



Stability and backward bifurcation in a malaria transmission model with applications to the control of malaria in China[☆]



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ABSTRACT

In this paper, we consider a deterministic malaria transmission model with standard incidence rate and treatment. Human population is divided into susceptible, infectious and recovered subclasses, and mosquito population is split into susceptible and infectious classes. It is assumed that, among individuals with malaria who are treated or recovered spontaneously, a proportion moves to the recovered class with temporary immunity and the other proportion returns to the susceptible class. Firstly, it is shown that two endemic equilibria may exist when the basic reproduction number $\mathcal{R}_0 < 1$ and a unique endemic equilibrium exists if $\mathcal{R}_0 > 1$. The presence of a backward bifurcation implies that it is possible for malaria to persist even if $\mathcal{R}_0 < 1$. Secondly, using geometric method, some sufficient conditions for global stability of the unique endemic equilibrium are obtained when $\mathcal{R}_0 > 1$. To deal with this problem, the estimate of the Lozinskiĭ measure of a 6×6 matrix is discussed. Finally, numerical simulations are provided to support our theoretical results. The model is also used to simulate the human malaria data reported by the Chinese Ministry of Health from 2002 to 2013. It is estimated that the basic reproduction number $\mathcal{R}_0 \approx 0.0161$ for the malaria transmission in China and it is found that the plan of eliminating malaria in China is practical under the current control strategies.

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1. Introduction

Malaria, one of the most common infectious diseases, is a major cause of mortality in the Africa region (see [1]) with a large negative impact on local economies (see [2]). Increased prevention and control measures have led to a reduction in malaria mortality rates by more than 25% globally and by 33% in the World Health Organization (WHO) African region since 2000 (see [3]). However, according to the World Malaria Report 2012, after a rapid expansion between 2004 and 2009, global funding for malaria prevention and control leveled off between 2010 and 2012, and progress in the delivery of some life-saving commodities have slowed. This means that many households will be unable to replace existing bed nets when required, exposing more people to the potentially deadly disease (see [4]). In 2010, there were about 219 million malaria cases and an estimated 660 000 malaria deaths. 90% of all malaria deaths occurred in the WHO African Region, mostly among children under five years

of age. In March 2013, WHO Fact Sheet reported that about 3.3 billion people – half of the world's population – are at risk of malaria. The Democratic Republic of Congo and Nigeria are the most affected countries in sub-Saharan Africa, while India is the most affected country in Southeast Asia. In 2011, it was reported that 99 countries and territories had ongoing malaria transmission (see [5]).

Malaria has been endemic in China for hundreds of years. It was said that Kangxi Emperor of the Qing Dynasty was infected with malaria in 1692 (see [7]). Before the establishment of the People's Republic of China in 1949, there were at least 30 million malaria cases every year. There were three large malaria outbreaks in 1954, 1960 and 1970, after the establishment of the People's Republic of China (see [8]). In the next thirty years, great progresses and outstanding achievements have been made in controlling and preventing malaria, and the number of cases declined rapidly from 24 million in the early 1970s to 24,088 in 2000. However, since 2000, there was a resurgence of malaria in some areas of China. Nearly 77.4% of the total malaria cases in China were reported in Anhui, Yunnan, Henan, Hubei, and Jiangsu provinces (see [9]). In 2006, the Ministry of Health of China developed the “2006–2015 National Malaria Control Program”. In 2007, malaria was integrated into the major communicable diseases program subject to free treatment. It was reported that there were 14,098 malaria cases in 2009 which was down 46.6 percent compared

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Table 1
Reported malaria cases in China, 2002–2013 (NHFPC [6]).

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Confirmed cases	35298	40681	38972	42319	64178	50148	26873	14491	7855	4498	2718	4128
Indigenous cases	31605	37290	32678	32726	55335	44069	22934	11119	4262	1308	182	85
Imported cases	3693	3391	6294	9593	8843	6079	3939	3372	3593	3190	2536	4043
Deaths cases	49	57	32	45	34	14	22	10	14	30	15	20

with 2008. This strongly demonstrates that the malaria control efforts are successful. On May 19, 2010, the Ministry of Health of China further published the “Action Plans for the Elimination of Malaria (2010 - 2020)”. Table 1 presents the data on malaria cases reported to disease prevention and control bureau of National Health and Family Planning Commission (NHFPC [6]) from 2002 to 2013, which indicate that the number of malaria infections decreased year after year from 2006 to 2012. However, in 2013, the number of cases increased again. In recent years, along with frequent international exchanges, more and more Chinese have traveled to Africa and Southeast Asian areas, in which malaria is hyperendemic, for business, tourism and work. As a result, the proportion of imported malaria cases increased every year in China. In fact, among the reported 2,451 malaria cases in 2012, the proportion of imported malaria cases reached 91.1% (see [10]). It is believed that this phenomenon may lead to the reemergence of malaria in China.

Malaria is caused by protozoal parasites of the genus *Plasmodium*. Five species of *Plasmodium* that cause disease in humans are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. Female anopheline mosquitoes transmit malaria during a blood feed by inoculating microscopic motile sporozoites, which seek out and invade hepatocytes and then multiply (liver stage). After about 7–9 days, the liver schizonts rupture to release merozoites into the blood and clinical symptoms such as fever, pain, chills and sweats may develop [11]. These merozoites invade red blood cells and begin the asexual cycle. Illness starts when total asexual parasite numbers in the circulation reach roughly 100 million. Some parasites develop into sexual forms (blood stage). Gametocytes are taken up by a feeding anopheline mosquito and reproduce sexually, forming an ookinete and then an oocyst in the mosquito gut. The oocyst bursts and liberates sporozoites, which migrate to the salivary glands to await inoculation at the next blood feed (mosquito Stage)[12]. The three stages complete the lifecycle of *Plasmodium* in the human body and the anopheline mosquito.

There has been a great deal of work about using mathematical models to study malaria transmission (see [15–33]) since the seminal papers of Ross [13] and Macdonald [14]. Earlier models mainly followed the structure of the Ross–Macdonald model involving infected hosts (humans) and vectors (mosquitoes) (see Macdonald [15], Bailey [16], Aron and May [17], Koella [18], etc). Recently, Ngwa and Shu [19] and Ngwa [20] proposed a deterministic compartmental model for malaria transmission involving variable human and mosquito populations. In their model, human population has a susceptible-exposed-infectious-recovered-susceptible (SEIRS) structure, and mosquito population has a SEI structure. Their results suggest that a threshold parameter R_0 exists and the disease could persist if and only if $R_0 > 1$. The disease-free equilibrium always exists and is globally stable when $R_0 \leq 1$. Chitnis et al. [21] extended the Ngwa model when human immigration is considered. When the basic reproduction number $R_0 > 1$, the existence of at least one endemic equilibrium point was proved. In the absence of disease-induced death, they proved that the transcritical bifurcation at $R_0 = 1$ is supercritical (forward). Numerical simulations showed that for larger values of the disease-induced death rate, a subcritical (backward) bifurcation is possible at $R_0 = 1$. Tumwiine et al. [23] studied a malaria transmission model in which some infected humans that recover from infection and immune humans after loss of immunity join the sus-

ceptible class again. It was shown that the disease-free equilibrium exists and is globally asymptotically stable if $R_0 \leq 1$ and disease-free equilibrium becomes unstable and the endemic equilibrium is globally asymptotically stable if $R_0 > 1$. Wan and Cui [22] proved mathematically that if the disease-induced death rate is large enough, there may be an endemic equilibrium when $R_0 < 1$ and the model undergoes a backward bifurcation and a saddle-node bifurcation, and the existence of a unique endemic equilibrium was proved when $R_0 > 1$. For other related studies, we refer to Tumwiine et al. [24], Chamchod and Britton [25], Vargas-De-León [26], Wang et al. [27], Agosto et al. [28], Okosun et al. [29], Buonomo and Vargas-De-León [30], Ngonghala et al. [31], and references cited therein.

Motivated by the above studies, we take a standard infection rate in modelling malaria transmission. It is generally known that among the recovered individuals due to the treatment or natural immunity, a portion of them return to the recovered class with temporary immunity and the other proportion move to the susceptible class (see Okosun et al. [29]). Therefore, we divide the total human population, denoted by N_h , into the following subclasses: individuals who are susceptible to infection with malaria (S_h), individuals with malaria symptoms (I_h), and recovered individuals (R_h). So that $N_h = S_h + I_h + R_h$. The total mosquito population, denoted by N_v , is divided into susceptible mosquitoes (S_v) and infectious mosquitoes (I_v). That is, $N_v = S_v + I_v$.

Susceptible humans are recruited at a rate A_h . They move to the infected class by acquiring malaria through contact with infectious mosquitoes at a rate $\beta I_v/N_h$, where β is the transmission rate per bite per unit time. The natural death rate of humans is μ . Infectious individuals are assumed to recover at a rate $m + bu_2$, where m is the rate of spontaneous recovery, u_2 is the control on treatment of infected individuals and $b \in [0, 1]$ is the efficacy of treatment. Among the recovered naturally, ρ_1 portion of them progress to a temporarily immune state and the remaining portion immediately become susceptible to re-infection. Similarly, among the recovered due to the treatment control, ρ_2 portion of them progress to a temporarily immune state and the remaining portion immediately become susceptible to re-infection. Untreated infected individuals die at a rate γ . Recovered individuals lose immunity at a rate δ and become susceptible again.

Susceptible mosquitoes are generated at a rate A_v . They move to the infected class by acquiring malaria through contact with infected humans at a rate $\kappa I_h/N_h$, where κ is the transmission rate for a mosquito to get infected by an infectious human. The death rate of mosquitoes is η . Fig. 1 illustrates the five compartments and model variables.

Combining the above described parameters and the flowchart (Fig. 1), we have

$$\frac{dS_h(t)}{dt} = A_h - \frac{\beta S_h(t)I_v(t)}{N_h} - \mu S_h(t) + m(1 - \rho_1)I_h(t) + bu_2(1 - \rho_2)I_h(t) + \delta R_h(t), \tag{1a}$$

$$\frac{dI_h(t)}{dt} = \frac{\beta S_h(t)I_v(t)}{N_h} - \mu I_h(t) - \gamma I_h(t) - (m + bu_2)I_h(t), \tag{1b}$$

$$\frac{dR_h(t)}{dt} = (m\rho_1 + bu_2\rho_2)I_h(t) - (\mu + \delta)R_h(t), \tag{1c}$$

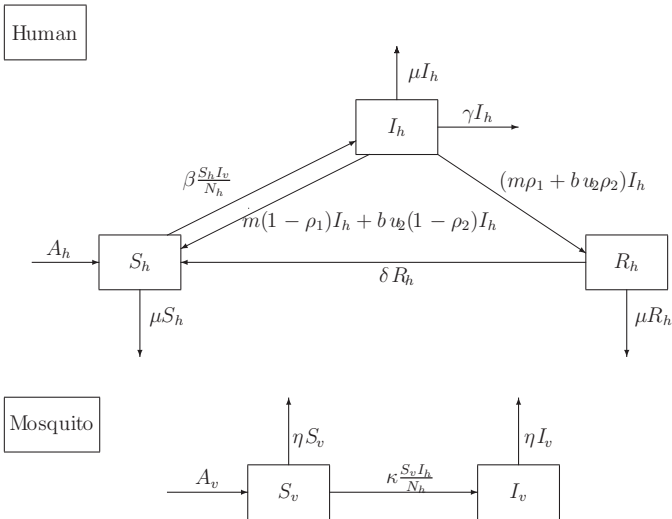


Fig. 1. Flowchart of the malaria transmission between mosquitoes and humans.

$$\frac{dS_v(t)}{dt} = A_v - \frac{\kappa S_v(t)I_h(t)}{N_h} - \eta S_v(t), \tag{1d}$$

$$\frac{dI_v(t)}{dt} = \frac{\kappa S_v(t)I_h(t)}{N_h} - \eta I_v(t). \tag{1e}$$

The organization of this paper is as follows. In Section 2, the basic properties on the positivity and boundedness of solutions, the basic reproduction number and the existence of an endemic equilibrium for the system are discussed. In Section 3, the occurrence of a backward bifurcation is considered. In Section 4, the stability of the disease-free equilibrium and endemic equilibrium is studied. In Section 5, some examples and simulations are given to illustrate theoretical results. In Section 6, the system is applied to simulate the malaria data in China. A brief discussion is given in Section 7.

