh}S_h^*}{N_h^*}\sigma_v \frac{C_{hv}S_v^*}{N_h^*} \quad \text{(i.e. } \mathcal{R}_{TBV} > 1)$$

and all real parts of the polynomial of $p_A(\lambda)$ are negative if $\mathcal{R}_{TBV} < 1$. □

3.2. **Endemic equilibrium and backward bifurcation.** If $E_h = 0$, $I_h = 0$, $R_h = 0$, $F_h = 0$, $J_h = 0$, $M_h = 0$, $E_v = 0$, or $I_v = 0$, then $(E_h, I_h, R_h, F_h, J_h, M_h, E_v, I_v) = (0, 0, 0, 0, 0, 0, 0, 0)$. Thus, if $(S_h^*, E_h^*, I_h^*, R_h^*, V_h^*, F_h^*, J_h^*, M_h^*, S_v^*, E_v^*, I_v^*, V_v^*)$ is an endemic equilibrium then all the components must be positive.

Let us further introduce notations

$$A = \sigma_h/(K_1K_2),\ B = \tau_h A/K_3,\ \alpha = \frac{1}{K_1} + A + B,\ \beta = \frac{1 - r_hB}{\mu_h},\ \gamma = \frac{C_{hv}A}{\mu_v} + \alpha.$$

It is worth to note that $1 - r_hB > 0$. Solving the equations at equilibrium gives (in terms of S_h^* and S_v^*)

$$S_h^* = \frac{\Lambda_h}{K_5 + \lambda_v^*(1 - r_hB)},\ E_h^* = \frac{\lambda_v^* S_h^*}{K_1},\ I_h^* = \lambda_v^* S_h^* A,\ R_h^* = \lambda_v^* S_h^* B, \tag{9}$$

$$V_h^* = \frac{\xi_h S_h^*}{\mu_h + \lambda_v^*(1 - r_hB)},\ F_h^* = \frac{\lambda_v^* V_h}{K_1},\ J_h^* = \lambda_v^* V_h^* A,\ M_h^* = \lambda_v^* V_h^* B, \tag{10}$$

$$\begin{aligned} S_v^* &= \frac{\Lambda_v}{\lambda_{h1}^* + \lambda_{h2}^* + \mu_v},\ E_v^* = \frac{\lambda_{h1}^* S_v^*}{\lambda_{h2}^* + K_4},\ I_v^* = \frac{\sigma_v \lambda_{h1}^* S_v^*}{\mu_v(\lambda_{h2}^* + K_4)}, \\ V_v^* &= \frac{\lambda_{h2}^*(\lambda_{h2}^* + \lambda_{h1}^* + K_4)}{\mu_v(\lambda_{h2}^* + K_4)} \end{aligned} \tag{11}$$

where $\lambda_v^* = C_{vh}I_v^*/N_h^*$, $\lambda_{h1}^* = C_{hv}I_h^*/N_h^*$, $\lambda_{h2}^* = C_{hv}^*(V_h^* + F_h^* + J_h^* + M_h^*)/N_h^*$.

Then, we have

$$N_h^* = S_h^* + E_h^* + I_h^* + R_h^* + V_h^* + F_h^* + J_h^* + M_h^* = \frac{\Lambda_h(1 + \alpha\lambda_v^*)}{\mu_h + \beta\lambda_v^*}.$$

Also,

$$\lambda_{h2}^* = \frac{C_{hv}(V_h^* + F_h^* + J_h^* + M_h^*)}{N_h^*} = \frac{C_{hv}\xi_h}{K_5 + \beta\lambda_v^*}.$$

Similarly,

$$\lambda_{h1}^* = \frac{C_{vh}I_h^*}{N_h^*} = \frac{C_{hv}\lambda_v^* A(\mu_h + \beta\lambda_v^*)}{(K_5 + \beta\lambda_v^*)(1 + \alpha\lambda_v^*)}$$

and

$$\lambda_v^* = \frac{C_{vh}I_v^*}{N_h^*} = \frac{C_{vh}\sigma_v\lambda_{h1}^*\Lambda_v(\mu_h + \beta\lambda_v^*)}{\mu_v(\lambda_{h2}^* + \lambda_{h1}^* + \mu_v)(\lambda_{h2}^* + K_4)\Lambda_h(1 + \alpha\lambda_v^*)}.$$

