Research Article

Malaria Transmission Model with Transmission-Blocking Drugs and a Time Delay

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A class of transmission-blocking drugs (TBDs) that block the transmission of parasites between humans and mosquitoes has recently been shown to be effective in controlling malaria transmission. In this paper, we develop a time-delay differential equation model for malaria using TBDs intervention, in which the human population consists of a treated class and a successfully treated class. In classifying the positive equilibria, the control reproduction number R_T was obtained and the forward and backward branching cases were explored. Then, by constructing a Lyapunov function, the disease-free equilibrium is globally asymptotically stable under certain conditions. In addition, when $R_T > 1$, the model exhibits Hopf bifurcation, the positive equilibrium becomes unstable from stable, and the model exhibits a periodic solution due to the change of time delay. On the other hand, it is concluded that the use of TBDs has a positive effect on disease control when the treatment rate and the efficacy of TBDs meet certain conditions. Finally, numerical simulation was used to observe the effect of treatment rate and the efficacy of TBDs on R_T , and it was found that the increase in the efficacy of TBDs had a more pronounced effect on disease control compared to treatment rate.

1. Introduction

Malaria is an insect-borne disease caused by *Plasmodium* infection through the bite of *Anopheles* mosquitoes or by importing the blood of a person with *Plasmodium* and is a major infectious disease that seriously endangers people's health and life safety. The first symptoms of malaria usually appear 10–15 days after people are bitten by mosquitoes that have been infected with the virus. The disease mainly manifests as periodic regular attacks with generalized chills, fever, and excessive sweating, and after many long-term attacks, it can cause anemia and splenomegaly. *Plasmodium falciparum* can lead to the most serious diseases (see [1]). WHO once ranked malaria as one of the top three global public health problems, along with AIDS and Tuberculosis. Data from 1980 to 2010 show that malaria infection rates have declined, but mortality remains a concern. To date, malaria remains a serious global epidemic, with about 40% of the world's population living

in malaria-endemic regions, 90% of which are on the African continent. More than 2 million people die from malaria each year, especially children under five years of age, pregnant women, and those suffering from other diseases (see [2]). The tropics and subtropics are the most malaria-prone regions, forming a "malaria belt" around the equator that includes Latin America, sub-Saharan Africa, South Asia, and Southeast Asia. WHO data show that, in 2017, there were an estimated 219 million cases of malaria in 87 countries, and in 2019, there were an estimated 229 million malaria cases worldwide, with an estimated 409,000 malaria deaths.

Early diagnosis and treatment of malaria can reduce disease and avert deaths, and since 2000, the expansion of vector control interventions has led to progress in malaria control, particularly in sub-Saharan Africa (see [3]). The best available treatments, particularly for *falciparum* malaria, are artemisinin-based combination therapies. However, these gains are jeopardized by the emergence of

resistance to antimalarial drugs in *Anopheles* mosquitoes. Furthermore, some studies have shown an increase in resistance to artemisinin combination therapies paired with drugs (see [4, 5]). Rather than relying on vector control to prevent mosquito bites, the transmission of gametocytes (the intraerythrocytic sexual stages) to the mosquito is potentially more amenable to direct intervention because it is easily targetable within the human blood compartment (see [6]). Most antimalarial drugs are inactive against the sexual stage of *P. falciparum*, and for effective long-term malaria control, measures are needed to stop the transmission of *P. falciparum* between humans and mosquitoes. Several studies have shown that a potential approach to directly block parasite transmission is to target *Plasmodium* using transmission-blocking interventions (TBIs), which can be broadly categorized as transmission-blocking drugs (TBDs) or transmission-blocking vaccines (TBVs) that target parasitic stages (see [7]). These drugs can be divided into two categories, one targeting the parasitic stage exposed only in mosquitoes and the other targeting the parasitic stage exposed only in humans. For TBDs that target parasites in humans, drugs can kill the asexual phase of the parasite, stopping/reducing development to gametes, drugs target immature and mature gametes in humans directly, or drugs provide chemotherapeutic prophylaxis by direct action on Sporozoa, thus stopping infection. From these aspects, there are many scholars working on transmission-blocking drugs that can block the different stages of the parasite within the host. Antimalarial drugs with transmission-blocking activity have been prioritized, and several are in various stages of clinical development (see [8]).

Exploring the dynamics of infectious diseases through mathematical modeling can be used to guide disease control. A number of mathematicians have explored the dynamics of malaria transmission between humans and mosquitoes by modeling differential equations. Following the studies of Ross (see [9]) and Macdonald (see [10]), a series of differential equation models for malaria have been proposed one after another from different perspectives (see [11–16]). In recent years, Ngwa proposed a deterministic differential equation model for malaria epidemics (see [17]), in which human and mosquito populations have SEIR and SEI structures, respectively, and most subsequent studies have followed this structure. Chitnis proposed a mathematical model for the transmission of malaria in populations and mosquitoes with ordinary differential equations (see [18]), and numerical simulations showed that, for larger disease lethality, subcritical (backward) bifurcation may occur when the basic reproduction number is equal to 1. In 2008, Chitnis identified important parameters of malaria transmission by sensitivity analysis of the mathematical model (see [19]). Ruan considered the incubation period of the parasite in humans and mosquitoes and proposed a delayed Ross-Macdonald model

(see [20]), which demonstrated that the basic reproduction number is a decreasing function of two time delays and that the prevalence of infection can be reduced by extending the incubation period in humans or mosquitoes. In the context of some progress in new antimalarial drug research, a regional deterministic model assessed the effectiveness of a malaria transmission-blocking vaccine targeting the parasitic stage of mosquitoes (see [21]). In addition, a mathematical model assessed the role of gametocytes (the infectious stage of the malaria parasite) in the dynamics of malaria transmission (see [22]), which was extended to include some hypothetical therapeutic features of an imperfect vaccine.

Mathematical models of drug in-host kinetics are often used to guide drug development, and these models often focus on assessing efficacy and response duration to guide patient treatment (see [23]). Based on this motivation, in this paper, we refer to the modeling ideas from the literature (see [24]) and add TBDs targeting parasite blockade in humans to the malaria model, assuming that a fraction of human infected patients are treated with TBDs and that a fraction of patients successfully block parasite transmission to mosquitoes after treatment with TBDs. In addition, usually, people develop the first symptoms of malaria after being infected with the virus for a period of time (see [25, 26]). Being undetected during the incubation period leads to an increased risk of malaria infection in humans by not treating the parasite promptly or using TBDs to block transmission to mosquitoes in a timely manner. Based on these two considerations, this paper develops a differential equation model considering TBDs and a time delay and is dedicated to analyzing the effect of the incubation period of *Plasmodium* in humans on the stability of the model's equilibrium, as well as the effect of treatment with TBDs on malaria control in humans, and to assessing the range of treatment rate and the efficacy of TBDs that can contribute most to malaria control under certain conditions.

2. Model Description

In this model, the total human population N_h is divided into susceptible individuals S_h , infected individuals I_h , patients treated with TBDs T_h , successful treatment with TBDs and not transmitting gamete cells to mosquito individuals P_h , and recovered individuals but partially lost their immunity R_h . The total mosquito population N_v is divided into susceptible mosquitoes S_v and infected mosquitoes I_v . At any time t , the human population has the expression $N_h(t) = S_h(t) + I_h(t) + T_h(t) + P_h(t) + R_h(t)$ and the mosquito population has the expression $N_v(t) = S_v(t) + I_v(t)$. The period from the time of human being infected with *Plasmodium* to the time of onset is recorded as the time delay τ . The model considered in this paper is

$$\begin{cases}
\frac{dS_h(t)}{dt} = \Lambda_h + \gamma_h R_h(t) + v P_h(t) - r \rho_v \frac{I_v(t-\tau)}{N_h(t-\tau)} S_h(t-\tau) e^{-d_h \tau} - d_h S_h(t), \\
\frac{dI_h(t)}{dt} = r \rho_v \frac{I_v(t-\tau)}{N_h(t-\tau)} S_h(t-\tau) e^{-d_h \tau} + \kappa_h \psi_2 T_h(t) - (d_h + \delta_h + \theta_h + \alpha_h) I_h(t), \\
\frac{dT_h(t)}{dt} = \alpha_h I_h(t) - \psi_1 T_h(t) - \kappa_h \psi_2 T_h(t) - (1 - \kappa_h) \psi_2 T_h(t) - d_h T_h(t), \\
\frac{dP_h(t)}{dt} = \psi_1 T_h(t) - v P_h(t) - d_h P_h(t), \\
\frac{dR_h(t)}{dt} = \theta_h I_h(t) + (1 - \kappa_h) \psi_2 T_h(t) - \gamma_h R_h(t) - d_h R_h(t), \\
\frac{dS_v(t)}{dt} = \Lambda_v - r \rho_h \frac{I_h(t) + \xi_t T_h(t) + \xi_r R_h(t)}{N_h(t)} S_v(t) - d_v S_v(t), \\
\frac{dI_v(t)}{dt} = r \rho_h \frac{I_h(t) + \xi_t T_h(t) + \xi_r R_h(t)}{N_h(t)} S_v(t) - d_v I_v(t),
\end{cases} \quad (1)$$