2. Basic properties

For the malaria transmission system (1) to be epidemiologically meaningful, it is important to prove that all solutions with non-negative initial data will remain non-negative for all time.

Theorem 2.1. *If initial values $S_h(0), I_h(0), R_h(0), S_v(0), I_v(0)$ are non-negative, then the solution $(S_h(t), I_h(t), R_h(t), S_v(t), I_v(t))$ of system (1) is non-negative for all $t \geq 0$. Moreover,*

$$\limsup_{t \rightarrow \infty} N_h(t) \leq \frac{A_h}{\mu} \quad \text{and} \quad \limsup_{t \rightarrow \infty} N_v(t) \leq \frac{A_v}{\eta}.$$

Furthermore, if $N_h(0) \leq \frac{A_h}{\mu}$, then $N_h(t) \leq \frac{A_h}{\mu}$, and if $N_v(0) \leq \frac{A_v}{\eta}$, then $N_v(t) \leq \frac{A_v}{\eta}$. In particular, the region

$$\Omega = \left\{ (S_h, I_h, R_h, S_v, I_v) \mid \in \mathbb{R}_+^5 : S_h + I_h + R_h \leq \frac{A_h}{\mu}, S_v + I_v \leq \frac{A_v}{\eta} \right\}$$

is positively invariant.

The proof is omitted for simplicity.

System (1) always has a disease-free equilibrium $E_0 = (\frac{A_h}{\mu}, 0, 0, \frac{A_v}{\eta}, 0)$. Applying the next generation matrix method in [34,35], we can calculate the basic reproduction number \mathcal{R}_0 of system (1) as follows

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\frac{\kappa \beta \mu A_v}{\eta^2 A_h (\mu + \gamma + m + bu_2)}},$$

where

$$F = \begin{pmatrix} 0 & \beta \\ \kappa \frac{A_v \mu}{\eta A_h} & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \mu + \gamma + m + bu_2 & 0 \\ 0 & \eta \end{pmatrix}.$$

Remark 2.1. In order to interpret the biological meaning of \mathcal{R}_0 , we rewrite it in the following form

$$\mathcal{R}_0 = \sqrt{\beta \cdot \kappa \cdot \frac{A_v/\eta}{A_h/\mu} \cdot \frac{1}{\mu + \gamma + m + bu_2} \cdot \frac{1}{\eta}}.$$

It can be seen that a primary case in the human population makes infectious contacts with mosquitoes at a rate $\beta \cdot \frac{A_v/\eta}{A_h/\mu}$ for an expected time $\frac{1}{\mu + \gamma + m + bu_2}$ and a primary case in the mosquito population makes infectious contacts with humans at a rate κ for an expected time $\frac{1}{\eta}$.

Remark 2.2. Observe that \mathcal{R}_0 is independent of the parameters ρ_1, ρ_2 and δ . It is easy to see that \mathcal{R}_0 is increasing in β, κ and A_v while it is decreasing with respect to η, γ and A_h .

From Theorem 2 given in [35], we have the following result regarding the stability of E_0 .

Theorem 2.2. *The disease-free equilibrium E_0 of system (1) is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

Let $E^* = (S_h^*, I_h^*, R_h^*, S_v^*, I_v^*)$ represent an endemic equilibrium of system (1). Using the approach in [36],

$$\lambda_h^* = \frac{\beta I_v^*}{N_h^*} \quad \text{and} \quad \lambda_v^* = \frac{\kappa I_h^*}{N_h^*}, \tag{2}$$

where $N_h^* = S_h^* + I_h^* + R_h^*$, then $S_h^*, I_h^*, R_h^*, S_v^*$ and I_v^* satisfy the following equations

$$A_h - \lambda_h^* S_h^* - \mu S_h^* + (m(1 - \rho_1) + bu_2(1 - \rho_2))I_h^* + \delta R_h^* = 0, \tag{3a}$$

$$\lambda_h^* S_h^* - (\mu + \gamma + m + bu_2)I_h^* = 0, \tag{3b}$$

$$(m\rho_1 + bu_2\rho_2)I_h^* - (\mu + \delta)R_h^* = 0, \tag{3c}$$

$$A_v - \lambda_v^* S_v^* - \eta S_v^* = 0, \tag{3d}$$

$$\lambda_v^* S_v^* - \eta I_v^* = 0. \tag{3e}$$

Solving (3b)–(3e) we obtain:

$$I_h^* = \frac{\lambda_h^* S_h^*}{\mu + \gamma + m + bu_2}, \quad R_h^* = \frac{(m\rho_1 + bu_2\rho_2)I_h^*}{\mu + \delta},$$

$$S_v^* = \frac{A_v}{\lambda_v^* + \eta}, \quad I_v^* = \frac{A_v \lambda_v^*}{\eta(\lambda_v^* + \eta)}.$$

Substituting them into (3a), we get

$$S_h^* = \frac{A_h(\mu + \delta)(\mu + \gamma + m + bu_2)}{\mu(\mu + \delta)(\mu + \gamma + m + bu_2) + \lambda_h^*[(\mu + \delta)(\mu + \gamma) + \mu(m\rho_1 + bu_2\rho_2)]}.$$

Moreover, by (2), we have

$$\lambda_h^* = \beta \frac{A_v \lambda_v^*}{\eta(\lambda_v^* + \eta)} \frac{\mu(\mu + \delta)(\mu + \gamma + m + bu_2) + \lambda_h^*[(\mu + \delta)(\mu + \gamma) + \mu(m\rho_1 + bu_2\rho_2)]}{A_h(\mu + \delta)(\mu + \gamma + m + bu_2) + \lambda_h^* A_h(\mu + \delta + m\rho_1 + bu_2\rho_2)} \tag{4}$$

and

$$\lambda_v^* = \frac{\kappa \lambda_h^*(\mu + \delta)}{(\mu + \delta)(\mu + \gamma + m + bu_2) + \lambda_h^*(\mu + \delta + m\rho_1 + bu_2\rho_2)}.$$

Substituting λ_v^* into (4), λ_h^* satisfies the following equation

$$a_1 \lambda_h^{*2} + a_2 \lambda_h^* + a_3 = 0, \tag{5}$$

where

$$a_1 = \eta(\mu + \delta + m\rho_1 + bu_2\rho_2) \times [\eta(\mu + \delta + m\rho_1 + bu_2\rho_2) + \kappa(\mu + \delta)],$$

$$a_2 = \eta^2(\mu + \delta)(\mu + \gamma + m + bu_2) \times \frac{(\mu + \delta)(\mu + \gamma) + \mu(m\rho_1 + bu_2\rho_2)}{\mu} (G - \mathcal{R}_0^2),$$

$$a_3 = \eta^2(\mu + \delta)^2(\mu + \gamma + m + bu_2)^2(1 - \mathcal{R}_0^2),$$

and

$$G = \frac{2\mu\eta(\mu + \delta + m\rho_1 + bu_2\rho_2) + \mu\kappa(\mu + \delta)}{\eta[(\mu + \delta)(\mu + \gamma) + \mu(m\rho_1 + bu_2\rho_2)]}.$$

Note that $\mathcal{R}_0 < 1 \Leftrightarrow a_3 > 0$ and $\mathcal{R}_0 < \sqrt{G} \Leftrightarrow a_2 > 0$. Moreover, $G = 1$ is equivalent to

$$\gamma = \mu + \frac{\mu\kappa}{\eta} + \frac{\mu(m\rho_1 + bu_2\rho_2)}{\mu + \delta} := \gamma^*,$$

and G is decreasing with respect to γ .

Let $\Delta(\mathcal{R}_0) = a_2^2 - 4a_1a_3$, we have $\Delta(\sqrt{G}) = -4a_1a_3$ and $\Delta(1) = a_2^2$. Therefore, when $\mathcal{R}_0 < 1$, there is a unique $\mathcal{R}^* \in (\sqrt{G}, 1)$ such that $\Delta(\mathcal{R}^*) = 0$. Thus, we have the following results on the existence of equilibria of model (1).

Theorem 2.3.

- (1). System (1) always has a disease-free equilibrium E_0 .
- (2). When $0 \leq \gamma \leq \gamma^*$, we have
 - (i) if $\mathcal{R}_0 > 1$, then system (1) has a unique endemic equilibrium $E^*(S_h^*, I_h^*, R_h^*, S_v^*, I_v^*)$;
 - (ii) if $\mathcal{R}_0 \leq 1$, then system (1) has no endemic equilibrium.
- (3). When $\gamma > \gamma^*$, we have
 - (i) if $\mathcal{R}_0 \geq 1$, then system (1) has a unique endemic equilibrium E^* ;
 - (ii) if $\mathcal{R}_0 < \sqrt{G} < 1$, then system (1) has no endemic equilibrium;
 - (iii) if $\sqrt{G} \leq \mathcal{R}_0 < 1$, then we further have
 - (iii1) when $\mathcal{R}_0 = \mathcal{R}^*$, system (1) also has a unique endemic equilibrium E^* ;
 - (iii2) when $\mathcal{R}^* < \mathcal{R}_0 < 1$, system (1) has two distinct endemic equilibria $E_1(S_h^1, I_h^1, R_h^1, S_v^1, I_v^1)$ and $E_2(S_h^2, I_h^2, R_h^2, S_v^2, I_v^2)$; where

$$I_h^i = \frac{\lambda_h^i A_h(\mu + \delta)}{\mu(\mu + \delta)(\mu + \gamma + m + bu_2) + \lambda_h^i [(\mu + \delta)(\mu + \gamma) + \mu(m\rho_1 + bu_2\rho_2)]},$$

$$i = 1, 2 \text{ and } \lambda_h^1 = \frac{-a_2 - \sqrt{\Delta}}{2a_1}, \lambda_h^2 = \frac{-a_2 + \sqrt{\Delta}}{2a_1};$$
 - (iii3) when $\sqrt{G} \leq \mathcal{R}_0 < \mathcal{R}^*$, system (1) has no endemic equilibrium.

Proof. Conclusions (1), (2) and (3)(i) can be easily proved, we hence omit them. In the following, we give a brief proof for conclusions (3)(ii) and (3)(iii).

When $\gamma > \gamma^*$, we have $\sqrt{G} < 1$. If $\sqrt{G} > \mathcal{R}_0$ and $\mathcal{R}_0 < 1$, then $a_2 > 0$ and $a_3 > 0$. Hence, Eq. (4) does not have any positive root. Conclusion (3)(ii) is proved.