Substituting λ_{h1}^* and λ_{h2}^* into λ_v^* and simplifying it gives the following polynomial equation of degree 4 in λ_v^*:

$$a_0(\lambda_v^*)^4 + b_0(\lambda_v^*)^3 + c_0(\lambda_v^*)^2 + d_0\lambda_v^* + e_0 = 0$$

where

$$\begin{aligned}
a_0 &= \mu_v\Lambda_h\left(C_{hv}A\beta+\alpha\mu_v\beta\right)\alpha\beta K_4,\\
b_0 &= \mu_v\Lambda_h\left[(C_{hv}A\mu_h+\mu_v\beta+\alpha x)\alpha\beta K_4+(C_{hv}A\beta+\alpha\mu_v\beta)(\alpha y+K_4\beta)\right]\\
&\quad -C_{vh}C_{hv}\sigma_v A\Lambda_v\beta^3,\\
c_0 &= \mu_v\Lambda_h\left[\alpha\beta K_4 x+(C_{hv}A\mu_h+\mu_v\beta+\alpha x)(\alpha y+K_4\beta)+(C_{hv}A\beta+\alpha\beta\mu_v)y\right]\\
&\quad -C_{vh}C_{hv}\sigma_v A\Lambda_v\beta^2(3\mu_h+\xi_h),\\
d_0 &= \mu_v\Lambda_h\left[(\alpha y+K_4\beta)x+(C_{hv}A\mu_h+\mu_v\beta+\alpha x)y\right]\\
&\quad -C_{vh}C_{hv}\sigma_v A\Lambda_v\mu_h\beta(3\mu_h+2\xi_h),\\
e_0 &= \mu_v\Lambda_h xy\left(1-\mathcal{R}_{BTV}^2\right),\\
x &= C_{hv}\xi_h+\mu_v K_5,\\
y &= C_{hv}\xi_h+K_4K_5.
\end{aligned}$$

Remark. If $\mathcal{R}_{BTV}>1$, then $e_0<0$. Thus, the forth-order polynomial must have a positive root, which implies that there is at least one endemic equilibrium.

3.2.1. *Special case:* $\xi_h=0$. For convenience, we also introduce the basic reproduction number for the case where there is no vaccination and denote it by $\mathcal{R}_0$

$$\mathcal{R}_0=\frac{1}{\mu_v}\sqrt{\frac{C_{vh}C_{hv}\sigma_v\sigma_h\Lambda_v\mu_h}{\Lambda_hK_1K_2K_4}}. \tag{12}$$

In the case of $\xi_h=0$, i.e., there is no vaccination employed, we have $\lambda_{h2}^*=0$ and hence $V_h^*=F_h^*=J_h^*=M_h^*=V_v^*=0$. It is clear that $\lambda_{h1}^*/\lambda_v^*=(C_{hv}I_h^*)/(C_{vh}I_v^*)$, so

$$\frac{I_h^*}{I_v^*}=\frac{C_{vh}}{C_{hv}}\cdot\frac{\lambda_{h1}^*}{\lambda_v^*}. \tag{13}$$

From Eq. 9 and noticing that $N_h^*=(1+\alpha\lambda_v^*)S_h^*$, we have

$$\lambda_{h1}^*=\frac{C_{hv}I_h^*}{N_h^*}=\frac{C_{hv}\lambda_v^*S_h^*A}{S_h^*(1+\alpha\lambda_v^*)}=\frac{C_{hv}\lambda_v^*A}{1+\alpha\lambda_v^*} \tag{14}$$

and

$$\frac{\lambda_{h1}^*}{\lambda_v^*}=\frac{C_{hv}A}{1+\alpha\lambda_v^*}. \tag{15}$$

From Eq. 9 and Eq. 11, we have

$$\frac{I_h^*}{I_v^*}=\frac{\lambda_v^*S_h^*AK_4\mu_v}{\sigma_vS_v^*\lambda_{h1}^*}. \tag{16}$$

Thus, from Eq. 13, Eq. 15, and Eq. 16, we have

$$\begin{aligned}
\frac{S_h^*}{S_v^*} &= \frac{\sigma_v}{\mu_vAK_4}\cdot\frac{\lambda_{h1}^*}{\lambda_v^*}\cdot\frac{I_h^*}{I_v^*}=\left(\frac{\lambda_{h1}^*}{\lambda_v^*}\right)^2\frac{C_{vh}\sigma_v}{C_{hv}\mu_vAK_4}=\frac{C_{hv}^2A^2}{(1+\alpha\lambda_v^*)^2}\cdot\frac{C_{vh}\sigma_v}{C_{hv}\mu_vAK_4}\\
&= \frac{C_{hv}C_{vh}\sigma_h\sigma_v}{K_1K_2K_4\mu_v(1+\alpha\lambda_v^*)^2}=\frac{\Lambda_h\mu_v}{\Lambda_v\mu_h(1+\alpha\lambda_v^*)^2}\mathcal{R}_0^2.
\end{aligned}$$