where Λ_h and Λ_v are the input of susceptible humans and susceptible mosquitoes, respectively, and d_h and d_v are the natural mortality rates of humans and mosquitoes, respectively. The exponential term $e^{-d_h \tau}$ represents the human survival rate during the incubation period. γ_h is the immune loss rate after human recovery, and v represents the rate of loss protection and transfer to the susceptible class. ψ_1 is the percentage of patients who were successfully protected after TBDs treatment, and ψ_2 is the percentage of patients who were not protected after TBDs treatment. Among the patients who were not protected after TBDs treatment, $\kappa_h \psi_2$ is the rate of being moved to infection class, and $(1 - \kappa_h) \psi_2$ is the rate of being moved to the recovery class. ψ_1 and ψ_2 are functions of p_e (p_e is the efficacy of TBDs), ψ_1 is proportional to p_e , and ψ_2 is inversely proportional to p_e , respectively, expressed as simple functions $\psi_1 = \eta_h p_e$ and $\psi_2 = \mu_h (1 - p_e)$. η_h is the effective rate of TBDs treatment. μ_h is the rate of ineffective TBDs treatment. α_h represents the rate of infected patients receiving TBDs treatment (abbreviated as treatment rate), δ_h is the human mortality rate due to disease, and θ_h is the human recovery rate after infection. $f_h = r \rho_v (I_h/N_h)$ is the human infection rate, where r is the average number of times a mosquito bites a human and ρ_v is the probability of human infection for each bite of mosquito. $f_v = r \rho_h ((I_h + \xi_t T_h + \xi_r R_h)/N_h)$ represents the infection rate of mosquitoes, and ρ_h represents the probability of mosquito infection per bite. ξ_t and ξ_r represent the relative infection rates respectively, and $0 < \xi_r < \xi_t < 1$. Let $\beta_{1h} = d_h + \delta_h + \theta_h + \alpha_h$, assuming that the input of the susceptible population is greater than the natural human mortality rate ($\Lambda_h > d_h$); otherwise, the human will go extinct.

Let $C = C([- \tau, 0], R_+^7)$ be a Banach space of continuous functions mapping the interval $[- \tau, 0]$ into R_+^7 with upper bound norm. According to the biological significance, the initial conditions of system (1) are given

$$\begin{aligned}
S_h(\theta) &= \varphi_1(\theta), \\
I_h(\theta) &= \varphi_2(\theta), \\
T_h(\theta) &= \varphi_3(\theta), \\
P_h(\theta) &= \varphi_4(\theta), \\
R_h(\theta) &= \varphi_5(\theta), \\
I_v(\theta) &= \varphi_6(\theta), \\
N_v(\theta) &= \varphi_7(\theta), \\
\theta &\in [- \tau, 0].
\end{aligned} \quad (2)$$

Among them

$$\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6, \varphi_7)^T \in C^+, \quad (3)$$

where

$$C^+ = \{ \varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6, \varphi_7)^T \in C: \varphi_i \geq 0, i = 1, 2, \dots, 7 \}. \quad (4)$$

According to the basic theory of functional differential equation, system (1) has a unique solution which satisfies the initial conditions.

According to the first five equations of system (1), for $t \geq 0$, there is

$$\dot{N}_h = \dot{S}_h + \dot{I}_h + \dot{T}_h + \dot{P}_h + \dot{R}_h = \Lambda_h - d_h N_h - \delta_h I_h. \quad (5)$$

Thus, $\lim_{t \rightarrow +\infty} \sup N_h(t) \leq (\Lambda_h/d_h) \equiv N_{h\max}$. Similarly, from the last two expressions of system (1), there is $\lim_{t \rightarrow +\infty} \sup N_v(t) \leq (\Lambda_v/d_v) \equiv N_{v\max}$. Therefore, the solution of system (1) is ultimately uniformly bounded.

Let

$$\Omega = \{(N_h, N_v) | 0 < N_h \leq N_{h\max}, 0 < N_v \leq N_{v\max}\}, \quad (6)$$

and then all trajectories in the first quadrant of system (1) will enter or stay in Ω . Therefore, all variables on Ω are nonnegative and ultimately uniformly bounded, and the initial value problem of system (1) satisfies the biological significance. Next, the dynamic properties of system (1) are considered on Ω .

In the third section, the control reproduction number and the classification of the equilibrium are calculated, which indicates that the system has a backward bifurcation. In the fourth section, the local stability and global stability of the disease-free equilibrium are discussed. In the fifth section, the influence of TBDs on the propagation of the model is discussed. In the sixth section, the local stability of the endemic equilibrium and the existence of Hopf bifurcation are analyzed. Finally, numerical simulation is used to verify the conclusions obtained in this paper.

3. The Existence of Equilibrium

In this section, the equilibria of the model are classified and the control reproduction number of the model is determined.

When there is no infection, the system has a stable state. Supposing that the disease-free equilibrium is $E_0 = (S_h^0, I_h^0, T_h^0, P_h^0, R_h^0, S_v^0, I_v^0)$, it is easy to obtain $E_0 = ((\Lambda_h/d_h), 0, 0, 0, 0, (\Lambda_v/d_v), 0)$.

When infection exists, the endemic equilibrium $E^* = (S_h^*, I_h^*, T_h^*, P_h^*, R_h^*, S_v^*, I_v^*)$ of system (1) satisfies the following equations:

$$\begin{cases} \Lambda_h + \gamma_h R_h^* + v P_h^* - f_h^* S_h^* e^{-d_h \tau} - d_h S_h^* = 0, \\ f_h^* S_h^* e^{-d_h \tau} + \kappa_h \psi_2 T_h^* - \beta_{1h} I_h^* = 0, \\ \alpha_h I_h^* - \psi_1 T_h^* - \kappa_h \psi_2 T_h^* - (1 - \kappa_h) \psi_2 T_h^* - d_h T_h^* = 0, \\ \psi_1 T_h^* - v P_h^* - d_h P_h^* = 0, \\ \theta_h I_h^* + (1 - \kappa_h) \psi_2 T_h^* - \gamma_h R_h^* - d_h R_h^* = 0, \\ \Lambda_v - f_v^* S_v^* - d_v S_v^* = 0, \\ f_v^* S_v^* - d_v I_v^* = 0. \end{cases} \quad (7)$$

From the first five equations, it follows that

$$\begin{cases} S_h^* = \frac{K_2 I_h^*}{T_1 f_h^* e^{-d_h \tau}}, \\ T_h^* = \frac{\alpha_h I_h^*}{T_1}, \\ P_h^* = \frac{\alpha_h \psi_1 I_h^*}{T_1 T_2}, \\ R_h^* = \frac{\theta_h T_1 + (1 - \kappa_h) \alpha_h \psi_2}{T_1 T_3} I_h^*, \\ I_h^* = \frac{a_1 f_h}{a_2 f_h + a_3}, \end{cases} \quad (8)$$

where

$$T_1 = \psi_1 + \psi_2 + d_h,$$

$$T_2 = v + d_h,$$

$$T_3 = \gamma_h + d_h,$$

$$K_1 = T_1 T_3 + \xi_t \alpha_h T_3 + \xi_r K_5,$$

$$K_2 = \beta_{1h} T_1 - \kappa_h \alpha_h \psi_2 > 0,$$

$$K_3 = \kappa_h \psi_2 \theta_h + (1 - \kappa_h) \psi_2 \beta_{1h},$$

$$K_4 = \frac{r \rho_v \Lambda_v d_h}{\Lambda_h d_v},$$

$$K_5 = \theta_h T_1 + \alpha_h \psi_2 (1 - \kappa_h),$$

$$a_1 = \Lambda_h T_1 T_2 T_3 e^{-d_h \tau} > 0,$$

$$a_2 = T_2 T_3 K_2 e^{-d_h \tau} - T_2 \gamma_h K_5 e^{-d_h \tau} - v \alpha_h \psi_1 T_3 e^{-d_h \tau} > 0,$$

$$a_3 = T_2 T_3 d_h K_2 > 0.$$

(9)

From the model, there are

$$N_h^* = \frac{\Lambda_h - \delta_h I_h^*}{d_h}, \quad (10)$$

$$N_v^* = \frac{\Lambda_v}{d_v}.$$

Substituting the expressions of I_h^* , T_h^* , R_h^* , and N_h^* in (8) and (10) into $f_v = r \rho_h ((I_h + \xi_t T_h + \xi_r R_h)/N_h)$, then

$$f_v^* = \frac{r\rho_h d_h a_1 K_1 f_h^*}{T_1 T_3 b_1 f_h^* + T_1 T_3 a_3 \Lambda_h}, \quad (11)$$

where $b_1 = a_2 \Lambda_h - a_1 \delta_h > 0$ and $K_1 = T_1 T_3 + \xi_t \alpha_h T_3 + \xi_r K_5 > 0$.