If $\sqrt{G} < \mathcal{R}_0 < 1$, then there exists a $\sqrt{G} < \mathcal{R}^* < 1$ such that $\Delta(\mathcal{R}^*) = 0$, and $\Delta(\mathcal{R}_0) < 0$ when $\sqrt{G} < \mathcal{R}_0 < \mathcal{R}^*$ and $\Delta(\mathcal{R}_0) > 0$ when $\mathcal{R}^* < \mathcal{R}_0 < 1$. It follows that conclusion (3)(iii) holds. \square

Remark 2.3. From the expression of G , we know that when $\gamma = 0$

$$G = \frac{2\mu\eta(\mu + \delta + m\rho_1 + bu_2\rho_2) + \mu\kappa(\mu + \delta)}{\mu\eta(\mu + \delta + m\rho_1 + bu_2\rho_2)} > 1.$$

Therefore, Theorem 2.3 shows that a forward (transcritical) bifurcation exhibits in system (1) when $\gamma = 0$.

The epidemiological implication of Remark 2.3 is that, if the disease-induced death rate γ is equal to zero, when \mathcal{R}_0 is less than unity, a small influx of infected mosquitoes into the population will

not generate a large outbreak, and the disease will die out. Furthermore, the disease will persist when \mathcal{R}_0 is larger than unity. However, if $\gamma > 0$, we will show in the next section that the disease may still persist even if $\mathcal{R}_0 < 1$.

3. The backward bifurcation

Conclusion (3)(iii) of Theorem 2.3 indicates that a backward bifurcation may occur for values of \mathcal{R}_0 when $\mathcal{R}^* < \mathcal{R}_0 < 1$. Consider $\mathcal{R}_0 = 1$. Let β^* be given by

$$\beta^* := \frac{\eta^2 A_h(\mu + \gamma + m + bu_2)}{\kappa \mu A_v}. \tag{6}$$

Let $N_v(t) = S_v(t) + I_v(t)$, then we have $\dot{N}_v(t) = A_v - \eta N_v(t)$. Therefore, $N_v(t) \rightarrow \frac{A_v}{\eta}$ as $t \rightarrow \infty$. Thus, in model (1) we can represent $S_v(t)$ by $\frac{A_v}{\eta} - I_v(t)$, and system (1) can be reduced to the following form with four equations:

$$\frac{dS_h(t)}{dt} = A_h - \frac{\beta S_h(t)I_v(t)}{N_h} - \mu S_h(t) + m(1 - \rho_1)I_h(t) + bu_2(1 - \rho_2)I_h(t) + \delta R_h(t), \tag{7a}$$

$$\frac{dI_h(t)}{dt} = \frac{\beta S_h(t)I_v(t)}{N_h} - \mu I_h(t) - \gamma I_h(t) - (m + bu_2)I_h(t), \tag{7b}$$

$$\frac{dR_h(t)}{dt} = (m\rho_1 + bu_2\rho_2)I_h(t) - (\mu + \delta)R_h(t), \tag{7c}$$

$$\frac{dI_v(t)}{dt} = \kappa \left(\frac{A_v}{\eta} - I_v(t) \right) \frac{I_h(t)}{N_h} - \eta I_v(t). \tag{7d}$$

Theorem 3.1. System (7) exhibits a backward bifurcation at $\mathcal{R}_0 = 1$ whenever $\gamma > \gamma^*$.

Proof. Let

$$\frac{dS_h(t)}{dt} = A_h - \frac{\beta S_h(t)I_v(t)}{S_h(t) + I_h(t) + R_h(t)} - \mu S_h(t) + m(1 - \rho_1)I_h(t) + bu_2(1 - \rho_2)I_h(t) + \delta R_h(t) := f_1,$$

$$\frac{dI_h(t)}{dt} = \frac{\beta S_h(t)I_v(t)}{S_h(t) + I_h(t) + R_h(t)} - \mu I_h(t) - \gamma I_h(t) - (m + bu_2)I_h(t) := f_2,$$

$$\frac{dR_h(t)}{dt} = (m\rho_1 + bu_2\rho_2)I_h(t) - (\mu + \delta)R_h(t) := f_3,$$

$$\frac{dI_v(t)}{dt} = \frac{\kappa \left(\frac{A_v}{\eta} - I_v(t) \right) I_h(t)}{S_h(t) + I_h(t) + R_h(t)} - \eta I_v(t) := f_4.$$

Choosing β as a bifurcation parameter. Solving $\mathcal{R}_0 = 1$ gives (6). The Jacobian matrix at the disease-free equilibrium E_0 with $\beta = \beta^*$ is

$$J(E_0) = \begin{pmatrix} -\mu & m(1 - \rho_1) + bu_2(1 - \rho_2) & \delta & -\beta^* \\ 0 & -(\mu + \gamma + m + bu_2) & 0 & \beta^* \\ 0 & m\rho_1 + bu_2\rho_2 & -(\mu + \delta) & 0 \\ 0 & k \frac{A_v \mu}{A_h \eta} & 0 & -\eta \end{pmatrix}.$$

Hence, its characteristic roots are $\lambda_1 = -\mu$, $\lambda_2 = -\mu - \delta$, $\lambda_3 = 0$ and $\lambda_4 = -\mu - \gamma - m - bu_2 - \eta$.

Now, we denote by $\mathbf{w} = (w_1, w_2, w_3, w_4)^T$ a right eigenvector corresponding to the zero eigenvalue. Then,

$$\mathbf{w} = \left(\left(-\frac{m\rho_1 + bu_2\rho_2}{\mu + \delta} - \frac{\mu + \gamma}{\mu} \right) w_2, w_2, \times \frac{m\rho_1 + bu_2\rho_2}{\mu + \delta} w_2, \kappa \frac{A_v \mu}{A_h \eta^2} w_2 \right)^T.$$

Furthermore, the left eigenvector $\mathbf{v} = (v_1, v_2, v_3, v_4)$ satisfying $\mathbf{v} \cdot \mathbf{w} = 1$ is given by

$$\begin{cases} -\mu v_1 = 0, \\ -(\mu + \gamma + m + bu_2)v_2 + \kappa \frac{A_v \mu}{A_h \eta} v_4 = 0, \\ -(\mu + \delta)v_3 = 0, \\ \beta^* v_2 - \eta v_4 = 0. \end{cases}$$

Therefore,

$$\mathbf{v} = \left(0, \frac{\kappa A_v \mu}{A_h \eta (\mu + \gamma + m + bu_2)} v_4, 0, v_4 \right).$$

Using β^* given by (6), we obtain

$$\begin{aligned} w_2 &= \frac{A_h \eta}{\kappa A_v \mu}, \\ v_4 &= \frac{\eta (\mu + \gamma + m + bu_2)}{\mu + \gamma + m + bu_2 + \eta}. \end{aligned}$$

By computing the second-order partial derivatives of f_i ($i = 1, 2, 3, 4$) at the disease-free equilibrium E_0 , we obtain

$$\begin{aligned} \frac{\partial^2 f_2}{\partial I_h \partial I_v} &= -\beta \frac{\mu}{A_h}, & \frac{\partial^2 f_2}{\partial R_h \partial I_v} &= -\beta \frac{\mu}{A_h}, \\ \frac{\partial^2 f_4}{\partial S_h \partial I_h} &= -\kappa \frac{A_v \mu^2}{\eta A_h^2}, \\ \frac{\partial^2 f_4}{\partial I_h \partial R_h} &= -\kappa \frac{A_v \mu^2}{\eta A_h^2}, & \frac{\partial^2 f_4}{\partial I_h \partial I_v} &= -\kappa \frac{\mu}{A_h}, \end{aligned}$$

and their cross derivatives are coincide. Moreover,

$$\frac{\partial^2 f_4}{\partial I_h^2} = -2\kappa \frac{A_v \mu^2}{\eta A_h^2}, \quad \frac{\partial^2 f_2}{\partial I_v \partial \beta} = 1,$$

and the other second-order partial derivatives of f_i ($i = 1, 2, 3, 4$) at the disease-free equilibrium E_0 are equal to zero.

According to coefficients \mathbf{a} and \mathbf{b} defined in Theorem 4.1 of Castillo-Chavez and Song [37], it follows that

$$\begin{aligned} \mathbf{a} &= v_2 \left(2w_2 w_4 \frac{\partial^2 f_2}{\partial I_h \partial I_v} (E_0, \beta^*) + 2w_3 w_4 \frac{\partial^2 f_2}{\partial R_h \partial I_v} (E_0, \beta^*) \right) \\ &\quad + v_4 \left(2w_1 w_2 \frac{\partial^2 f_4}{\partial S_h \partial I_h} (E_0, \beta^*) + w_2^2 \frac{\partial^2 f_4}{\partial I_h^2} (E_0, \beta^*) \right) \\ &\quad + 2w_2 w_3 \frac{\partial^2 f_4}{\partial I_h \partial R_h} (E_0, \beta^*) + 2w_2 w_4 \frac{\partial^2 f_4}{\partial I_h \partial I_v} (E_0, \beta^*) \end{aligned}$$

and

$$\mathbf{b} = v_2 w_4 \frac{\partial^2 f_2}{\partial I_v \partial b} (E_0, \beta^*).$$

Substituting the eigenvectors and the above partial derivatives into \mathbf{a} and \mathbf{b} , we obtain

$$\mathbf{a} = \frac{2\eta^2 (\mu + \gamma + m + bu_2)}{\kappa A_v (\mu + \gamma + m + bu_2 + \eta)} \left(\frac{\gamma}{\mu} - 1 - \frac{\kappa}{\eta} - \frac{m\rho_1 + bu_2\rho_2}{\mu + \delta} \right)$$

and

$$\mathbf{b} = \frac{\kappa A_v \mu}{A_h \eta (\mu + \gamma + m + bu_2 + \eta)}.$$

Obviously, the coefficient \mathbf{b} is positive. When $\gamma > \gamma^*$, \mathbf{a} is positive. It follows that model (7) undergoes a backward bifurcation when $\gamma > \gamma^*$. \square

Remark 3.1. It is interesting to point out that γ is a threshold value not only for the existence of equilibria (Theorem 2.3) but also for the existence of the backward bifurcation (Theorem 3.1). To the best of our knowledge, this phenomenon has not been observed in any literature.

Remark 3.2. The backward bifurcation also provides some information on the local stability of the endemic equilibria. For example, we may obtain that the endemic equilibrium E_2 is locally asymptotically stable and the endemic equilibrium E_1 is unstable. In fact, in Section 5, numerical simulations (see Fig. 6) show that E_1 is unstable and E_2 is locally asymptotically stable.

Remark 3.3. The existence of a backward bifurcation shows that even if $\mathcal{R}_0 < 1$ by some control measures, malaria may still persist. The control of malaria becomes more difficult when $\gamma > \gamma^*$.

It is worth stating that the sign of \mathbf{a} is negative when $0 \leq \gamma \leq \gamma^*$. Therefore, we have the following result.

Theorem 3.2. When $0 \leq \gamma \leq \gamma^*$, if $\mathcal{R}_0 < 1$, then the disease-free equilibrium E_0 of system (7) is locally asymptotically stable, and if $\mathcal{R}_0 > 1$, then the unique endemic equilibrium E^* is locally asymptotically stable and the disease-free equilibrium E_0 is unstable.

Remark 3.4. If the disease-induced death rate satisfies $0 \leq \gamma \leq \gamma^*$, then the disease can be eradicated as long as the basic reproduction number \mathcal{R}_0 is less than unity by some control strategies.

4. Stability of equilibria

Firstly, on the global stability of the disease-free equilibrium, we have the following result.