From Eq. 9, Eq. 11, and Eq. 14, we also have

$$\frac{S_h^*}{S_v^*}=\frac{\Lambda_h(\mu_v+\lambda_{h1}^*)}{\Lambda_v(\mu_h+\lambda_v^*(1-r_hB))}=\frac{\Lambda_h\left\{\mu_v(1+\alpha\lambda_v^*)+C_{hv}A\lambda_v^*\right\}}{\Lambda_v\left[\mu_h+\lambda_v^*(1-r_hB)\right](1+\alpha\lambda_v^*)}.$$

Equating the above two equalities and simplifying it, we have

$$\frac{1+\gamma\lambda_v^*}{1+\beta\lambda_v^*}=\frac{\mathcal{R}_0^2}{1+\alpha\lambda_v^*}.$$

The endemic equilibria of the model satisfy the following quadratic (in terms of λ_v^*)

$$a_0 (\lambda_v^*)^2 + b_0 \lambda_v^* + c_0 = 0$$

where $a_0 = \gamma\alpha$, $b_0 = \gamma + \alpha - \beta\mathcal{R}_0^2$, and $c_0 = 1 - \mathcal{R}_0^2$.

Thus, the positive endemic equilibria of the model without vaccination are obtained by solving for λ_v^* from the quadratic and substituting the results (positive values of λ_v^*) into the expressions for $E_h^*, E_v^*, I_h^*, I_v^*, S_h^*, S_v^*$, and R_h^*. The solution for λ_v^* is:

$$\lambda_v^* = \frac{-b_0 \pm \sqrt{b_0^2 - 4a_0c_0}}{2a_0}.$$

Thus, the following result can be easily established.

Theorem 3.4. *Under the assumption that there is no vaccination, i.e., $\xi_h = 0$, the model (5) has*

(i) a unique endemic equilibrium if $c_0 < 0 \Leftrightarrow \mathcal{R}_0 > 1$,
(ii) a unique endemic equilibrium if $b_0 < 0$, and $c_0 = 0$ or $b_0^2 - 4a_0c_0 = 0$,
(iii) two endemic equilibria if $b_0 < 0$, $c_0 > 0$ and $b_0^2 - 4a_0c_0 > 0$, or
(iv) no endemic equilibrium otherwise.

Case (iii) indicates the possibility of backward bifurcation (where the locally-asymptotically stable DFE co-exists with a locally-asymptotically endemic equilibrium when $\mathcal{R}_0 < 1$) in the model when $\mathcal{R}_0 < 1$. To check for this, the discriminant $b_0^2 - 4a_0c_0$ is set to zero and solved for the critical value of $\mathcal{R}_0$, denoted by $\mathcal{R}_c$, given by:

$$\mathcal{R}_c = \sqrt{1 - \frac{b_0^2}{4a_0}} = \sqrt{1 - \frac{\mu_v b_0^2}{\alpha(C_{hv} + \alpha)}}.$$

Thus, the following result is established:

Lemma 3.5. *Under the assumption that there is no vaccination, i.e., $\xi_h = 0$, the model (5) undergoes backward bifurcation when case (iii) of Theorem 3.4 holds and $\mathcal{R}_c < \mathcal{R}_0 < 1$.*

The results of the above lemma is illustrated by simulating the model with the following set of parameter values: $\mu_h = 1/55$, $\mu_v = 365/21$, $r_h = 365/(68.5)$, $\tau_h = 0.4$, $\delta = 0.1$, $\sigma_h = 365/14$, $\sigma_v = 365/12$, $\Lambda_h = 10^5$, $\Lambda_v = 365 \times (10^4)$. The associated bifurcation diagrams are depicted in Figure 2. Here the parameters $C_{hv} = C_{vh}$ are bifurcation parameters. It can be easily shown that there is no backward bifurcation if δ is small. The additional death rate due to infection triggers the backward bifurcation, which agrees with the other study [31].