It can be obtained from the last two equations of (7) that

$$\begin{aligned} S_v^* &= \frac{\Lambda_v}{f_v^* + d_v}, \\ I_v^* &= \frac{\Lambda_v f_v^*}{d_v (f_v^* + d_v)}. \end{aligned} \quad (12)$$

Substituting the expressions of I_v^* and N_h^* in (12) and (10) into $f_h = r\rho_v (I_v/N_h)$, then

$$f_h^* = \frac{r\rho_v \Lambda_v d_h (a_2 f_h^* + a_3) f_v^*}{d_v (f_v^* + d_v) (b_1 f_h^* + a_3 \Lambda_h)}. \quad (13)$$

From (11) and (13), the quadratic equation of one variable about f_h^* is obtained as follows:

$$F(f_h^*) = l_1 f_h^{*2} + l_2 f_h^* + l_3 = 0, \quad (14)$$

where

$$\begin{aligned} l_1 &= r\rho_h d_h d_v a_1 b_1 K_1 + T_1 T_3 d_v^2 b_1^2, \\ l_2 &= \frac{\Lambda_h d_h d_v^2 a_1 a_2 K_2 T_3}{e^{-d_h \tau}} \left(\frac{e^{-d_h \tau} (r\rho_h d_h a_1 a_3 K_1 + 2T_1 T_3 d_v b_1 a_3)}{d_h d_v a_1 a_2 K_2 T_3} - R_T \right), \\ l_3 &= T_1 T_3 d_v^2 \Lambda_h^2 a_3^2 (1 - R_T), \\ R_T &= \frac{r^2 \rho_h \rho_v \Lambda_v d_h K_1 e^{-d_h \tau}}{\Lambda_h d_v^2 K_2 T_3}. \end{aligned} \quad (15)$$

R_T is defined as the control reproduction number of the model.

It follows that the number of positive equilibria of system (1) depends on the number of positive roots of equation (14). For equation (14), there are $F(0) = T_1 T_3 d_v^2 \Lambda_h^2 a_3^2 (1 - R_T)$ and $l_1 > 0$. When $R_T > 1$, there are $F(0) < 0$ and $\lim_{f_h^* \rightarrow +\infty} F(f_h^*) > 0$. Thus, when $R_T > 1$, equation (14) must have a unique positive root, denoted as f_h^* .

Let

$$\begin{aligned} M &= \frac{e^{-d_h \tau} (r\rho_h d_h a_1 a_3 K_1 + 2T_1 T_3 d_v b_1 a_3)}{d_h d_v a_1 a_2 K_2 T_3}, \\ N &= \frac{\Lambda_h d_h d_v^2 a_1 a_2 K_2 T_3}{e^{-d_h \tau}}, \\ Q &= T_1 T_3 d_v^2 \Lambda_h^2 a_3^2, \end{aligned} \quad (16)$$

and then $M > 0$, $N > 0$, and $Q > 0$.

When $R_T = 1$, there are $l_3 = 0$ and $F(f_h^*) = l_1 f_h^{*2} + l_2 f_h^*$. Thus, when $l_2 < 0$, namely, $M < 1$, equation (14) has a unique positive root.

When $R_T < 1$, there is $F(0) > 0$. If $M > 1$, equation (14) has no positive roots; positive roots of equation (14) are possible only when $M < 1$. Further, for equation (14) to have positive roots, the condition $M < R_T$ needs to be satisfied.

The discriminant of $F(f_h^*) = 0$ is $\Delta = l_2^2 - 4l_1 l_3$; rearrange it as a function of R_T and call it $\Delta(R_T)$.

Let

$$R^* \triangleq \frac{MN^2 - 2l_1 Q + 2\sqrt{l_1^2 Q^2 + l_1 N^2 Q(1 - M)}}{N^2}. \quad (17)$$

By simple computations, it has $\Delta(0) > 0$, $\Delta(M) < 0$, $\Delta(R^*) = 0$, and $\Delta(1) > 0$. Thus, $0 < M < R^* < 1$.

If $R^* < R_T < 1$, equation (14) has two positive roots, denoted as f_h^* and f_h^{**} . If $R_T = R^*$, equation (14) has a positive root, denoted as f_h^* . If $0 < R_T < R^*$, equation (14) has no positive root. Based on the above analysis, the following theorem can be obtained.

Theorem 1. System (1) always has a disease-free equilibrium $E_0 = ((\Lambda_h/d_h), 0, 0, 0, 0, (\Lambda_v/d_v), 0)$. In addition, system (1) also has the following endemic equilibrium:

(i) If $R_T > 1$, system (1) has a unique positive equilibrium $E^* = (S_h^*, I_h^*, T_h^*, P_h^*, R_h^*, S_v^*, I_v^*)$

(ii) If $M < 1$, there are three situations:

- (1) If $R_T = 1$, system (1) has a unique positive equilibrium $E^* = (S_h^*, I_h^*, T_h^*, P_h^*, R_h^*, S_v^*, I_v^*)$
- (2) If $R^* < R_T < 1$, system (1) has two positive equilibria $E^* = (S_h^*, I_h^*, T_h^*, P_h^*, R_h^*, S_v^*, I_v^*)$ and $E^{**} = (S_h^{**}, I_h^{**}, T_h^{**}, P_h^{**}, R_h^{**}, S_v^{**}, I_v^{**})$
- (3) If $R_T = R^*$, system (1) has a unique positive equilibrium $E' = (S_h', I_h', T_h', P_h', R_h', S_v', I_v')$

The positive roots of equation (14) are expressed as

$$\begin{aligned}
f_h^* &= \frac{-l_2 + \sqrt{\Delta}}{2l_1}, \\
f_h^{**} &= \frac{-l_2 - \sqrt{\Delta}}{2l_1}, \\
f_h' &= \frac{-l_2}{2l_1}.
\end{aligned} \tag{18}$$

4. Stability of the Disease-Free Equilibrium

In this section, the local stability of the disease-free equilibrium is discussed by using the characteristic equation of the linear approximation equation of system (1). In addition, the global stability of the disease-free equilibrium is obtained by constructing the Lyapunov function when the time delay is zero.

4.1. Local Stability of the Disease-Free Equilibrium. For the local stability of the disease-free equilibrium E_0 , the following conclusions are obtained.

Theorem 2. *If $R_T < 1$, the disease-free equilibrium E_0 is locally asymptotically stable for any $\tau \geq 0$; if $R_T > 1$, E_0 is unstable for any $\tau \geq 0$.*

Proof. It is shown that the characteristic equation of system (1) at E_0 is

$$L_0(\lambda, \tau) = \lambda^4 + A_3\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 + e^{-\lambda\tau}(B_2\lambda^2 + B_1\lambda + B_0) = 0, \tag{19}$$

where

$$\begin{aligned}
A_3 &= T_1 + T_3 + d_v + \beta_{1h}, \\
A_2 &= K_2 + d_v T_3 + (T_3 + d_v) + (T_1 + \beta_{1h}), \\
A_1 &= d_v T_3 (T_1 + \beta_{1h}) + (T_3 + d_v) K_2, \\
A_0 &= d_v T_3 K_2, \\
B_2 &= -r\rho_v K_4 e^{-d_h\tau}, \\
B_1 &= -r\rho_v K_4 (T_1 + T_3 + \theta_h \xi_r + \alpha_h \xi_t) e^{-d_h\tau}, \\
B_0 &= -r\rho_v K_4 K_1 e^{-d_h\tau}.
\end{aligned} \tag{20}$$

When $\tau = 0$, equation (19) is rewritten as

$$L_1(\lambda) = \lambda^4 + m_3\lambda^3 + m_2\lambda^2 + m_1\lambda + m_0 = 0, \tag{21}$$

where $m_3 = A_3$, $m_2 = A_2 + B_2$, $m_1 = A_1 + B_1$, and $m_0 = A_0 + B_0$.