Theorem 4.1. If $\mathcal{R}_0^2 < \Lambda$, then the disease-free equilibrium E_0 of system (7) is globally asymptotically stable, where

$$\Lambda = 1 - \frac{\kappa \beta \gamma A_v}{\eta^2 A_h (\mu + \gamma + m + bu_2)}.$$

Proof. By Theorem 2.2, E_0 is locally stable when $\mathcal{R}_0 < 1$. Let

$$\mathcal{R}_1 = \frac{\kappa \beta \frac{A_v}{\eta}}{\eta \frac{A_h}{\mu + \gamma} (\mu + \gamma + m + bu_2)}.$$

We notice that $\mathcal{R}_1 = \mathcal{R}_0^2 + 1 - \Lambda$, thus $\mathcal{R}_1 < 1$ is equivalent to $\mathcal{R}_0^2 < \Lambda$. If $\mathcal{R}_1 < 1$, then there is a sufficiently small constant $\varepsilon > 0$ such that

$$\frac{\kappa \beta \left(\frac{A_v}{\eta} + \varepsilon \right)}{\eta \left(\frac{A_h}{\mu + \gamma} - \varepsilon \right) (\mu + \gamma + m + bu_2)} < 1.$$

Let $(S_h(t), I_h(t), R_h(t), I_v(t))$ be any positive solution of system (7), then there is a T_1 such that

$$N_v(t) \leq \frac{A_v}{\eta} + \varepsilon \quad \text{for all } t \geq T_1.$$

Since

$$\begin{aligned} \dot{N}_h(t) &= A_h - \mu N_h(t) - \gamma I_h(t), \\ &\geq A_h - (\mu + \gamma) N_h(t), \end{aligned}$$

we conclude that there is a $T_2 > T_1$ such that

$$N_h(t) \geq \frac{A_h}{\mu + \gamma} - \varepsilon \quad \text{for all } t \geq T_2.$$

Consider the following Lyapunov function

$$V(I_h, I_v) = I_v + \frac{\eta}{\beta} I_h.$$

Computing the derivative of $V(I_h, I_v)$ along the solutions of system (7), we have

$$\begin{aligned} \dot{V}(I_h, I_v) &= \dot{I}_v + \frac{\eta}{\beta} \dot{I}_h, \\ &= \kappa \frac{S_v I_h}{N_h} - \eta I_v + \eta \frac{S_h I_v}{N_h} - \frac{\eta}{\beta} (\mu + \gamma + m + bu_2) I_h, \end{aligned}$$

$$\begin{aligned}
 &= \left(\kappa \frac{S_v}{N_h} - \frac{\eta}{\beta} (\mu + \gamma + m + bu_2) \right) I_h - \eta \left(1 - \frac{S_h}{N_h} \right) I_v, \\
 &\leq \left(\kappa \frac{A_v/\eta + \varepsilon}{A_h/\mu + \gamma - \varepsilon} - \frac{\eta}{\beta} (\mu + \gamma + m + bu_2) \right) I_h \quad (8)
 \end{aligned}$$

for all $t \geq T_2$. Obviously, we have $\dot{V}(I_h, I_v) \leq 0$ for all $I_h \geq 0$ and $I_v \geq 0$. Let $M = \{(S_h, I_h, R_h, I_v) : \dot{V}(I_h, I_v) = 0\}$, then $M \subset \{(S_h, I_h, R_h, I_v) : I_h = 0\}$. Let $N \subset M$ be the largest invariant set with respect to system (7) and let $(S_h(t), I_h(t), R_h(t), I_v(t))$ be any solution of system (7) in N , then $(S_h(t), I_h(t), R_h(t), I_v(t))$ is defined and bounded on $t \in \mathbb{R} = (-\infty, +\infty)$.

Since $N \subset \{(S_h, I_h, R_h, I_v) : I_h = 0\}$, we have $I_h(t) \equiv 0$. From (7d), we obtain

$$\begin{aligned}
 \frac{dR_h(t)}{dt} &= -(\mu + \delta)R_h(t), \\
 \frac{dI_v(t)}{dt} &= -\eta I_v(t).
 \end{aligned}$$

By solving these two equations, it is obvious that $R_h(t) \equiv 0$ and $I_v(t) \equiv 0$. Furthermore, from (7a), we have

$$\frac{dS_h(t)}{dt} = A_h - \mu S_h(t).$$

Hence, $S_h(t) \equiv \frac{A_h}{\mu}$. Thus, we obtain $(S_h(t), I_h(t), R_h(t), I_v(t)) \equiv E_0$. This shows that $N \equiv \{E_0\}$. By LaSalle’s invariance principle, E_0 is globally attractive. Therefore, the disease-free equilibrium E_0 is globally asymptotically stable when $\mathcal{R}_0^2 < \Lambda$. \square

In the case of the occurrence of a backward bifurcation in model (1), the above result shows that in order to eliminate malaria, basic reproduction number \mathcal{R}_0 must be lower than a threshold value Λ , and Λ is strictly less than 1.

In Theorem 4.1, when $\gamma = 0$, then $\Lambda = 1$. Therefore, we have the following corollary.

Corollary 4.1. *When $\gamma = 0$ in system (1), if $\mathcal{R}_0 < 1$, then the disease-free equilibrium E_0 of system (1) is globally asymptotically stable.*

Now we discuss the global stability of the endemic equilibrium. For system (7),

$$\tilde{\Omega} = \left\{ (S_h, I_h, R_h, I_v) \in \mathbb{R}_+^4 : S_h + I_h + R_h \leq \frac{A_h}{\mu}, I_v \leq \frac{A_v}{\eta} \right\}$$

is a positively invariant set. By Theorem 2.3, there is a unique endemic equilibrium in the interior of $\tilde{\Omega}$ when $\mathcal{R}_0 > 1$. We use the geometric approach to discuss its global stability. However, up to now, this method is usually applied to three-dimensional systems. In the following, we expand its application to four-dimensional systems.

Theorem 4.2. *If $\mathcal{R}_0 > 1$, then the endemic equilibrium of system (7) is globally asymptotically stable provided that*

$$\begin{aligned}
 \mu &> \max \left\{ m\rho_1 + bu_2\rho_2 + \max\{\eta, \gamma + m + bu_2\} \right. \\
 &\quad \left. - \delta, \frac{(3\eta + \delta)\eta A_h + 2\beta A_v \gamma}{\eta A_h - 2\beta A_v} \right\}. \quad (9)
 \end{aligned}$$

Proof. Firstly, $\tilde{\Omega}$ is simply connected in \mathbb{R}^4 and system (7) has a unique endemic equilibrium in the interior of $\tilde{\Omega}$ when $\mathcal{R}_0 > 1$. Moreover, the instability of the disease-free equilibrium (Theorem 2.2) implies the uniform persistence of system (7) (see [39]), i.e. there exists a constant $c > 0$ such that any solution $x(t, x_0) = (S_h(t), I_h(t), R_h(t), I_v(t))$ with $x_0 = (S_h(0), I_h(0), R_h(0), I_v(0))$ in the interior of $\tilde{\Omega}$ satisfies

$$\min \left\{ \liminf_{t \rightarrow \infty} S_h(t), \liminf_{t \rightarrow \infty} I_h(t), \liminf_{t \rightarrow \infty} R_h(t), \liminf_{t \rightarrow \infty} I_v(t) \right\} > c.$$

The uniform persistence together with boundedness of $\tilde{\Omega}$ is equivalent to the existence of a compact absorbing set Γ in the interior of

$\tilde{\Omega}$ (see [40]). Therefore, it remains to find conditions for which the Bendixson’s criterion can be verified.

The Jacobian matrix J of system (7) is given by:

$$\begin{pmatrix}
 -\mu - \beta I_v \frac{I_h + R_h}{N_h^2} & m(1 - \rho_1) + bu_2(1 - \rho_2) + \beta I_v \frac{S_h}{N_h^2} & \delta + \beta I_v \frac{S_h}{N_h^2} & -\beta \frac{S_h}{N_h} \\
 \beta I_v \frac{I_h + R_h}{N_h^2} & -(\mu + \gamma + m + bu_2) - \beta I_v \frac{S_h}{N_h^2} & -\beta I_v \frac{S_h}{N_h^2} & \beta \frac{S_h}{N_h} \\
 0 & m\rho_1 + bu_2\rho_2 & -(\mu + \delta) & 0 \\
 -\kappa \left(\frac{A_v}{\eta} - I_v \right) \frac{I_h}{N_h^2} & \kappa \left(\frac{A_v}{\eta} - I_v \right) \frac{S_h + R_h}{N_h^2} & -\kappa \left(\frac{A_v}{\eta} - I_v \right) \frac{I_h}{N_h^2} & -\kappa \frac{I_h}{N_h} - \eta
 \end{pmatrix}.$$

For a general 4×4 matrix

$$\begin{pmatrix}
 a_{11} & a_{12} & a_{13} & a_{14} \\
 a_{21} & a_{22} & a_{23} & a_{24} \\
 a_{31} & a_{32} & a_{33} & a_{34} \\
 a_{41} & a_{42} & a_{43} & a_{44}
 \end{pmatrix}$$

the second additive compound matrix is given by

$$\begin{pmatrix}
 a_{11} + a_{22} & a_{23} & a_{24} & -a_{13} & -a_{14} & 0 \\
 a_{32} & a_{11} + a_{33} & a_{34} & a_{12} & 0 & -a_{14} \\
 a_{42} & a_{43} & a_{11} + a_{44} & 0 & a_{12} & a_{13} \\
 -a_{31} & a_{21} & 0 & a_{22} + a_{33} & a_{34} & -a_{24} \\
 -a_{41} & 0 & a_{21} & a_{43} & a_{22} + a_{44} & a_{23} \\
 0 & -a_{41} & a_{31} & -a_{42} & a_{32} & a_{33} + a_{44}
 \end{pmatrix}.$$

Hence, the second additive compound matrix $J^{[2]}$ of J is given by

$$\begin{pmatrix}
 M_{11} & -\beta I_v \frac{S_h}{N_h^2} & \beta \frac{S_h}{N_h} & -\delta - \beta I_v \frac{S_h}{N_h^2} & \beta \frac{S_h}{N_h} & 0 \\
 m\rho_1 + bu_2\rho_2 & M_{22} & 0 & q_1 & 0 & \beta \frac{S_h}{N_h} \\
 q_2 & -q_3 & M_{33} & 0 & q_1 & \delta + \beta I_v \frac{S_h}{N_h^2} \\
 0 & \beta I_v \frac{I_h + R_h}{N_h^2} & 0 & M_{44} & 0 & -\beta \frac{S_h}{N_h} \\
 q_3 & 0 & \beta I_v \frac{I_h + R_h}{N_h^2} & -q_3 & M_{55} & -\beta I_v \frac{S_h}{N_h^2} \\
 0 & q_3 & 0 & -q_2 & m\rho_1 + bu_2\rho_2 & M_{66}
 \end{pmatrix}.$$

where

$$M_{11} = -\mu - \beta I_v \frac{I_h + R_h}{N_h^2} - (\mu + \gamma + m + bu_2) - \beta I_v \frac{S_h}{N_h^2},$$

$$M_{22} = -\mu - \beta I_v \frac{I_h + R_h}{N_h^2} - (\mu + \delta),$$

$$M_{33} = -\mu - \beta I_v \frac{I_h + R_h}{N_h^2} - \kappa \frac{I_h}{N_h} - \eta,$$

$$M_{44} = -(\mu + \gamma + m + bu_2) - \beta I_v \frac{S_h}{N_h^2} - (\mu + \delta),$$

$$M_{55} = -(\mu + \gamma + m + bu_2) - \beta I_v \frac{S_h}{N_h^2} - \kappa \frac{I_h}{N_h} - \eta,$$

$$M_{66} = -(\mu + \delta) - \kappa \frac{I_h}{N_h} - \eta,$$

$$q_1 = m(1 - \rho_1) + bu_2(1 - \rho_2) + \beta I_v \frac{S_h}{N_h^2},$$

$$q_2 = \kappa \left(\frac{A_v}{\eta} - I_v \right) \frac{S_h + R_h}{N_h^2},$$

$$q_3 = \kappa \left(\frac{A_v}{\eta} - I_v \right) \frac{I_h}{N_h^2}.$$

Let

$$P = P(S_h, I_h, R_h, I_v) = \begin{pmatrix}
 \frac{a_1}{I_h} & 0 & 0 & 0 & 0 & 0 \\
 0 & \frac{a_1}{I_h} & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & \frac{a_1}{I_h} & 0 & 0 \\
 0 & 0 & \frac{a_2}{I_v} & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & \frac{a_2}{I_v} & 0 \\
 0 & 0 & 0 & 0 & 0 & \frac{a_2}{I_v}
 \end{pmatrix}, \quad (10)$$

where a_1 and a_2 are two undetermined positive constants, then

$$P_f P^{-1} = \text{diag}\left(-\frac{I_h}{I_h}, -\frac{I_h}{I_h}, -\frac{I_h}{I_h}, -\frac{I_v}{I_v}, -\frac{I_v}{I_v}, -\frac{I_v}{I_v}\right).$$