Furthermore, for the special case $\xi_h = 0$, we can establish conditions under which DFE is globally asymptotically stable (GAS), i.e, the disease elimination is independent of the initial sizes of the sub-population under certain conditions.

Theorem 3.6. *Assume $\Lambda_h \leq \Lambda_v$. If $0 < \mathcal{R}_0 < \mathcal{R}_c < 1$ and $\mathcal{R}_0 < 1/\sqrt{\kappa}$, where*

$$\kappa = \max\left\{\frac{\mu_v K_4}{\sigma_h \mu_h C_{vh}}, \frac{\mu_v \Lambda_h K_1 K_2}{\sigma_v \mu_h C_{hv}}\right\}.$$

When there is no vaccination, i.e., $\xi_h = 0$, the DFE is the only equilibrium in

$$\mathbb{D} = \left\{(E_h, E_v, I_h, I_v, S_h, S_v, R_h) \in \mathbb{R}_+^7 : S_h + E_h + I_h + R_h \leq \frac{\Lambda_h}{\mu_h};\right.$$

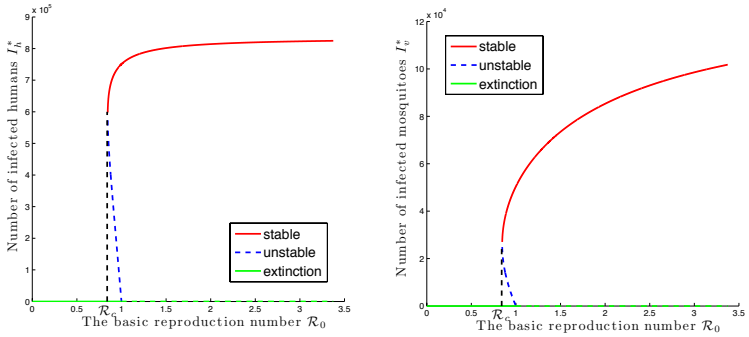

FIGURE 2. The backward bifurcation diagram for $\xi_h = 0$. The parameters are $\mu_h = 1/55$, $\mu_v = 365/21$, $r_h = 365/68.5$, $\tau_h = 0.4$, $\delta = 0.1$, $\sigma_h = 365/14$, $\sigma_v = 365/12$, $\Lambda_h = 10^5$, $\Lambda_v = 365 \times (10^4)$.

$$S_v + E_v + I_v \leq \frac{\Lambda_v}{\mu_v} \Bigg\}$$

and it is globally asymptotically stable in $\mathbb{D}$.

Proof. Consider the Lyapunov function

$$\mathcal{F} = f_1 E_h + f_2 I_h + f_3 E_v + f_4 I_v$$

where, $f_1 = \sigma_h$, $f_2 = K_1$, $f_3 = \sigma_v/\Lambda_h$. and $f_4 = K_4/\Lambda_v$.

Differentiating with respect to t, we have

$$\frac{d\mathcal{F}}{dt} = f_1 \frac{dE_h}{dt} + f_2 \frac{dI_h}{dt} + f_3 \frac{dE_v}{dt} + f_4 \frac{dI_v}{dt}.$$

Thus,

$$\begin{aligned}
\frac{d\mathcal{F}}{dt} &= \sigma_h \left(\frac{C_{vh} I_v}{N_h} S_h - K_1 E_h \right) + K_1 \left(\sigma_h E_h - K_2 I_h \right) \\
&\quad + \frac{\sigma_v}{\Lambda_h} \left(\frac{C_{hv} I_h}{N_h} S_v - K_4 E_v \right) + \frac{K_4}{\Lambda_v} \left(\sigma_v E_v - \mu_v I_v \right) \\
&\leq \sigma_h \left(C_{vh} I_v - K_1 E_h \right) + K_1 \left(\sigma_h E_h - K_2 I_h \right) \\
&\quad + \frac{\sigma_v}{\Lambda_h} \left(\frac{C_{hv} \Lambda_v}{\mu_v} I_h - K_4 E_v \right) + \frac{K_4}{\Lambda_v} \left(\sigma_v E_v - \mu_v I_v \right) \quad \text{(assume } N_h \geq 1\text{)} \\
&= \left(K_1 \sigma_h - K_1 \sigma_h \right) E_h + \left(\frac{\sigma_v K_4}{\Lambda_v} - \frac{\sigma_v K_4}{\Lambda_h} \right) E_v \\
&\quad + \left(\frac{\sigma_v C_{hv} \Lambda_v}{\mu_v \Lambda_h} - K_1 K_2 \right) I_h + \left(\sigma_h C_{vh} - \frac{\mu_v K_4}{\Lambda_v} \right) I_v \\
&\leq \left(\frac{\sigma_v C_{hv} \Lambda_v}{\mu_v \Lambda_h} - K_1 K_2 \right) I_h + \left(\sigma_h C_{vh} - \frac{\mu_v K_4}{\Lambda_v} \right) I_v \quad \text{(assume } \Lambda_h \leq \Lambda_v\text{)} \\
&= K_1 K_2 \left(\frac{\sigma_v C_{hv} \Lambda_v}{\mu_v \Lambda_h K_1 K_2} - 1 \right) I_h + \frac{\mu_v K_4}{\Lambda_v} \left(\frac{\Lambda_v \sigma_h C_{vh}}{\mu_v K_4} - 1 \right) I_v \\
&= K_1 K_2 \left(\frac{K_4 \mu_v}{\sigma_h \mu_h C_{vh}} \mathcal{R}_0^2 - 1 \right) I_h + \frac{\mu_v K_4}{\Lambda_v} \left(\frac{\Lambda_h K_1 K_2 \mu_v}{\sigma_v \mu_h C_{hv}} \mathcal{R}_0^2 - 1 \right) I_v
\end{aligned}$$