When $R_T < 1$, there are

$$\begin{aligned}
m_3 &= A_3 > 0, \\
m_2 &= A_2 + B_2 > K_2 + d_v(T_1 + T_3) + T_3(T_1 + \beta_{1h}) > 0, \\
m_1 &= A_1 + B_1 > d_v T_1 T_3 + T_3 K_2 > 0, \\
m_0 &= A_0 + B_0 = d_v T_3 K_2 (1 - R_T) > 0.
\end{aligned} \tag{22}$$

Next, consider the signs of $\Delta_2 = m_3 m_2 - m_1$ and $\Delta_3 = m_1 (m_3 m_2 - m_1) - m_0 m_3^2$.

$$\begin{aligned}
\Delta_2 &= m_3 m_2 - m_1 \\
&> a_3 [d_v T_1 + T_3 (T_1 + \beta_{1h})] + (T_1 + \beta_{1h}) K_2 \\
&\quad + (d_v + T_3) d_v T_3 + r\rho_v K_4 (T_1 + T_3 + \theta_h \xi_r + \alpha_h \xi_t) > 0, \\
\Delta_3 &= m_1 (m_3 m_2 - m_1) - m_0 m_3^2 \\
&> (T_3 K_2 + d_v T_1 T_3) [K_2 (T_1 + \beta_{1h}) + d_v T_3 (d_v + T_3)] \\
&\quad + T_3^2 K_2 a_3 (T_1 + \beta_{1h}) + d_v T_1^2 T_3 a_3 (d_v + T_3) + r\rho_v K_4 a_3 T_1 T_3 (T_1 + T_3) > 0.
\end{aligned} \tag{23}$$

According to the Routh–Hurwitz criterion, when $\tau = 0$ and $R_T < 1$, the disease-free equilibrium E_0 is locally asymptotically stable. Next, the local stability of disease-free equilibrium E_0 is discussed when $\tau > 0$. Suppose that, for some $\tau > 0$, equation (19) has a pure imaginary root $\lambda = i\omega$, $\omega > 0$. Substituting $\lambda = i\omega$ into equation (19), then equation (19) becomes

$$\begin{aligned}
&\omega^4 - A_3\omega^3 i - A_2\omega^2 + A_1\omega i + A_0 + (\cos \omega\tau - i \sin \omega\tau) \\
&\quad \cdot (-B_2\omega^2 + B_1\omega i + B_0) = 0.
\end{aligned} \tag{24}$$

Separating the real part and the imaginary part gives

$$\begin{cases} (-B_2\omega^2 + B_0)\cos \omega\tau + B_1\omega \sin \omega\tau = -\omega^4 + A_2\omega^2 - A_0, \\ B_1\omega \cos \omega\tau - (-B_2\omega^2 + B_0)\sin \omega\tau = A_3\omega^3 - A_1\omega. \end{cases} \tag{25}$$

Then ω must be the root of the following equation:

$$\omega^8 + c_3\omega^6 + c_2\omega^4 + c_1\omega^2 + c_0 = 0. \tag{26}$$

Let $z = \omega^2$; then equation (26) becomes the following equation:

$$z^4 + c_3z^3 + c_2z^2 + c_1z + c_0 = 0, \tag{27}$$

where

$$\begin{aligned}
c_3 &= A_3^2 - 2A_2, \\
c_2 &= A_2^2 + 2A_0 - 2A_1A_3 - B_2^2, \\
c_1 &= A_1^2 - 2A_0A_2 - B_1^2 + 2B_0B_2, \\
c_0 &= A_0^2 - B_0^2.
\end{aligned} \tag{28}$$

When $R_T < 1$, there are

$$\begin{aligned}
c_0 &= d_v^2 T_3^2 K_2^2 (1 - R_T^2) > 0, \\
c_1 &> d_v^2 T_1^2 T_3^2 + k_2^2 T_3^2 + 2r^2 \rho_v^2 K_4^2 \xi_r \alpha_h \psi_2 (1 - \kappa_h) \\
&\quad + 2d_v^2 T_3^2 \kappa_h \alpha_h \psi_2 > 0, \\
c_2 &> K_2^2 + d_v^2 (T_3^2 + T_1^2) + T_3^2 (T_1^2 + \beta_{1h}^2) > 0, \\
c_3 &> T_1^2 + T_3^2 + \beta_{1h}^2 + d_v^2 > 0.
\end{aligned} \tag{29}$$

Therefore, when $R_T < 1$, equation (27) has no positive root.

According to the above analysis, when $R_T < 1$, all the roots of the characteristic equation (19) have negative real parts, and the disease-free equilibrium E_0 is locally asymptotically stable. When $R_T > 1$, there are $L_0(0, \tau) = d_v T_3 K_2 (1 - R_T) < 0$ and $\lim_{\lambda \rightarrow +\infty} L_0(\lambda, \tau) > 0$, the characteristic equation (19) has at least one positive real root, and then the disease-free equilibrium E_0 is unstable. $\square$

4.2. Global Stability of the Disease-Free Equilibrium. From the above discussion, the disease-free equilibrium E_0 is locally asymptotically stable when $R_T < 1$. In this section, the global stability of disease-free equilibrium E_0 is considered at $\tau = 0$.

Let

$$\begin{aligned}
\tilde{R} &= \frac{d_h^2 K_1}{\Lambda_h K_2 T_3}, \\
\Gamma &= \left\{ (S_h, I_h, T_h, P_h, R_h, S_v, I_v) \in R_+^7 : 0 < S_h + I_h + T_h + P_h + R_h \leq \frac{\Lambda_h}{d_h}; 0 < S_v + I_v \leq \frac{\Lambda_v}{d_v} \right\}.
\end{aligned} \tag{30}$$

Theorem 3. If $R_T < \tilde{R}$, the disease-free equilibrium E_0 is globally asymptotically stable in Γ at $\tau = 0$.

Proof. It can be seen from the above section that the disease-free equilibrium E_0 is locally asymptotically stable. Next, only the global attraction of the disease-free equilibrium E_0 is required to be proved.

By calculation, there is

$$\tilde{R} = \frac{d_h^2 K_1}{\Lambda_h K_2 T_3} \leq \frac{d_h^2 K_1}{\Lambda_h d_h K_1 + K_6} < 1, \tag{31}$$

where $K_6 = \Lambda_h [\delta_h T_1 T_3 + \theta_h T_1 \gamma_h + \alpha_h \psi_1 T_3 + \alpha_h \psi_2 (1 - \kappa_h) \gamma_h] > 0$.

Constructing the Lyapunov function on Γ ,

$$V = \frac{r \rho_h \Lambda_v}{d_h d_v} I_h + \frac{r \rho_h \Lambda_v}{d_h d_v} T_h + \frac{r \rho_h \Lambda_v}{d_h d_v} R_h + I_v. \tag{32}$$

$V(t)$ is positive and bounded according to the non-negative uniform boundedness of the solution. The total derivative of $V(t)$ along the solution x_i of system (1) is

$$\begin{aligned}
\dot{V}(x_t) &= \frac{r\rho_h\Lambda_v}{d_h d_v} \dot{I}_h + \frac{r\rho_h\Lambda_v}{d_h d_v} \dot{T}_h + \frac{r\rho_h\Lambda_v}{d_h d_v} \dot{R}_h + \dot{I}_v \\
&= \frac{r\rho_h\Lambda_v}{d_h d_v} \left(r\rho_v \frac{I_v}{N_h} S_h e^{-d_h \tau} + \kappa_h \psi_2 T_h - \beta_{1h} I_h + \alpha_h I_h - \psi_1 T_h - \psi_2 T_h - d_h T_h \right) \\
&\quad + \frac{r\rho_h\Lambda_v}{d_h d_v} [\theta_h I_h + (1 - \kappa_h) \psi_2 T_h - \gamma_h R_h - d_h R_h] + r\rho_h \frac{I_h + \xi_t T_h + \xi_r R_h}{N_h} S_v - d_v I_v \\
&\leq \frac{r\rho_h\Lambda_v}{d_h d_v} [r\rho_v I_v e^{-d_h \tau} - (d_h + \delta_h) I_h - \psi_1 T_h - d_h T_h - \gamma_h R_h - d_h R_h] \\
&\quad + \frac{r\rho_h\Lambda_v}{d_v} (I_h + T_h + R_h) - d_v I_v \\
&\leq d_v \left(\frac{R_T}{\bar{R}} - 1 \right) I_v - \frac{r\rho_h\Lambda_v}{d_h d_v} (\delta_h I_h + \psi_1 T_h + \gamma_h R_h).
\end{aligned} \tag{33}$$

When $R_T < \bar{R}$, there is $\dot{V}(x_t) \leq 0$, if and only if $I_v = 0$, $I_h = 0$, $T_h = 0$, and $R_h = 0$, and there is $\dot{V}(x_t) = 0$. Define the set

$$\Sigma = \left\{ (S_h, I_h, T_h, P_h, R_h, S_v, I_v) \in \Gamma \mid \frac{dV}{dt} = 0 \right\}. \tag{34}$$

Let M be the largest invariant set in Σ . From system (1) and the invariant property of M , $M = \{E_0\}$ can be obtained. According to the Lyapunov–LaSalle principle, the solutions of system (1) with initial conditions in Γ all approach the disease-free equilibrium E_0 at $t \rightarrow +\infty$. That is, when $R_T < \bar{R}$, there is $(S_h(t), I_h(t), T_h(t), P_h(t), R_h(t), S_v(t), I_v(t)) \rightarrow ((\Lambda_h/d_h), 0, 0, 0, 0, (\Lambda_v/d_v), 0)$; the disease-free equilibrium E_0 is globally asymptotically stable. $\square$

5. Assessment of TBDs

In order to effectively control malaria for a long time, it is necessary to know what conditions the parameters meet when the use of TBDs plays a positive role in disease control. In this section, the impact of the use of TBDs on malaria transmission is analyzed. Firstly, the treatment rate α_h was taken as the main parameter to consider the influence of α_h on the control reproduction number R_T .