Let

$$Q(S_h, I_h, R_h, I_v) = P_f P^{-1} + P_f^{[2]} P^{-1} \\ = \begin{pmatrix} M_{11} - \frac{I_h}{I_h} & -\beta I_v \frac{S_h}{N_h^2} & -\delta - \beta I_v \frac{S_h}{N_h^2} & \frac{a_1}{a_2} \beta \frac{S_h I_v}{N_h I_h} & \frac{a_1}{a_2} \beta \frac{S_h I_v}{N_h I_h} & 0 \\ m\rho_1 + bu_2\rho_2 & M_{22} - \frac{I_h}{I_h} & q_1 & 0 & 0 & \frac{a_1}{a_2} \beta \frac{S_h I_v}{N_h I_h} \\ 0 & \beta I_v \frac{I_h + R_h}{N_h^2} & M_{44} - \frac{I_h}{I_h} & 0 & 0 & \frac{a_1}{a_2} \beta \frac{S_h I_v}{N_h I_h} \\ q_2 \frac{a_2 I_h}{a_1 I_v} & -q_3 \frac{a_2 I_h}{a_1 I_v} & 0 & M_{33} - \frac{I_v}{I_v} & q_1 & \delta + \beta I_v \frac{S_h}{N_h^2} \\ q_3 \frac{a_2 I_h}{a_1 I_v} & 0 & -q_3 \frac{a_2 I_h}{a_1 I_v} & \beta I_v \frac{I_h + R_h}{N_h^2} & M_{55} - \frac{I_v}{I_v} & -\beta I_v \frac{S_h}{N_h^2} \\ 0 & q_3 \frac{a_2 I_h}{a_1 I_v} & -q_2 \frac{a_2 I_h}{a_1 I_v} & 0 & m\rho_1 + bu_2\rho_2 & M_{66} - \frac{I_v}{I_v} \end{pmatrix}.$$

The matrix $Q(S_h, I_h, R_h, I_v)$ can be written in block form:

$$Q(S_h, I_h, R_h, I_v) = \begin{pmatrix} Q_{11} & Q_{12} & Q_{13} & Q_{14} \\ Q_{21} & Q_{22} & Q_{23} & Q_{24} \\ Q_{31} & Q_{32} & Q_{33} & Q_{34} \\ Q_{41} & Q_{42} & Q_{43} & Q_{44} \end{pmatrix}, \quad (11)$$

where

$$Q_{11} = M_{11} - \frac{I_h}{I_h}, \quad Q_{12} = \left(-\beta I_v \frac{S_h}{N_h^2}, -\delta - \beta I_v \frac{S_h}{N_h^2}\right), \\ Q_{13} = \left(\frac{a_1}{a_2} \beta \frac{S_h I_v}{N_h I_h}, \frac{a_1}{a_2} \beta \frac{S_h I_v}{N_h I_h}\right), \quad Q_{14} = 0, \\ Q_{21} = (m\rho_1 + bu_2\rho_2, 0)^T, \quad Q_{24} = \left(\frac{a_1}{a_2} \beta \frac{S_h I_v}{N_h I_h}, \frac{a_1}{a_2} \beta \frac{S_h I_v}{N_h I_h}\right)^T, \\ Q_{22} = \begin{pmatrix} M_{22} - \frac{I_h}{I_h} & q_1 \\ \beta I_v \frac{I_h + R_h}{N_h^2} & M_{44} - \frac{I_h}{I_h} \end{pmatrix}, \quad Q_{23} = \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}, \\ Q_{31} = \left(q_2 \frac{a_2 I_h}{a_1 I_v}, q_3 \frac{a_2 I_h}{a_1 I_v}\right)^T, \quad Q_{34} = \left(\delta + \beta I_v \frac{S_h}{N_h^2}, -\beta I_v \frac{S_h}{N_h^2}\right)^T, \\ Q_{32} = \begin{pmatrix} -q_3 \frac{a_2 I_h}{a_1 I_v} & 0 \\ 0 & -q_3 \frac{a_2 I_h}{a_1 I_v} \end{pmatrix}, \quad Q_{33} = \begin{pmatrix} M_{33} - \frac{I_v}{I_v} & q_1 \\ \beta I_v \frac{I_h + R_h}{N_h^2} & M_{55} - \frac{I_v}{I_v} \end{pmatrix}, \\ Q_{41} = 0, \quad Q_{42} = \left(q_3 \frac{a_2 I_h}{a_1 I_v}, -q_2 \frac{a_2 I_h}{a_1 I_v}\right), \\ Q_{43} = (0, m\rho_1 + bu_2\rho_2), \quad Q_{44} = M_{66} - \frac{I_v}{I_v}.$$

Let $z = (z_1, z_2, z_3, z_4, z_5, z_6)$ denote a vector in $R^6 \cong R^{(4)}$, we select a norm in R^6 as

$$|(z_1, z_2, z_3, z_4, z_5, z_6)| = \max\{|z_1|, |z_2| + |z_3|, |z_4| + |z_5|, |z_6|\} \quad (12)$$

and let $\sigma(Q)$ be the Lozinskiĭ measure of Q with respect to the induced matrix norm $|\cdot|$ in R^6 , defined by

$$\sigma(Q) = \lim_{h \rightarrow 0^+} \frac{|I + hQ| - 1}{h}.$$

Using a similar argument as in [41], we have the following estimate

$$\sigma(Q(S_h, I_h, R_h, I_v)) \leq \sup\{g_1, g_2, g_3, g_4\},$$

where

$$g_1 = \sigma_1(Q_{11}) + |Q_{12}| + |Q_{13}| + |Q_{14}|,$$

$$g_2 = \sigma_1(Q_{22}) + |Q_{21}| + |Q_{23}| + |Q_{24}|,$$

$$g_3 = \sigma_1(Q_{33}) + |Q_{31}| + |Q_{32}| + |Q_{34}|,$$

$$g_4 = \sigma_1(Q_{44}) + |Q_{41}| + |Q_{42}| + |Q_{43}|,$$

$|Q_{ij}|$ ($i \neq j, i, j = 1, 2, 3, 4$) are matrix norms with respect to the l_1 vector norm, and σ_1 denotes the Lozinskiĭ measure with respect to

the l_1 norm (see [38]). To calculate the values of g_i , we firstly obtain that

$$\sigma_1(Q_{11}) = -\mu - \beta \frac{I_v}{N_h} - (\mu + \gamma + m + bu_2) - \frac{I_h}{I_h},$$

$$\sigma_1(Q_{22}) = -2\mu - \delta - \frac{I_h}{I_h},$$

$$\sigma_1(Q_{33}) = -\mu - \eta - \kappa \frac{I_h}{N_h} - \frac{I_v}{I_v},$$

$$\sigma_1(Q_{44}) = -(\mu + \delta) - \kappa \frac{I_h}{N_h} - \eta - \frac{I_v}{I_v},$$

and

$$|Q_{12}| = \delta + \beta I_v \frac{S_h}{N_h^2}, \quad |Q_{13}| = \beta \frac{a_1}{a_2} \frac{S_h I_v}{N_h I_h},$$

$$|Q_{14}| = 0, \quad |Q_{21}| = m\rho_1 + bu_2\rho_2,$$

$$|Q_{23}| = 0, \quad |Q_{24}| = 2\beta \frac{a_1}{a_2} \frac{S_h I_v}{N_h I_h},$$

$$|Q_{31}| = \kappa \frac{a_2}{a_1} \left(\frac{A_v}{\eta} - I_v\right) \frac{I_h}{N_h I_v}, \quad |Q_{32}| < \kappa \frac{a_2}{a_1} \left(\frac{A_v}{\eta} - I_v\right) \frac{I_h}{N_h I_v},$$

$$|Q_{34}| = \delta + 2\beta I_v \frac{S_h}{N_h^2}, \quad |Q_{41}| = 0,$$

$$|Q_{42}| < \kappa \frac{a_2}{a_1} \left(\frac{A_v}{\eta} - I_v\right) \frac{I_h}{N_h I_v}, \quad |Q_{43}| = m\rho_1 + bu_2\rho_2.$$

Moreover, from (7b) and (7d), we have

$$\frac{\dot{I}_h}{I_h} = \beta \frac{S_h I_v}{N_h I_h} - (\mu + \gamma + m + bu_2),$$

and

$$\frac{\dot{I}_v}{I_v} = \kappa \left(\frac{A_v}{\eta} - I_v\right) \frac{I_h}{N_h I_v} - \eta.$$

Choosing $\frac{a_1}{a_2} = \frac{1}{2}$, then we further have

$$g_1 < -\mu + \delta,$$

$$g_2 = -(\mu + \delta) + \gamma + m(1 + \rho_1) + bu_2(1 + \rho_2),$$

$$g_3 < 3\frac{\dot{I}_v}{I_v} + 3\eta + \delta + 2\beta \frac{A_v(\mu + \gamma)}{\eta A_h} - \mu - \kappa \frac{I_h}{N_h},$$

$$g_4 < \frac{\dot{I}_v}{I_v} + \eta + m\rho_1 + bu_2\rho_2 - (\mu + \delta) - \kappa \frac{I_h}{N_h}.$$

Let

$$\bar{b} = \min\left\{\mu - \delta, \quad \mu + \delta - \gamma - m(1 + \rho_1) - bu_2(1 + \rho_2),\right.$$

$$\left.\mu - 3\eta - \delta - 2\beta \frac{A_v(\mu + \gamma)}{\eta A_h}, \quad \mu + \delta - \eta - m\rho_1 - bu_2\rho_2\right\},$$

from condition (9), we have $\bar{b} > 0$ and

$$g_1 \leq -\bar{b}, \quad g_2 \leq -\bar{b}, \quad g_3 < 3\frac{\dot{I}_v}{I_v} - \bar{b}, \quad g_4 < \frac{\dot{I}_v}{I_v} - \bar{b}.$$