$$\leq \quad K_1K_2\left(\kappa\mathcal{R}_0^2-1\right)I_h+\frac{\mu_vK_4}{\Lambda_v}\left(\kappa\mathcal{R}_0^2-1\right)I_v$$

Thus, $d\mathcal{F}/dt\leq 0$ if $\mathcal{R}_0<1/\sqrt{\kappa}$. And $d\mathcal{F}/dt=0$ if and only if $E_h=I_h=E_v=I_v=0$. Further, the largest compact invariant set in $\{(E_h,E_v,I_h,I_v,S_h,S_v,R_h)\in D|d\mathcal{F}/dt=0\}$ is the singleton $\{(0,0,0,0,\Lambda_h/\mu_h,\Lambda_v/\mu_v,0)\}$. It follows from LaSalle Invariance Principle (Chapter 2, Theorem 6.4 of [17]) that every solution in Eq. (5) with initial conditions in $\mathbb{D}$ converges to DFE as $t\to\infty$. That is, $(E_h(t),\ E_v(t),\ I_h(t),\ I_v(t))\to(0,0,0,0)$ as $t\to\infty$. Substituting $E_h=I_h=E_v=I_v=0$ in Eq. (5) gives $S_h(t)\to\Lambda_h/\mu_h,\ S_v(t)\to\Lambda_v/\mu_v$, and $R_h(t)\to 0$ as $t\to\infty$. Thus, $[E_h(t),E_v(t),I_h(t),I_v(t),S_h(t),S_v(t),R_h(t)]\to(0,0,0,0,\Lambda_h/\mu_h,\Lambda_v/\mu_v,0)$ as $t\to\infty$ for $0<\mathcal{R}_0<\mathcal{R}_c<1$ and $\mathcal{R}_0<1/\sqrt{\kappa}$, so that the disease free equilibiurm is GAS in $\mathbb{D}$ if $0<\mathcal{R}_0<\mathcal{R}_c<1$ and $\mathcal{R}_0<1/\sqrt{\kappa}$. □

The above result shows that the disease can be eliminated from the community if $0<\mathcal{R}_0<\mathcal{R}_c<1$ and $\mathcal{R}_0<1/\sqrt{\kappa}$.

4. **Assessment of transmission-blocking vaccines.** In this section, the potential impact of the transmission-blocking vaccines is assessed.

The derivative of $\mathcal{R}_{TBV}$ with respect to ξ_h is:

$$\frac{d\mathcal{R}_{TBV}}{d\xi_h} = -\sqrt{\frac{\sigma_h\sigma_vC_{hv}C_{vh}\mu_h\Lambda_v\mu_h}{K_1K_2\mu_v\Lambda_h}}\sqrt{\frac{1}{(\mu_vK_5+C_{hv}\xi_h)^3(\frac{C_{hv}\xi_h}{K_5}+K_4)^3}}$$
$$\left[(\mu_v+C_{hv})(\frac{C_{hv}\xi_h}{K_5}+K_4)+(\mu_vK_5+C_{hv}\xi_h)\frac{C_{hv}\mu_h}{K_5^2}\right].$$

It is clear that the basic reproduction number for model (5) is a decreasing function of ξ_h, and $\mathcal{R}_{TBV}=\mathcal{R}_0$ for $\xi_h=0$. Thus, introducing the blocking-transmission vaccine will reduce the burden of the infection.