Let

$$\begin{aligned}
c_0 &= r^2 \rho_h \rho_v \Lambda_v d_h e^{-d_h \tau}, \\
c_1 &= T_1 (T_3 + \xi_r \theta_h), \\
c_2 &= T_1 (d_h + \delta_h + \theta_h), \\
d_0 &= T_3 \Lambda_h d_v^2, \\
d_1 &= \xi_t T_3 + \xi_r \psi_2 (1 - \kappa_h), \\
d_2 &= T_1 - \kappa_h \psi_2.
\end{aligned} \tag{35}$$

The derivative of R_T with respect to α_h is

$$\frac{dR_T}{d\alpha_h} = \frac{c_0 (c_2 d_1 - c_1 d_2)}{d_0 (c_2 + d_2 \alpha_h)^2}, \tag{36}$$

if and only if $c_2 d_1 - c_1 d_2 < 0$, and there is $(dR_T/d\alpha_h) < 0$. In general, when the control reproduction number is less than one, the disease can finally disappear, so there is the following theorem.

Theorem 4. For system (1),

- (1) When $(c_2 d_1 / c_1 d_2) < 1$, the TBDs have a positive effect on reducing the burden of disease
- (2) When $(c_2 d_1 / c_1 d_2) = 1$, the TBDs have no effect on reducing the burden of disease
- (3) When $(c_2 d_1 / c_1 d_2) > 1$, the TBDs have a negative effect on reducing the burden of disease

It is generally believed that the more the people who receive the TBDs treatment, the more the effectiveness on controlling malaria. However, humans treated with TBDs remain infectious; the increase in the number of T_h does not control the disease well. It is worth noting the percentage of humans treated with TBDs who were successfully protected. Next, taking the efficacy of TBDs p_e as the main parameter, to observe which conditions the parameters meet, the TBDs have a positive effect on reducing the burden of disease.

The expression $c_2 d_1 - c_1 d_2$ is rewritten as the expression $T_1 (E_1 + E_2 p_e)$ about the efficacy of TBDs p_e , where

$$\begin{aligned}
E_1 &= (d_h + \delta_h + \theta_h) \xi_r T_3 - d_h T_3 - d_h \theta_h \xi_r - (1 - \kappa_h) T_3 \mu_h + (d_h + \delta_h) \xi_r (1 - \kappa_h) \mu_h, \\
E_2 &= (1 - \kappa_h) T_3 \mu_h - (T_3 + \theta_h \xi_r) \eta_h - (d_h + \delta_h) \xi_r (1 - \kappa_h) \mu_h.
\end{aligned} \tag{37}$$

According to Theorem 4 and equation (36), the following theorem can be obtained.

Theorem 5. For system (1),

- (1) When $E_1 > 0$ and $E_2 > 0$, for any $p_e \in [0, 1]$, the TBDs have a negative effect on reducing the burden of disease
- (2) When $E_1 > 0$ and $E_2 < 0$, if $p_e \in [\min((-E_1/E_2), 1), 1]$, the TBDs have a positive effect on reducing the burden of disease

(3) When $E_1 < 0$ and $E_2 > 0$, if $p_e \in [0, \min((-E_1/E_2), 1)]$, the TBDs have a positive effect on reducing the burden of disease

(4) When $E_1 < 0$ and $E_2 < 0$, for any $p_e \in [0, 1]$, the TBDs have a positive effect on reducing the burden of disease

6. Stability of Positive Equilibrium and Hopf Bifurcation

6.1. Local Stability of Positive Equilibrium. When $R_T > 1$, there is a unique positive equilibrium in system (1), and the characteristic equation of system (1) at E^* is

$$L_2(\lambda, \tau) = \lambda^7 + F_6\lambda^6 + F_5\lambda^5 + F_4\lambda^4 + F_3\lambda^3 + F_2\lambda^2 + F_1\lambda + F_0 + e^{-\lambda\tau}(J_6\lambda^6 + J_5\lambda^5 + J_4\lambda^4 + J_3\lambda^3 + J_2\lambda^2 + J_1\lambda + J_0) = 0. \quad (38)$$

The coefficients of equation (38) are given in Appendix. When $\tau = 0$, the characteristic equation is written as

$$L_3(\lambda) = \lambda^7 + H_6\lambda^6 + H_5\lambda^5 + H_4\lambda^4 + H_3\lambda^3 + H_2\lambda^2 + H_1\lambda + H_0 = 0, \quad (39)$$

where $H_i = F_i + J_i, i = 1, 2, \dots, 6$.

Define

$$\begin{aligned} \Delta_1 &= H_6, \\ \Delta_2 &= \begin{vmatrix} H_6 & 1 \\ H_4 & H_5 \end{vmatrix}, \\ \Delta_3 &= \begin{vmatrix} H_6 & 1 & 0 \\ H_4 & H_5 & H_6 \\ H_2 & H_3 & H_4 \end{vmatrix}, \\ \Delta_4 &= \begin{vmatrix} H_6 & 1 & 0 & 0 \\ H_4 & H_5 & H_6 & 1 \\ H_2 & H_3 & H_4 & H_5 \\ H_0 & H_1 & H_2 & H_3 \end{vmatrix}, \\ \Delta_5 &= \begin{vmatrix} H_6 & 1 & 0 & 0 & 0 \\ H_4 & H_5 & H_6 & 1 & 0 \\ H_2 & H_3 & H_4 & H_5 & H_6 \\ H_0 & H_1 & H_2 & H_3 & H_4 \\ 0 & 0 & H_0 & H_1 & H_2 \end{vmatrix}, \\ \Delta_6 &= \begin{vmatrix} H_6 & 1 & 0 & 0 & 0 & 0 \\ H_4 & H_5 & H_6 & 1 & 0 & 0 \\ H_2 & H_3 & H_4 & H_5 & H_6 & 1 \\ H_0 & H_1 & H_2 & H_3 & H_4 & H_5 \\ 0 & 0 & H_0 & H_1 & H_2 & H_3 \\ 0 & 0 & 0 & 0 & H_0 & H_1 \end{vmatrix}, \\ \Delta_7 &= H_0\Delta_6. \end{aligned} \quad (40)$$

According to the Routh–Hurwitz criterion, if $\Delta_i > 0, i = 1, 2, \dots, 7$, then all the roots of equation (39) have negative real parts.

Theorem 6. When $R_T > 1$ and $\tau = 0$, if $\Delta_i > 0, i = 1, 2, \dots, 7$, then the positive equilibrium E^* is locally asymptotically stable.

In the classification of equilibria in section three, the occurrence of backward bifurcation means that there are two positive equilibria in the system at $R^* < R_T < 1$. The stability analysis of these two positive equilibria will be explained in numerical simulation.

6.2. Existence of Hopf Bifurcation. Suppose that equation (38) has a pure imaginary root $\lambda = i\omega (\omega > 0)$. $\lambda = 0$ is not the root of equation (38) since $A_0 + B_0 \neq 0$. Substituting $\lambda = i\omega$ into equation (38) and separating real and imaginary parts, it follows that

$$\begin{cases} p_1 \cos \omega\tau + p_2 \sin \omega\tau = F_6\omega^6 - F_4\omega^4 + F_2\omega^2 - F_0, \\ p_2 \cos \omega\tau - p_1 \sin \omega\tau = \omega^7 - F_5\omega^5 + F_3\omega^3 - F_1\omega, \end{cases} \quad (41)$$

where $p_1 = -J_6\omega^6 + J_4\omega^4 - J_2\omega^2 + J_0$ and $p_2 = J_5\omega^5 - J_3\omega^3 + J_1\omega$.