Along each solution $(S_h(t), I_h(t), R_h(t), I_v(t))$ of system (7) with initial value $(S_h(0), I_h(0), R_h(0), I_v(0)) \in \Gamma$, when $t > T$ we have

$$\frac{1}{t} \int_0^t g_1 ds \leq -\bar{b},$$

$$\frac{1}{t} \int_0^t g_2 ds \leq -\bar{b},$$

$$\frac{1}{t} \int_0^t g_3 ds < \frac{1}{t} \int_0^T g_3 ds + \frac{3}{t} \ln \frac{I_v(t)}{I_v(T)} - \bar{b} \frac{t - T}{t},$$

$$\frac{1}{t} \int_0^t g_4 ds < \frac{1}{t} \int_0^T g_4 ds + \frac{1}{t} \ln \frac{I_v(t)}{I_v(T)} - \bar{b} \frac{t - T}{t}.$$

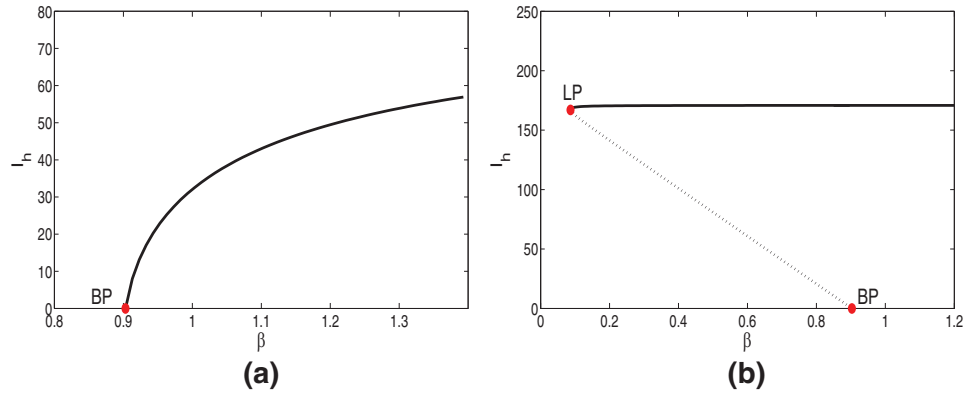


Fig. 2. (a) The forward bifurcation diagram from I_h versus β for system (1), when $\delta = 0.002$. (b) The backward bifurcation diagram from I_h versus β for system (1), when $\delta = 2.7902$. Other parameters are $A_h = 1000$, $\mu = 0.014$, $m = 0.05$, $\rho_1 = 0.78$, $b = 0.2$, $u_2 = 40$, $\rho_2 = 0.93$, $\gamma = 5.8$, $\eta = 0.03$, $A_v = 2000$, $\kappa = 0.4935$.

Furthermore, we have

$$\begin{aligned} & \frac{1}{t} \int_0^t \sigma(Q(S_h, I_h, R_h, I_v)) ds \\ & \leq \sup \left\{ -\bar{b}, -\bar{b}, \frac{1}{t} \int_0^T g_3 ds + \frac{3}{t} \ln \frac{I_v(t)}{I_v(T)} \right. \\ & \quad \left. - \bar{b} \frac{t-T}{t}, \frac{1}{t} \int_0^T g_4 ds + \frac{1}{t} \ln \frac{I_v(t)}{I_v(T)} - \bar{b} \frac{t-T}{t} \right\}. \end{aligned}$$

Therefore,

$$\bar{q} = \limsup_{t \rightarrow \infty} \sup_{x_0 \in \Gamma} \frac{1}{t} \int_0^t \sigma(Q(x(s), x_0)) ds \leq -\bar{b} < 0. \quad \square$$

In the above analysis, we split Q into a 4×4 block matrix. Now, we can split Q into a 2×2 block matrix, then the following theorem is obtained.

Theorem 4.3. *If $\mathcal{R}_0 > 1$, then the endemic equilibrium of system (7) is globally asymptotically stable provided that*

$$\begin{aligned} \mu > \max \left\{ m\rho_1 + bu_2\rho_2, \frac{\eta A_h(\gamma + m + bu_2 - \delta) + \beta A_v \gamma}{\eta A_h - \beta A_v}, \right. \\ & \left. \frac{3\eta^2 A_h + 2\beta A_v \gamma}{\eta A_h - 2\beta A_v}, \frac{\eta A_h[m(1 - \rho_1) + bu_2(1 - \rho_2)] + \beta A_v \gamma}{\eta A_h - \beta A_v} \right\}. \end{aligned} \quad (13)$$

Proof. Let us split $Q = Q(S_h, I_h, R_h, I_v)$ into blocks with the following partition

$$Q = \begin{pmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{pmatrix}, \quad (14)$$

where Q_{ij} ($i, j = 1, 2$) are 3×3 matrices. We select a norm in \mathbb{R}^6 as

$$|(z_1, z_2, z_3, z_4, z_5, z_6)| = \max\{|z_1| + |z_2| + |z_3|, |z_4| + |z_5| + |z_6|\}. \quad (15)$$

According to the discussion given in [41], we have

$$\sigma(Q) \leq \sup\{g_1, g_2\},$$

where

$$g_1 = \sigma_1(Q_{11}) + |Q_{12}|, \quad g_2 = \sigma_1(Q_{22}) + |Q_{21}|.$$

In a similar way as in the proof of Theorem 4.2, we can prove that if inequalities (12) hold, then

$$\bar{q} = \limsup_{t \rightarrow \infty} \sup_{x_0 \in \Gamma} \frac{1}{t} \int_0^t \sigma(Q(x(s), x_0)) ds < 0.$$

Therefore, the endemic equilibrium of system (7) is globally asymptotically stable. \square

The following two examples show that inequalities (9) and (13) given in Theorems 4.2 and 4.3, respectively, are different from each other.

Example 4.1. Take $A_h = 1000$, $\beta = 0.59$, $\mu = 3.7$, $m = 0.05$, $\rho_1 = 0.78$, $b = 0.2$, $u_2 = 0.6$, $\rho_2 = 0.93$, $\delta = 0.4$, $\gamma = 2.8$, $A_v = 20$, $\kappa = 0.4935$ and $\eta = 0.05$. By numerical calculations, we obtain the basic reproduction number $\mathcal{R}_0 \approx 1.1367 > 1$, and inequalities in (9) hold. However, inequalities in (13) do not hold. Since $\beta \frac{A_v(\mu + \gamma)}{\eta A_h} + \gamma + m + bu_2 = 4.504$ and $\mu + \delta = 4.1$.

Example 4.2. In Example 4.1, we keep some parameters unchanged, and only adjust the value of the recovery rate. Let $\delta = 0.9$, by numerical calculations, the basic reproduction number $\mathcal{R}_0 \approx 1.1367 > 1$, and inequalities in (13) hold. However, inequalities in (9) do not hold. Since $3\eta + \delta + 2\beta \frac{A_v(\mu + \gamma)}{\eta A_h} = 4.118$ and $\mu = 3.7$.

Remark 4.1. From Theorems 4.2 and 4.3, and Examples 4.1 and 4.2, we can see that by choosing different matrix functions $P(x)$ as in (10), different matrix divisions as in (11) and (14), and different norms as in (12) and (15), we can establish different sufficient conditions on the global stability of the endemic equilibrium of system (7). This shows that the global stability of system (7) may be very complex.

5. Numerical simulations

In this section, we implement numerical simulations to confirm the above theoretical analysis and explore more patterns of dynamical behaviors of model (1).

If we increase the value of parameter δ and keep the other parameters unchanged, by comparing Fig. 2(a) and (b), it is found that some more complicated dynamical behaviors of system (1) occur. Fixing $\delta = 0.002$, it has a forward bifurcation as shown in Fig. 2(a). However, fixing $\delta = 2.7902$, it has a backward bifurcation as in Fig. 2(b). Their qualitative difference indicates that the recurrence of the disease can lead to a backward bifurcation. In addition, with the help of the MatCont package [42,43], we found a saddle-node bifurcation point (LP) at $\beta = 0.086673$ and a branch point (BP) at $\beta = 0.902996$. The dashed curve indicates the unstable equilibrium and the solid curve represents the stable equilibrium in all bifurcation diagrams.

The equilibria of system (1) are entirely determined by these coefficients a_1, a_2, a_3 in (5). Therefore, $A_h = 1000$, $\mu = 0.014$, $m = 0.05$, $\rho_1 = 0.78$, $b = 0.2$, $\beta = 0.6$, $\rho_2 = 0.93$, $\gamma = 5.8$, $\eta = 0.03$, $A_v = 2000$, $\kappa = 0.4935$, three curves $a_2 = 0$, $\Delta = 0$ and $a_3 = 0$ divide the first quadrant of the $u_2 - \delta$ plane into four regions. There are a stable endemic equilibrium and an unstable disease-free equilibrium in the area below the line $a_3 = 0$. Other three regions are shown in Fig. 3.

In the following, the number and stability of equilibria are shown in Fig. 4 when the parameter u_2 or δ changes, respectively. Fig. 4(a)

Table 2
Three typical patterns of dynamical behaviors of system (1).

Pattern	Range of u_2 (range of R_0)	Steady states of system (1)
1	$u_2 > 205.709772$ ($R_0 < 0.44269$)	A globally stable disease-free equilibrium (see Fig. 5)
2	$16.74 < u_2 < 205.709772$ ($0.44269 < R_0 < 1$)	A locally stable disease-free equilibrium, an unstable endemic equilibrium and a locally stable endemic equilibrium (see Fig. 6)
3	$0 < u_2 < 16.74$ ($R_0 > 1$)	An unstable disease-free equilibrium and a globally stable endemic equilibrium (see Fig. 7)

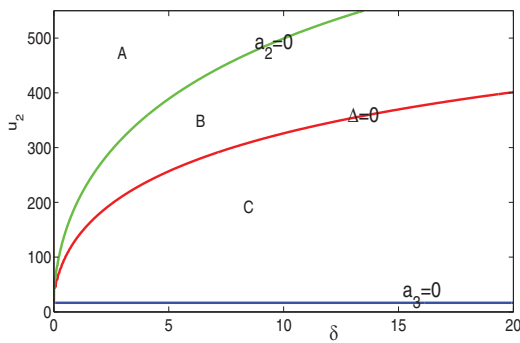


Fig. 3. For system (1), there is a stable disease-free equilibrium in regions A and B; there are an unstable endemic equilibrium, a stable endemic equilibrium and an unstable disease-free equilibrium in region C.

displays the dynamics of system (1) when u_2 changes, in turn, from region C, region B to region A; Fig. 4(b) shows that when δ changes, in turn, from region A, region B to region C.

Fig. 4 (a) reflects the role of the treatment in controlling the disease. The increase of the treatment rate has an influence in eliminating the disease. However, Fig. 4 also shows that a backward bifurcation occurs in the process of increasing the treatment rate. In Table 2, three typical patterns of dynamical behavior of system (1) are listed. As an example, we take a value of the treatment u_2 corresponding to each pattern to illustrate the three types of dynamical behaviors of system (1). The values of all parameters are the same as in Fig. 4.

Firstly, if $u_2 > 205.709772$, i.e., $0 < R_0 < 0.44269$, that is, the treatment rate is relatively large (or equivalently, the basic reproduction number is relatively small), then the disease-free equilibrium is the unique steady state and is globally asymptotically stable. Fig. 5 illustrates this pattern where the treatment rate is chosen as $u_2 = 300$ ($R_0 = 0.37398$). In Figs. 5–7, blue and red colours denote stable equilibria, black colour denotes unstable equilibria.