The quantity $\mathcal{R}_{TBV}$ can be expressed as a function of the fraction of vaccinated individuals at the steady-state, given by $p=V_h^*/N_h^*$. Then, S_h^* and S_v^* are expressed in terms of p as follows:

$$S_h^*=N_h^*\left(1-p\right)\quad\text{and}\quad S_v^*=\frac{\Lambda_vK_5}{\mu_vK_5+C_{hv}\xi_h}=\frac{N_h^*\Lambda_v}{\mu_vN_h^*+C_{hv}p}.$$

Then,

$$\mathcal{R}_{TBV} = \sqrt{\frac{\sigma_h\sigma_vC_{hv}C_{vh}S_h^*S_v^*}{K_1K_2N_h^*\mu_vN_h^*\left(\frac{C_{hv}V_h^*}{N_h^*}+K_4\right)}}=\sqrt{\frac{\mathcal{R}_0^2\left(1-p\right)}{\left(1+\frac{C_{hv}}{\mu_vN_h^*}p\right)\left(1+\frac{C_{hv}}{K_4}p\right)}}.$$

Let $a=C_{hv}/(\mu_vN_h^*)$ and $b=C_{hv}/K_4$. Then,

$$\mathcal{R}_{TBV}=\mathcal{R}_0\sqrt{\frac{(1-p)}{(1+ap)\left(1+bp\right)}}.$$

Since $0\leq p\leq 1$ from the above formula we have $\mathcal{R}_{TBV}\leq\mathcal{R}_0$ ($\mathcal{R}_{TBV}<\mathcal{R}_0$ if $p>0$) which means the basic reproduction number is reduced if some fraction of susceptible individuals in the population receive the transmission-blocking vaccines. Also,

$$\frac{d\mathcal{R}_{TBV}}{dp}=\frac{\mathcal{R}_0}{\mathcal{R}_{TBV}}\left(\frac{-\left(1+ap\right)\left(1+bp\right)-\left(1-p\right)\left[a\left(1+bp\right)+b\left(1+ap\right)\right]}{\left(1+ap\right)^2\left(1+bp\right)^2}\right).$$

It follows from the above formula that $d\mathcal{R}_{TBV}/dp < 0$ whenever $0 < p \leq 1$. That is, $\mathcal{R}_{TBV}$ is a decreasing function of the vaccinated fraction, p, where $0 < p \leq 1$. Further, based of the fact that a reduction in reproduction number implies reduction in disease burden, the above analyses show that the transmission-blocking vaccine will have a positive impact in reducing disease burden.

Numerical simulations are carried out to assess the impact of TBVs. Figure 3 shows the prevalence of infection with the vaccination rate $\xi_h = 0, 0.3, 0.4, 0.5$, respectively. It suggests that the disease can be eliminated with the vaccination rate $\xi_h = 0.4$. It is also observed that the reduction of infection in vectors is quicker than the reduction in humans. This might be a direct implication of the transition-blocking vaccine targeting at vectors rather than humans. The basic reproduction numbers are $\mathcal{R}_{TBV} = 3.3749, 0.251, 0.216, 0.1937$ for $\xi_h = 0, 0.3, 0.4, 0.5$, respectively. This suggests that the disease might still persist if the vaccination rate is not high enough.