Then ω satisfies the equation

$$\omega^{14} + H_6\omega^{12} + H_5\omega^{10} + H_4\omega^8 + H_3\omega^6 + H_2\omega^4 + H_1\omega^2 + H_0 = 0, \quad (42)$$

where

$$\begin{aligned}
H_6 &= F_6^2 - J_6^2 - 2F_5, \\
H_5 &= F_5^2 + 2F_3 - 2F_4F_6 + 2J_4J_6 - J_5^2, \\
H_4 &= F_4^2 + 2F_2F_6 - 2F_1 - 2F_3F_5 - J_4^2 - 2J_2J_6 + 2J_3J_5, \\
H_3 &= F_3^2 + 2F_1F_5 - 2F_0F_6 - 2F_2F_4 - J_3^2 + 2J_0J_6 + 2J_2J_4 - 2J_1J_5, \\
H_2 &= F_2^2 + 2F_0F_4 - 2F_1F_3 - J_2^2 - 2J_0J_4 + 2J_1J_3, \\
H_1 &= F_1^2 - 2F_0F_2 - J_1^2 + 2J_0J_2, \\
H_0 &= F_0^2 - J_0^2.
\end{aligned} \tag{43}$$

Let $z = \omega^2$, and define

$$\begin{aligned}
G(z) &= z^7 + H_6z^6 + H_5z^5 + H_4z^4 + H_3z^3 \\
&\quad + H_2z^2 + H_1z + H_0 = 0.
\end{aligned} \tag{44}$$

Therefore, if equation (38) has a pure imaginary root, then equation $G(z) = 0$ has a positive real root. Assume that

equation (44) has seven positive real roots, denoted as $z_k, k = 1, 2, \dots, 7$.

It can be obtained by calculation that

$$\begin{cases} \cos \sqrt{z_k} \tau = U_k, \\ \sin \sqrt{z_k} \tau = V_k, \end{cases} \tag{45}$$

where

$$\begin{aligned}
U_k &\triangleq \frac{p_3(F_6z_k^3 - F_4z_k^2 + F_2z_k - F_0) + z_k p_4(z_k^3 - F_5z_k^2 + F_3z_k - F_1)}{p_3^2 + z_k p_4^2}, \\
V_k &\triangleq \frac{\sqrt{z_k} p_4(F_6z_k^3 - F_4z_k^2 + F_2z_k - F_0) - \sqrt{z_k} p_3(z_k^3 - F_5z_k^2 + F_3z_k - F_1)}{p_3^2 + z_k p_4^2},
\end{aligned} \tag{46}$$

$$p_3 = -J_6z_k^3 + J_4z_k^2 - J_2z_k + J_0,$$

$$p_4 = J_5z_k^2 - J_3z_k + J_1.$$

Then

$$\tau_k^{(j)} = \begin{cases} \frac{1}{\sqrt{y_k}} [\arccos U_k + 2j\pi], & V_k \geq 0, \\ \frac{1}{\sqrt{y_k}} [2\pi - \arccos U_k + 2j\pi], & V_k < 0, \end{cases} \tag{47}$$

where $k = 1, 2, \dots, 7$ and $j = 0, 1, 2, \dots$. Therefore, the characteristic equation $L_2(\lambda, \tau_k^{(j)}) = 0$ has a pair of pure imaginary roots $\pm i\sqrt{z_k}$.

Let

$$\tau_0 = \tau_{k_0}^{(0)} = \min\{\tau_k^{(j)} | k = 1, 2, \dots, 7; j = 0, 1, 2, \dots\}, \tag{48}$$

$$\omega_0 = \omega_{k_0}.$$

Assuming that $\lambda(\tau) = \alpha(\tau) + i\omega(\tau)$ is the root of equation (38), then $\alpha(\tau_0) = 0$ and $\omega(\tau_0) = \omega_0$.

Theorem 7. Suppose that equation (44) has root $z = \omega_0^2$ and $G'(z) \neq 0$; then $(d\text{Re}(\lambda)/d\tau)|_{\tau=\tau_0}$ and $G'(z)$ have the same sign.

Proof. Firstly, the derivative of λ with respect to τ in the characteristic equation (38) is calculated as follows:

$$\begin{aligned}
\left(\frac{d\lambda}{d\tau}\right)^{-1} &= -\frac{7\lambda^6 + 6F_6\lambda^5 + 5F_5\lambda^4 + 4F_4\lambda^3 + 3F_3\lambda^2 + 2F_2\lambda + F_1}{\lambda(\lambda^7 + F_6\lambda^6 + F_5\lambda^5 + F_4\lambda^4 + F_3\lambda^3 + F_2\lambda^2 + F_1\lambda + F_0)} \\
&\quad + \frac{6J_6\lambda^5 + 5J_5\lambda^4 + 4J_4\lambda^3 + 3J_3\lambda^2 + 2J_2\lambda + J_1}{\lambda(J_6\lambda^6 + J_5\lambda^5 + J_4\lambda^4 + J_3\lambda^3 + J_2\lambda^2 + J_1\lambda + J_0)} - \frac{\tau}{\lambda}.
\end{aligned} \tag{49}$$

TABLE 1: Parameter value range.

Parameter	Range of possible values	Baseline value used	Dim	Reference
Λ_h	$[2.7 \times 10^{-5}, 1000]$	100	$H \times \text{day}^{-1}$	Estimated
Λ_v	$[0.002, 2200]$	200	$V \times \text{day}^{-1}$	Estimated
d_h	$[2.74 \times 10^{-5}, 0.033]$	0.012	day^{-1}	See [24]
d_v	$[0.03302, 0.1]$	0.08	day^{-1}	See [24]
γ_h	$[5 \times 10^{-4}, 1]$	0.01	day^{-1}	Estimated
ν	$[0, 0.1]$	0.01	day^{-1}	See [24]
p_e	$[0, 1]$	0.5	1	See [24]
α_h	$[0, 1]$	0.75	day^{-1}	See [24]
δ_h	$[1 \times 10^{-5}, 5 \times 10^{-2}]$	0.08	day^{-1}	See [24]
θ_h	$[3.5 \times 10^{-5}, 0.2]$	0.2	day^{-1}	See [24]
r	$[0.1, 30]$	5	$H \times V^{-1} \times \text{day}^{-1}$	See [24]
ρ_h	$[0.01, 1]$	0.003	1	See [24]
ρ_v	$[0.072, 1]$	0.24	1	See [24]
ξ_t	$[0.02, 1]$	0.4	1	See [24]
ξ_r	$[0.005, 1]$	0.2	1	See [24]
η_h	$[0, 0.2]$	0.1	day^{-1}	See [24]
μ_h	$[0, 0.2]$	0.2	day^{-1}	See [24]
κ_h	$[0, 1]$	0.6	day^{-1}	See [24]

Substituting $\lambda = i\omega_0$ into equation (49), it follows that

$$\text{Re} \left[\left(\frac{d\lambda}{d\tau} \right)^{-1} \Big|_{\tau=\tau_0} \right] = \frac{G'(\omega_0^2)}{(J_6\omega_0^6 - J_4\omega_0^4 - J_2\omega_0^2 - J_0)^2 + (J_5\omega_0^5 - J_3\omega_0^3 - J_1\omega_0)^2}. \quad (50)$$

Therefore, it can be obtained that

$$\begin{aligned} \text{sign} \left\{ \frac{d\text{Re}(\lambda)}{d\tau} \Big|_{\tau=\tau_0} \right\} &= \text{sign} \left\{ \text{Re} \left[\left(\frac{d\lambda}{d\tau} \right)^{-1} \Big|_{\tau=\tau_0} \right] \right\} \\ &= \text{sign} \{ G'(\omega_0^2) \}. \end{aligned} \quad (51)$$

□

Based on Theorem 7 and Hopf bifurcation theory, the following conclusions can be drawn.

Theorem 8. Suppose that E^* is locally asymptotically stable when $\tau = 0$ and $R_T > 1$; there are the following conclusions:

- (1) If equation (44) has no positive real root, then the equilibrium E^* is locally asymptotically stable for any $\tau \geq 0$
- (2) If equation (44) has a positive real root, when $\tau \in [0, \tau_0)$, the equilibrium E^* is locally asymptotically stable, while when $\tau > \tau_0$, E^* is unstable
- (3) If z_{k_0} is a single root of equation (44), then at $\tau = \tau_0$, system (1) will undergo a Hopf bifurcation

Proof

- (1) If $G(z) = 0$ has no positive real root, then the root of the characteristic equation on the left side of the imaginary axis is still there and does not cross the

imaginary axis. Therefore, for any $\tau \geq 0$, the equilibrium E^* is locally asymptotically stable.