Secondly, if $16.74 < u_2 < 205.709772$, i.e., $0.44269 < R_0 < 1$, the treatment rate becomes a bit smaller, then bistability occurs, where the stable disease-free equilibrium coexists with a stable endemic equilibrium. For this pattern, we choose $u_2 = 150$ ($R_0 = 0.50681$) to obtain Fig. 6 in which the numerical solutions of system (1) tend to either the disease-free equilibrium or an endemic equilibrium.

Thirdly, if $0 < u_2 < 16.74$, i.e., $R_0 > 1$, the treatment rate is small enough, then the unstable disease-free equilibrium coexists with a stable endemic equilibrium. For this pattern, the treatment rate is chosen as $u_2 = 10$ ($R_0 = 1.08232$). As depicted in Fig. 7, all solutions tend to the endemic equilibrium in this case.

From Figs. 5–7, the numerical simulations show that for larger values of δ , a subcritical transcritical bifurcation occurs at $R_0 = 1$ in Fig. 4 (or Fig. 2(b)). Next, the following numerical simulations (Figs. 8 and 9) will show that for smaller values of δ , there is a supercritical transcritical bifurcation at $R_0 = 1$ in Fig. 2(a). That is, the increase of the loss rate of immunity for humans induces a backward bifurcation.

6. Applications to malaria in China

In this section, we first use system (1) to simulate the malaria data from National Health and Family Planning Commission of the People’s Republic of China (NHFPC, Table 1). Then we examine the current control strategies on the elimination of malaria in China.

The definition of malaria elimination is that there is no local transmission for at least three years [49]. Therefore, parameters were estimated using two sets of data (indigenous data and death data) in Table 1 by the least squares method (LSM). This consists of minimizing the residual sum of squares (RSS)

$$RSS = \sum_{i=1}^n (Y_i - f(Y_i, \theta))^2, \tag{16}$$

where Y_i are observed data and θ is the parameter to be estimated. Let observed variables be $G(t)$ and $D(t)$. $G(t)$ serves to keep track of the

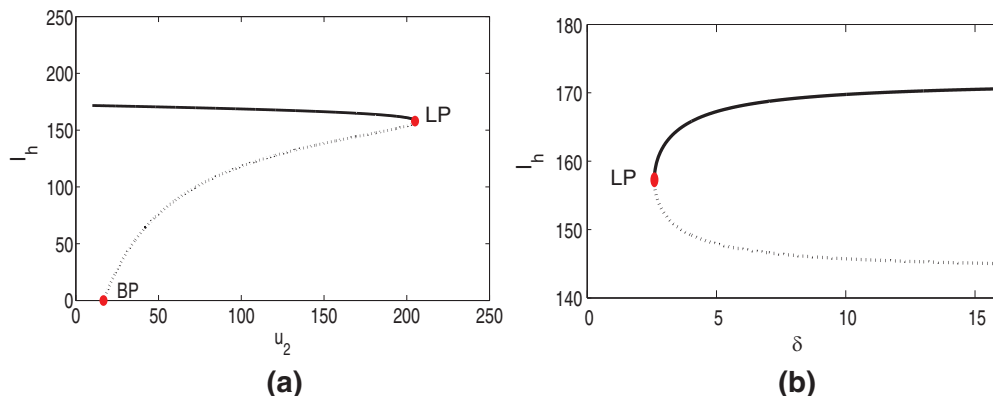


Fig. 4. Bifurcation diagrams (a) the I_h component of equilibria versus the treatment rate u_2 for system (1) by fixing $\delta = 2.7902$; (b) the I_h component of equilibria versus the parameter δ for system (1) by fixing $u_2 = 300$. Keeping the other parameters the same as those in Fig. 3.

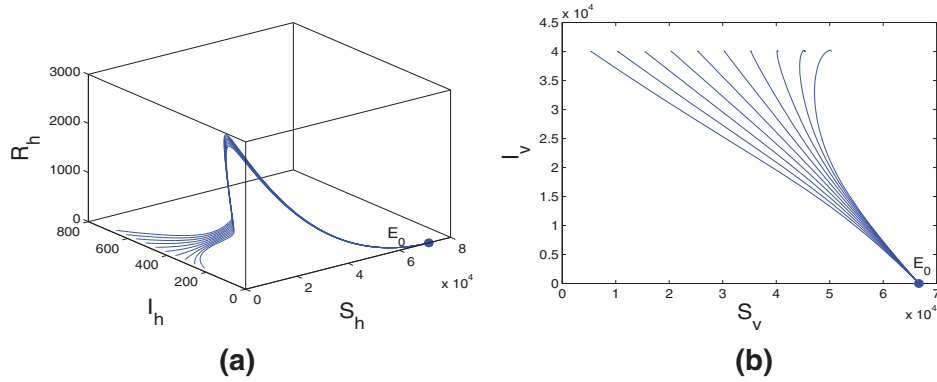


Fig. 5. System (1) has a globally stable disease-free equilibrium $E_0 = (7.1429, 0, 0, 6.6667, 0)$, when $\delta = 2.7902$ and $u_2 = 300(R_0 = 0.37398)$.

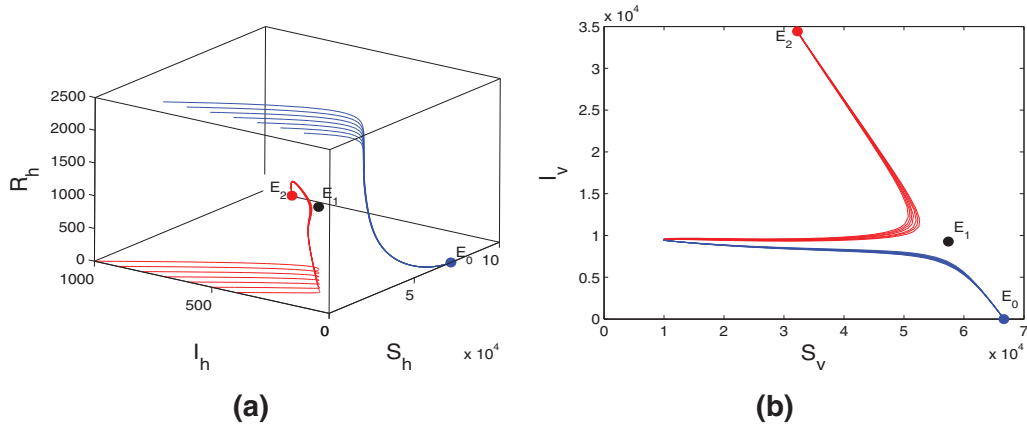


Fig. 6. Choose $\delta = 2.7902$ and $u_2 = 150(R_0 = 0.50681)$, system (1) has two stable equilibria: a disease-free equilibrium E_0 and an endemic equilibrium $E_2 = (739.62, 166.22, 1656.18, 32248.12, 34418.55)$. The other endemic equilibrium $E_1 = (12578.59, 138.39, 1378.81, 57396.91, 9269.75)$ is unstable.

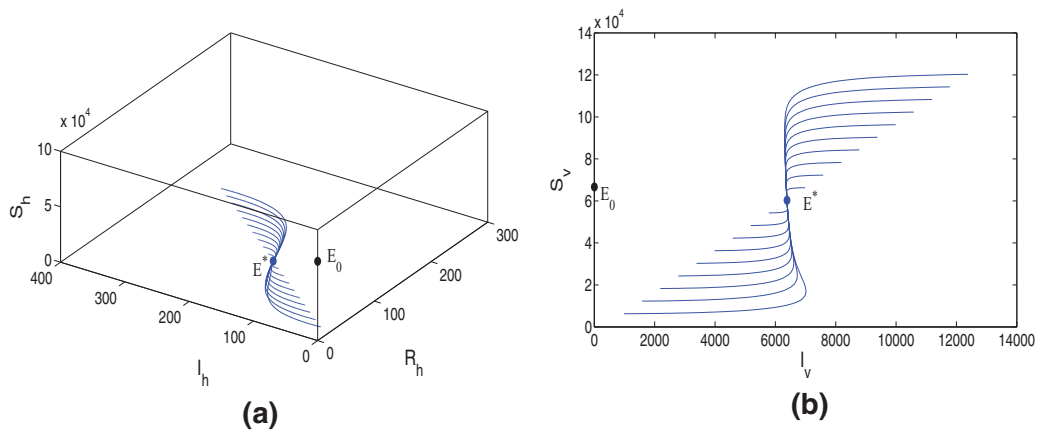


Fig. 7. System (1) has a globally stable endemic equilibrium $E^* = (11.17, 171.69, 116.27, 6384.54, 60282.13)$ and an unstable disease-free equilibrium E_0 , where $\delta = 2.7902$ and $u_2 = 10(R_0 = 1.0823)$.

cumulative number of human malaria cases and $D(t)$ is the cumulative data of human malaria deaths. Furthermore, refer to system (1), it is clear that $dG/dt = \beta S_h(t)I_v(t)/N_h$ and $dD/dt = \gamma I_h(t)$.

First step: In the absence of concrete estimates, the host recruitment rate A_h is estimated by using China’s demographic data from year 2002 to 2013. Assume the demographic equation $dN_h/dt = A_h - \mu N_h$. Fixed $\mu = 0.00708 \text{ year}^{-1}$ by 2008 China Statistical Yearbook (CSY), the estimated value of A_h is $1.6349 \times 10^7 \text{ humans} \times \text{year}^{-1}$ using LSM by DEDiscover software [50]. It is realistic that the range of birth population per year from 2002 to 2013 by CSY is $[1.584 \times 10^7, 1.647 \times 10^7]$. A reasonable match is shown in Fig. 10.

Second step: For the purpose of simulating system (1), we require knowledge of the initial conditions. The initial values of human

are chosen as follows: $S_h(0) = 1.2845 \times 10^9$, $I_h(0) = 35475$ and refer to [47], $R_h(0) = 0$. We assume 0.53 to at most 2 mosquitoes per people [46], therefore, the size of the mosquito population is $[6.8 \times 10^8, 2.569 \times 10^9]$. The initial conditions of $S_v(0)$ and $I_v(0)$ are estimated as parameters.

Third step: Values or ranges for several of the system parameters used in system (1) can be obtained from existing studies on malaria. The duration of the infectious period for humans without treatment is from 12 to 24 months; however, with treatment, it reduces to 9.5 months [46]. Therefore, the range of m is $[1, 2] \text{ year}^{-1}$ and u_2 is $\frac{24}{19} \text{ year}^{-1}$. According to the decline rate of malaria parasites in clinical treatment, we estimate that the efficacy of treatment is $b = 0.935$ [45] and $\rho_2 = 0.9$ [12]. We also assume that the range can vary from

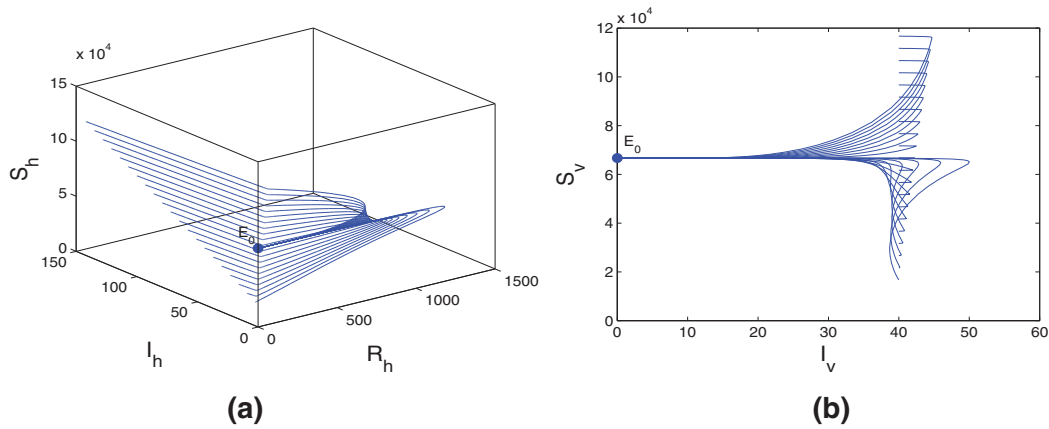


Fig. 8. System (1) has a globally stable disease-free equilibrium $E_0 = (7.1429, 0, 0, 6.6667, 0)$, where $\delta = 0.002$ and $\beta = 0.8 (R_0 = 0.9412)$.