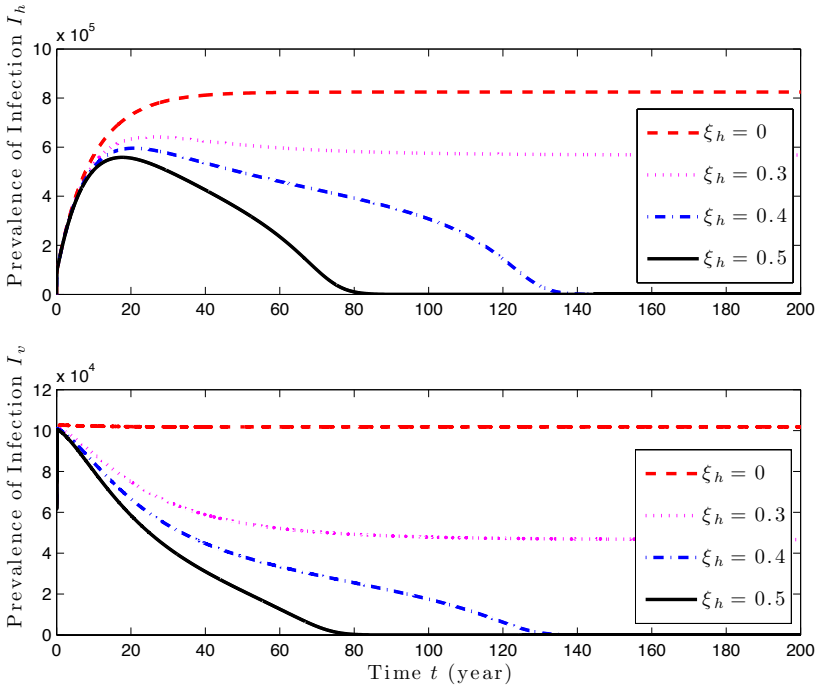

FIGURE 3. Simulation of the model assessing the impact of TBVs. The parameters are $\mu_h = 1/55$, $\mu_v = 365/21$, $r_h = 365/68.5$, $\tau_h = 0.4$, $\delta = 0.1$, $\sigma_h = 365/14$, $\sigma_v = 365/12$, $\Lambda_h = 10^5$, $\Lambda_v = 365 \times (10^4)$.

5. **Sensitivity analysis.** Next we carry out sensitivity analysis to assess the effectiveness of the control parameters. Following the approach in [5], the normalized forward sensitivity index of a variable, x, that depends differentially on a parameter, p, is defined as: $\Gamma_p^x = (\partial x/\partial p) \times (p/x)$. The sensitivity index quantifies the ratio of relative changes on the variable x in response to corresponding changes in

the parameter p. The variable x is most sensitive to the parameter with the largest sensitivity index value (in magnitude) and least sensitive to the parameter with the smallest sensitivity index value (in magnitude). The sensitivity indices of the basic reproduction number, $\mathcal{R}_{TBV}$, with respect to the different parameters are listed in Table 2. The parameter values are the same as in Table 1 while $\delta_h = 0.1$, $\tau_h = 0.4$, $C_{hv} = 65$, $C_{vh} = 65$, and $\xi_h = 0.18$.

TABLE 2. Sensitivity indices of $\mathcal{R}_{TBV}$ for model (5)

Parameter	Sensitivity index	Parameter	Sensitivity index	Parameter	Sensitivity index
Λ_h	$+0.5000$	σ_h	$+0.0003$	C_{vh}	$+0.5000$
r_h	$+0.0000$	τ_h	-0.3860	σ_v	$+0.3576$
δ_h	-0.0965	ξ_h	-0.5149	Λ_v	$+0.5000$
μ_h	$+0.9970$	C_{hv}	-0.1626	μ_v	-0.6951

The basic reproduction number is most sensitive to the natural death rate of humans, μ_h, the death rate of mosquitoes parameter, μ_v, and the vaccination rate parameter, ξ_h. More specifically, the basic reproduction number ($\mathcal{R}_{TBV}$) decreases by 6.95% for an increase in the death rate of mosquito by 10%, and decreases $\mathcal{R}_{TBV}$ by 5.15% for an increase the vaccination coverage by 10%. The public health implication of these results is that the disease can be controlled effectively by increasing the living standard of the population in the endemic region (or decreasing μ_h), increasing the vaccination coverage (or increasing ξ_h), and by controlling the mosquito population (or increasing μ_v) simultaneously. This further confirms that the importance of the current vector control strategies such as the use of ITNs and IRS even in the presence of vaccination.

In the endemic areas, the prevalence of the disease is subject to malaria-related mortality and other malaria-related epidemiological parameters. Therefore, it is also important to explore the sensitivity of the infectious human population in these parameters. We use the Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC) techniques [18] to perform the sensitivity analysis to identify the parameters that have significant importance to I_h. More specifically, we sample the twelve parameters of the model system (5) and measure their statistical impact on I_h. The baseline value for each parameter is set to be the values used in Table 2, and the respective minimum and maximum values for each parameter range are set to 67% and 133% of the mean value. For each parameter, 1000 input values are obtained by sampling a uniform probability distribution. We calculate the PRCCs, which evaluates the monotonicity of the model output (I_h) in terms of the model parameters, from the sampling data. Values of PRCC closer to $+1$ or -1 , imply stronger correlation between the output, I_h in our case, and the input parameter. A negative sign means the input parameter is inversely proportional to the output (I_h). In order to understand the dynamics of PRCCs over time, we calculated the PRCCs for a five-year period. The result is presented in Fig. 4 for statistically significant (p-value $< 10^{-5}$) PRCCs, the non-statistically significant PRCCs are omitted. It again confirms that the prevalence of the infection is most sensitive to the mosquito death rate, and the vaccination rate. It is not surprising to see that the the prevalence of the infection is also very sensitive to the treatment rate.