- (2) From the definition of τ_0 , it can be seen that there is no positive root of equation $G(z) = 0$ in the set $\tau \in [0, \tau_0)$, and the root of its characteristic equation still does not cross the imaginary axis. Therefore, when $\tau \in [0, \tau_0)$, the equilibrium E^* is locally asymptotically stable. When $\tau > \tau_0$, equation $G(z) = 0$ has a root with a positive real part; thus, E^* is unstable.
- (3) If z_{k_0} is a single root of equation $G(z) = 0$, then $G'(z_{k_0}) \neq 0$ and $(d\text{Re}(\lambda)/d\tau)|_{\tau=\tau_0} \neq 0$. If $(d\text{Re}(\lambda)/d\tau)|_{\tau=\tau_0} < 0$, then the root of the characteristic equation (38) at τ slightly less than τ_0 has a positive real part, which contradicts the definition of τ_0 . Therefore, $(d\text{Re}(\lambda)/d\tau)|_{\tau=\tau_0} > 0$ and $G'(\omega_0^2) > 0$. If $(d\text{Re}(\lambda)/d\tau)|_{\tau=\tau_0} > 0$, when the value of τ is slightly less than τ_0 , it can be seen from Theorem 6 that all the roots of (38) have negative real parts. When the value of τ is slightly greater than τ_0 , equation (38) has the root with positive real part, which means that system (1) has Hopf bifurcation. □

7. Numerical Simulation

In this section, the conclusions of the paper will be verified by numerical simulation and some of the conclusions will be extended. When selecting parameters, we refer to the parameter range in reference (see [24]), as shown in Table 1.

FIGURE 1: The bifurcation diagrams (a, b) show the change of the number of infected individuals I_h with the control reproduction number R_T .

FIGURE 2: For different initial values, some trajectories tend to disease-free equilibrium E_0 and others to positive equilibrium E^* .

FIGURE 3: All trajectories tend to disease-free equilibrium E_0 .

FIGURE 4: Effects of increased efficacy of TBDs p_e on the number of malaria patients I_h . FIGURE 5: Diagram of the influence of α_h and p_e on the control reproduction number R_T .

Let $\Lambda_h = 100$, $d_h = 0.012$, $d_v = 0.08$, $\delta_h = 0.08$, $\Lambda_v = 200$, $r = 5$, $\rho_h = 0.003$, $\theta_h = 0.2$, $v = 0.01$, $\alpha_h = 0.1$, $\xi_t = 0.4$, $\xi_r = 0.2$, $\eta_h = 0.1$, $\mu_h = 0.2$, $p_e = 0.1$, $\kappa_h = 0.6$, and $\tau = 3$. When $\gamma_h = 0.01$, system (1) exhibits forward bifurcation (Figure 1(a)). When $\gamma_h = 0.6$, system (1) exhibits backward bifurcation (Figure 1(b)); if $\rho_v = 0.88$, then $R^* < R_T < 1$; the system has a bistable phenomenon. The disease-free equilibrium E_0 and the positive equilibrium E^* are locally asymptotically stable, while the positive equilibrium E^{**} is unstable (Figure 2).

Let $\Lambda_h = 5$, $d_h = 0.012$, $d_v = 0.06$, $\delta_h = 0.08$, $\gamma_h = 0.6$, $\Lambda_v = 100$, $r = 0.1$, $\rho_h = 0.002$, $\rho_v = 0.005$, $\theta_h = 0.2$, $v = 0.01$, $\alpha_h = 0.1$, $\xi_t = 0.4$, $\xi_r = 0.2$, $\eta_h = 0.1$, $\mu_h = 0.2$, $p_e = 0.1$, $\kappa_h = 0.6$, and $\tau = 0$; there is $R_T < \tilde{R} < 1$; the disease-free equilibrium E_0 is globally asymptotically stable (Figure 3). Compared with Figure 2, the selected initial values all tend to the disease-free equilibrium E_0 .

In Figures 4(a) and 4(b), the parameters $\gamma_h = 0.9$, $\Lambda_v = 200$, $r = 5$, $\rho_h = 0.003$, $\rho_v = 0.9$, $\theta_h = 0.2$, $v = 0.01$,

$\alpha_h = 0.1$, $\xi_t = 0.4$, $\xi_r = 0.2$, $\eta_h = 0.1$, $\mu_h = 0.2$, and $\kappa_h = 0.6$ are shared, and p_e is a variable. In Figure 4(a), let $\Lambda_h = 100$, $d_h = 0.015$, $d_v = 0.08$, $\delta_h = 0.08$, and $\tau = 3$. In Figure 4(b), let $\Lambda_h = 80$, $d_h = 0.013$, $d_v = 0.09$, $\delta_h = 0.24$, and $\tau = 0.1$. When parameters meet conditions $E_1 = -0.03202 < 0$, $E_2 = -0.02078 < 0$, and $R_T > 1$, according to Theorem 5 (1), with the increase of the efficacy of TBDs $p_e \in [0, 1]$, the number of infected humans I_h gradually decreased (Figure 4(a)). When parameters meet conditions $E_1 = 0.00133 > 0$, $E_2 = -0.0182 < 0$, and $R^* < R_T < 1$, take an initial value that tends to the equilibrium E^* . According to Theorem 5 (3), when $p_e \in [0, 0.073]$, the improvement of the efficacy of TBDs had no significant effect on disease control, while when $p_e \in [0.073, 1]$, the improvement of the efficacy of TBDs has a significant effect on disease control, and the trajectory eventually tends to the disease-free equilibrium E_0 (Figure 4(b)).

Let $d_h = 0.013$, let α_h and p_e be variables, and other parameters are the same as those in Figure 4(a). It can be

FIGURE 6: When $\tau = 4.2$ is less than the threshold $\tau_1^0 = 4.48$, the positive equilibrium E^* is locally asymptotically stable.

FIGURE 7: When $\tau = 5$ is greater than the threshold $\tau_1^0 = 4.58$, E^* is unstable and the system has a stable periodic solution.

found that when the treatment rate α_h is large enough and the efficacy of TBDs p_e is low, the control reproduction number is still greater than 1; when p_e is large enough, the control reproduction number is less than 1 (Figure 5).

Let $\Lambda_h = 855$, $d_h = 0.01$, $d_v = 0.055$, $\delta_h = 0.02$, $\gamma_h = 0.8$, $\Lambda_v = 2100$, $r = 5$, $\rho_h = 0.003$, $\rho_v = 0.8$, $\theta_h = 0.2$, $v = 0.2$, $\alpha_h = 0.02$, $\xi_t = 0.07$, $\xi_r = 0.03$, $\eta_h = 0.2$, $\mu_h = 0.16$, $p_e = 0.16$, and $\kappa_h = 0.2$; there is $R_T > 1$. In Figure 6, when $\tau = 4.2$, there is only one positive real root in equation (44), and the bifurcation threshold $\tau_1^0 = 4.48$ is obtained. In this case, $\tau < \tau_1^0$, the positive equilibrium E^* is locally asymptotically stable in Figure 6. In Figure 7, when $\tau = 5$, only one positive real root exists in equation (44), and the bifurcation threshold is $\tau_1^0 = 4.58$. In this case, $\tau > \tau_1^0$, the positive equilibrium E^* is unstable, and the system has a periodic solution. According to Theorem 8, at τ_1^0 , system (1) undergoes a Hopf bifurcation.

8. Conclusion

In this paper, we establish a time-delay differential equation model with transmission-blocking drugs intervention, the effect of time delay on the stability of the equilibrium was obtained, and the effective range of treatment rate and the

efficacy of TBDs under certain conditions was assessed. In the classification of equilibria, the model appears to have backward bifurcation. The bistable case suggests that disease may exist even if the control reproduction number is less than 1, and the existence of the disease depends on the initial conditions. The global stability of the disease-free equilibrium provides a reference for malaria eradication under certain conditions. In addition, when the parameters meet some conditions, the treatment rate and the efficacy of TBDs play a positive role in disease control. In contrast, the increase in the efficacy of TBDs was more significant for disease control. It is found through Figure 4(b) that, in the bistable case, the trajectory that originally tends to the disease equilibrium starts to converge to the disease-free equilibrium after increasing the efficacy of TBDs p_e , that is, making the initial value of disease extinction larger in range with increasing the efficacy of TBDs p_e . Therefore, the development of the transmission-blocking drugs and the improvement of the efficacy of TBDs will play an important role in the long-term control of malaria. When considering the influence of time delay on the model, we find that when the control reproduction number is greater than 1, the model exhibits Hopf bifurcation. When the time delay is less

than the bifurcation value, the positive equilibrium is locally asymptotically stable; when the time delay is slightly greater than the bifurcation value, the positive equilibrium is unstable and the system has a periodic solution. The appearance of periodic solution corresponds to the phenomenon of malaria periodic outbreaks in reality.