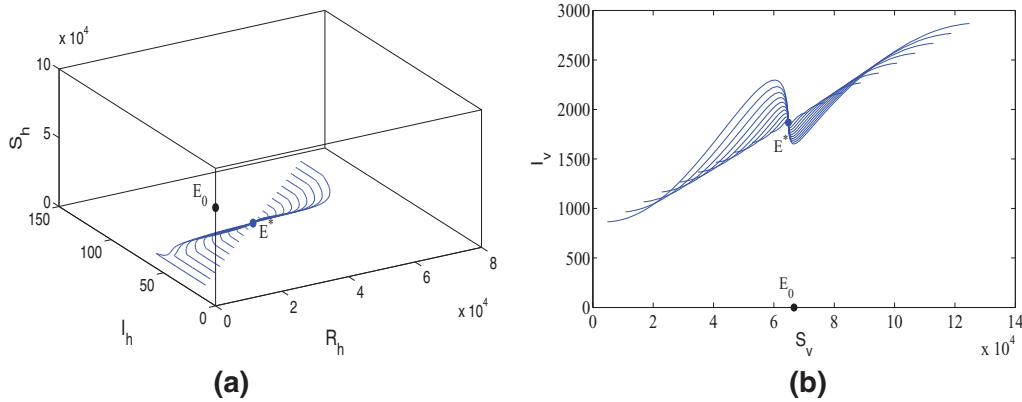


Fig. 9. System (1) has a globally stable endemic equilibrium $E^* = (7427, 72, 33891, 64799, 1867)$ and an unstable disease-free equilibrium E_0 , where $\delta = 0.002$ and $\beta = 3 (R_0 = 1.8227)$.

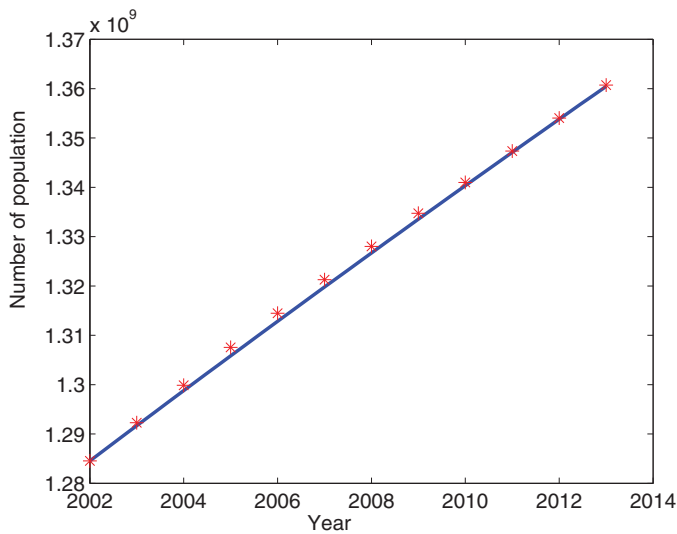


Fig. 10. Comparisons of the demographic data from the China Statistical Yearbook and the solution of the demographic equation.

3 months to 50 years for the average duration of the immune period [46]. Then, the range of δ is $[0.02, 4] \text{ year}^{-1}$. It is assumed that the mosquito birth rate is 0.013 per day [48]. Therefore, the recruitment rate of mosquitoes is $[3.2 \times 10^{10}, 1.9 \times 10^{11}] \text{ mosquitoes} \times \text{year}^{-1}$.

Finally, under these assumptions, all the unknown parameters are estimated using LSM by DEDiscover software and the optimal value of RSS is 0.0199. Table 3 lists the estimates of these parameters and their corresponding 95% confidence intervals (CI).

Table 3

The system parameter values with 95% CI and p values.

Parameter	Estimated value	95% CI	p value
A_v	8.2825×10^{10}	$8.2825 \times 10^{10} - 8.2826 \times 10^{10}$	<0.0001
β	0.0087	0.0080–0.0095	<0.0001
δ	3.9592	3.9403–3.9782	<0.0001
η	0.1271	0.1249–0.1294	<0.0001
γ	0.0029	0.0026–0.0032	<0.0001
κ	4.1960×10^{-5}	$5.0948 \times 10^{-6} - 7.8826 \times 10^{-5}$	0.0285
m	1.9268	1.8744–1.9792	<0.0001
ρ_1	0.1427	0.1384–0.1470	<0.0001
$S_v(0)$	9.4712×10^8	$9.4711 \times 10^8 - 9.4712 \times 10^8$	<0.0001
$I_v(0)$	5.3053×10^6	$5.3053 \times 10^6 - 5.3054 \times 10^6$	<0.0001

Using some rational assumptions and parameter values in Table 3, numerical simulations of the cumulative human malaria cases and cumulative human malaria deaths using system (1) are shown in Figs. 11 (a) and (b), respectively. The results indicate that simulations of our system can provide a match to the cumulative data on indigenous cases and death cases in Mainland China from 2002 to 2013. Furthermore, we estimate that the basic reproduction number $R_0 \approx 0.0161$ for malaria transmission in China, and $\gamma^* \approx 0.0095$. Our theoretical analysis shows that malaria can be eliminated in China in the future. This means that the current malaria elimination action plans in China are practicable.

7. Discussion

In this paper, we focused on a deterministic system of malaria transmission with treatment. Nowadays, there is still no licensed

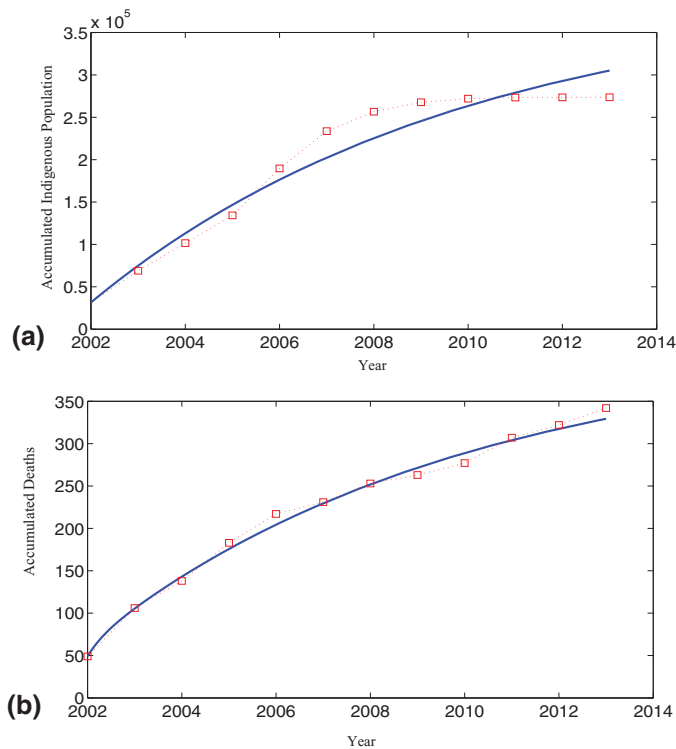


Fig. 11. (a) The comparison between the cumulative numbers of newly indigenous cases in Mainland China from 2002 to 2013 and the simulation of our system. (b) The comparison between the cumulative numbers of human malaria deaths in Mainland China from 2002 to 2013 and the simulation of our system.

vaccine for preventing malaria. Therefore, in our system, human population is divided into susceptible, infectious and recovered subclasses, and mosquito population is split into susceptible and infectious classes. It is founded for malaria that humans who recovered spontaneously or treated may be still susceptible. Therefore, a malaria system with treatment is developed. The efficacy of treatment is described by the parameter b .

Firstly, we calculated the basic reproduction number \mathcal{R}_0 and investigated the existence and stability of equilibria. We can see that under the conditions in Theorem 2.3 (3)(iii2), the disease-free equilibrium E_0 coexists with two endemic equilibria E_1 and E_2 . These results indicate that a backward bifurcation may occur in system (1). It is important to seek conditions for the existence of the backward bifurcation. This problem was discussed in Section 3. From Theorem 3.1, it is found that the disease mortality rate plays a significant role in the occurrence of a backward bifurcation. As we all know, the existence of a backward bifurcation means that the disease cannot be eradicated by simply reducing the value of basic reproduction number \mathcal{R}_0 below 1. In this case, the disease mortality rate

$$\gamma^* = \mu + \frac{\mu\kappa}{\eta} + \frac{\mu(m\rho_1 + bu_2\rho_2)}{\mu + \delta}$$

is also a key threshold for eradicating malaria. From the expression of \mathcal{R}_0 , it is possible that increasing η may be effective in reducing $\mathcal{R}_0 < 1$. However, at the same time, we find that γ^* will get smaller. Thus, the condition $\gamma > \gamma^*$ easily holds.

Secondly, in general, global stability of equilibria is one of the most difficult problems in the stability analysis of many classes of biological models and it is essential in ruling out other scenarios such as periodic solutions. In Section 4, global stability of the endemic equilibrium E^* when $\mathcal{R}_0 > 1$ is studied by utilizing a general approach established in [38]. This method has been used mostly for three-dimensional systems (see [23,30]). However, we need to deal with global stability for a four-dimensional system. Sufficient

conditions for the global stability of E^* are obtained by choosing the matrix function $P(x)$ and estimating the Lozinskiĭ measure for a 6×6 matrix. Different global stability conditions may be obtained depending on different $P(x)$ and different divisions for the 6×6 matrix. However, numerical simulations show that the same conclusion may be still reached even if these conditions do not hold.

As an application, we used our system to simulate the reported human malaria cases in China from 2002 to 2013 (see Fig. 10) and obtained reasonable matches. Malaria elimination in China is still confronted by many difficulties and challenges, that is the increase of imported *Plasmodium falciparum* cases and more deaths every year. More recently, the malaria deaths in 2011 were twice as that of 2010. For imported malaria, it is typical that African migrant workers who came from Guangxi province collectively returned to their homes. This made the number of imported malaria cases up sharply (see [44]). This indicates that the surveillance on moving population from malaria endemic areas should be strengthened. In addition, it may be a better control strategy to strengthen border crossing check-ups mechanism such as in the frontier regions of Yunnan and Guangxi provinces.

This work is just a preliminary exploration of global analysis in a higher dimensional system modelling the transmission dynamics of malaria between humans and mosquitoes. The nonlinear dynamics of the system deserve further consideration. Also it will be interesting to study the impacts of seasonal and climate changes on the transmission of malaria in our system. Finally, we are also very concerned about the imported cases, which is affecting the transmission of malaria now. We leave these for future investigation.

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