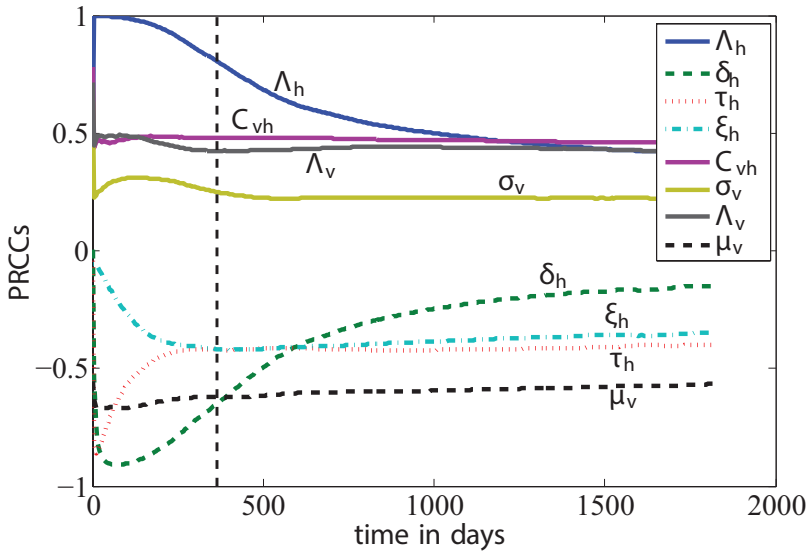

FIGURE 4. Dynamics of statistically significant PRCCs of parameter values of model (5) with respect to I_h for 5 years. The non-statistically significant PRCCs are omitted. The dashed-dotted vertical line denotes day 365.

6. **Conclusion.** The paper presents a mathematical model of the transmission dynamics of malaria which incorporates transmission-blocking vaccines. The model allows for the assessment of the role of effective contact rate of humans and mosquitoes, the role of disease induced mortality rate, and the role of the vaccination rate on the disease spread. The model was rigorously analyzed to gain insights into their qualitative dynamics. The following results were obtained.

(i) Without vaccination (or when $\xi_h = 0$) the model tells that a backward bifurcation occurs when the disease-induced mortality rate is large. Untreated malaria is a lethal disease with high mortality rate, and generally a backward bifurcation is expected. Moreover, we show that when there is no vaccination the disease free equilibrium is globally stable if the basic reproduction number, $\mathcal{R}_0$, is less than $\mathcal{R}_c$, a critical value to avoid the backward bifurcation (see Theorem 3.6.)

(ii) The main goal of the paper is to study the impact of mosquito-stage transmission-blocking vaccines on the disease transmission. The basic reproduction number of the model, $\mathcal{R}_{TBV}$, is calculated, and it is shown that it decreases as the vaccination rate increases. Since a reduction in the basic reproduction number implies reduction in disease burden, the model suggests that transmission-blocking vaccines will have a positive impact on reducing the disease burden.

(iii) Numerical simulations are carried out to observe the change in the prevalence of infection for various vaccination rates. The results suggest that the disease can be reduced (can even be eliminated) as the vaccination coverage increases. However, if the vaccination rate is not high enough, the disease might still

persist. Also, it is observed that the reduction of infection in vectors is quicker than the reduction in humans. This might be a direct implication of the transition-blocking vaccine targeting at vectors rather than humans.

(iv) Sensitivity analysis is performed, and the result suggests that both the basic reproduction number and the prevalence of the infection are highly sensitive to the vaccination rate (ξ_h), as well as the death rate of mosquitoes (μ_v) and the death rate of humans (μ_h). The public health implication of these results is that the vaccination is as important as other disease control strategies, such as vector control strategies, treatment of infected individuals, and improving the living standard in the endemic areas.

A future work is to extend the mathematical model to study the impact of the TBVs in combination with other human-stage vaccines on the disease transmission. Also, it will be interesting to study how to optimize the control strategies with the current ITNs and IRS.

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