Appendix

$$r_1 = S_h^* \cdot \frac{\partial f_h}{\partial S_h} \Big|_{E^*} = S_h^* \cdot \frac{\partial f_h}{\partial I_h} \Big|_{E^*} = S_h^* \cdot \frac{\partial f_h}{\partial T_h} \Big|_{E^*}$$

$$= S_h^* \cdot \frac{\partial f_h}{\partial P_h} \Big|_{E^*} = S_h^* \cdot \frac{\partial f_h}{\partial R_h} \Big|_{E^*} = -f_h^* \frac{S_h^*}{N_h^*},$$

$$r_2 = S_h^* \cdot \frac{\partial f_h}{\partial I_v} \Big|_{E^*} = f_h^* \frac{S_h^*}{I_v^*},$$

$$r_3 = S_v^* \cdot \frac{\partial f_v}{\partial S_h} \Big|_{E^*} = S_v^* \cdot \frac{\partial f_v}{\partial P_h} \Big|_{E^*} = -f_v^* \cdot \frac{S_v^*}{N_h^*},$$

$$r_4 = S_v^* \cdot \frac{\partial f_v}{\partial I_h} \Big|_{E^*} = \frac{S_v^*}{N_h^*},$$

$$C_1 = f_h^* + r_1,$$

$$C_2 = -v + r_1,$$

$$C_3 = -\gamma_h + r_1,$$

$$C_4 = -\kappa_h \psi_2,$$

$$C_5 = -(1 - \kappa_h) \psi_2,$$

$$C_6 = r_3 + r_4,$$

$$C_7 = r_3 + \xi_t r_4,$$

$$C_8 = r_3 + \xi_r r_4,$$

$$C_9 = f_v^* + d_v,$$

$$D_{11} = \alpha_h C_1,$$

$$D_{12} = d_v + C_9,$$

$$D_{13} = d_v C_9,$$

$$D_{14} = C_4 (T_2 + T_3) + \gamma_h C_5 - v \psi_1,$$

$$D_{15} = C_4 T_2 T_3 + \gamma_h C_5 T_2 - v \psi_1 T_3,$$

$$D_{21} = -\alpha_h \gamma_1,$$

$$D_{22} = d_v + C_9 + d_h,$$

$$D_{23} = d_v C_9 + d_v d_h + C_9 d_h,$$

$$D_{24} = d_v C_9 d_h,$$

$$D_{25} = T_2 + T_3 - C_5 + \psi_1,$$

$$D_{26} = T_2 T_3 - T_2 C_5 + \psi_1 T_3,$$

$$D_{31} = d_v + T_1 + T_2 + C_9,$$

$$D_{32} = d_v (T_1 + T_2 + C_9) + C_9 (T_1 + T_2) + T_1 T_2,$$

$$D_{33} = d_v C_9 T_1 + d_v C_9 T_2 + d_v T_1 T_2 + C_9 T_1 T_2,$$

$$D_{34} = d_v T_1 T_2 C_9,$$

$$D_{35} = C_1 - r_1,$$

$$D_{36} = C_1 (\beta_{1h} + T_3) - \theta_h r_1 - r_1 (d_h + T_3),$$

$$D_{37} = C_1 \beta_{1h} T_3 - \theta_h r_1 d_h - r_1 d_h T_3 - C_1 \theta_h \gamma_h,$$

$$D_{41} = -r_2 \psi_1 \alpha_h,$$

$$D_{42} = d_v + T_3,$$

$$D_{43} = d_v T_3,$$

$$D_{44} = r_3 (d_h + v),$$

$$D_{51} = r_2 \alpha_h,$$

$$D_{52} = d_v + T_2,$$

$$D_{53} = d_v T_2,$$

$$D_{54} = -C_7,$$

$$D_{55} = -C_7 (d_h + T_3) + C_5 C_8 + r_3 r_4,$$

$$D_{56} = -C_7 d_h T_3 + C_5 C_8 d_h + r_3 C_4 T_3 + r_3 C_5 \gamma_h,$$

$$D_{61} = r_2,$$

$$D_{62} = d_v + T_1 + T_2,$$

$$D_{63} = d_v T_2 + d_v T_1 + T_1 T_2,$$

$$D_{64} = d_v T_1 T_2,$$

$$D_{65} = r_3 - C_6,$$

$$D_{66} = r_3 (\beta_{1h} + T_3) - C_6 (d_h + T_3) - \theta_h C_8,$$

$$D_{67} = -\theta_h C_8 d_h + r_3 \beta_{1h} T_3 - r_3 \theta_h \gamma_h - C_6 d_h T_3,$$

$$D_{71} = d_v + C_9 + d_h,$$

$$D_{72} = d_v C_9 + C_9 d_h + d_v d_h,$$

$$D_{73} = d_v C_9 d_h,$$

$$D_{74} = T_2 + T_3,$$

$$D_{75} = T_2 T_3,$$

$$D_{76} = \beta_{1h} + T_1,$$

$$D_{77} = T_1 \beta_{1h} + \alpha_h C_4,$$

$$F_6 = D_{76} + D_{74} + D_{71},$$

$$F_5 = D_{77} + D_{76} (D_{74} + D_{71}) + D_{75} + D_{72} + D_{71} D_{74},$$

$$F_4 = D_{77} (D_{74} + D_{71}) + D_{76} (D_{75} + D_{72} + D_{71} D_{74})$$

$$+ D_{71} D_{75} + D_{72} D_{74} + D_{73},$$

$$F_3 = D_{77} (D_{75} + D_{72} + D_{71} D_{74})$$

$$+ D_{76} (D_{71} D_{75} + D_{72} D_{74} + D_{73}) + (D_{72} D_{75} + D_{73} D_{74}),$$

$$F_2 = D_{77} (D_{71} D_{75} + D_{72} D_{74} + D_{73})$$

$$+ D_{76} (D_{72} D_{75} + D_{73} D_{74}) + D_{73} D_{75},$$

$$F_1 = D_{77} (D_{72} D_{75} + D_{73} D_{74}) + D_{76} D_{73} D_{75},$$

$$F_0 = D_{73} D_{75} D_{77},$$

$$J_6 = D_{35},$$

$$J_5 = D_{21} + D_{36} + D_{31} D_{35} + D_{61} D_{65},$$

$$\begin{aligned}
J_4 &= D_{11}C_4 + D_{21}(D_{25} + D_{22}) + D_{37} + D_{31}D_{36} + D_{32}D_{35} \\
&\quad + D_{51}D_{54} + D_{61}(D_{66} + D_{62}D_{65}), \\
J_3 &= D_{11}(D_{14} + D_{12}C_4) + D_{21}(D_{26} + D_{22}D_{25} + D_{23}) \\
&\quad + D_{31}D_{37} + D_{32}D_{36} + D_{33}D_{35} \\
&\quad + D_{41}r_3 + D_{51}(D_{55} + D_{52}D_{54}) \\
&\quad + D_{61}(D_{67} + D_{62}D_{66} + D_{63}D_{65}), \\
J_2 &= D_{11}(D_{15} + D_{12}D_{14} + D_{13}C_4) \\
&\quad + D_{21}(D_{24} + D_{22}D_{26} + D_{23}D_{25}) \\
&\quad + D_{32}D_{37} + D_{33}D_{36} + D_{34}D_{35} + D_{41}(D_{44} + D_{42}r_3) \\
&\quad + D_{51}(D_{56} + D_{52}D_{55} + D_{53}D_{54}) \\
&\quad + D_{61}(D_{62}D_{67} + D_{63}D_{66} + D_{64}D_{65}), \\
J_1 &= D_{11}(D_{12}D_{15} + D_{13}D_{14}) + D_{21}(D_{23}D_{26} + D_{24}D_{25}) \\
&\quad + D_{33}D_{37} + D_{34}D_{36} + D_{41}(D_{42}D_{44} + D_{43}r_3) \\
&\quad + D_{51}(D_{52}D_{56} + D_{53}D_{55}) + D_{61}(D_{63}D_{67} + D_{64}D_{66}), \\
J_0 &= D_{11}D_{13}D_{15} + D_{21}D_{24}D_{26} + D_{34}D_{37} + D_{41}D_{43}D_{44} \\
&\quad + D_{51}D_{53}D_{56} + D_{61}D_{64}D_{67}.
\end{aligned} \tag{A.1}$$

Data Availability

Previously reported data were used to support this study. These prior datasets are cited at relevant places within the text as references.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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