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Research article

Controlling malaria in a population accessing counterfeit antimalarial drugs

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Abstract: A mathematical model is developed for describing malaria transmission in a population consisting of infants and adults and in which there are users of counterfeit antimalarial drugs. Three distinct control mechanisms, namely, effective malarial drugs for treatment and insecticide-treated bednets (ITNs) and indoor residual spraying (IRS) for prevention, are incorporated in the model which is then analyzed to gain an understanding of the disease dynamics in the population and to identify the optimal control strategy. We show that the basic reproduction number, R_0, is a decreasing function of all three controls and that a locally asymptotically stable disease-free equilibrium exists when $R_0 < 1$. Moreover, under certain circumstances, the model exhibits backward bifurcation. The results we establish support a multi-control strategy in which either a combination of ITNs, IRS and highly effective drugs or a combination of IRS and highly effective drugs is used as the optimal strategy for controlling and eliminating malaria. In addition, our analysis indicates that the control strategies primarily benefit the infant population and further reveals that a high use of counterfeit drugs and low recrudescence can compromise the optimal strategy.

Keywords: malaria; structured population; reproduction numbers; backward bifurcation; optimal control; counterfeit drugs

1. Introduction

Malaria, although preventable and treatable, continues to be one of the most prevalent and lethal human infections worldwide [1]. Globally, 627,000 deaths were recorded in 2020, with Sub-Saharan Africa accounting for almost 96% of them [2]. Children under 5 years become the most vulnerable

to infection and death after losing their maternal antibodies, which protect them during their first six months [3, 4].

A massive deployment of effective prevention and treatment tools by the World Health Organization (WHO) in 2000 has led to a reduction of cases in the Americas and the Western Pacific Region, no indigenous cases in the European Region, a decline of 66% in all age mortality rates in Africa and 663 million cases being averted in Sub-Saharan Africa from 2001 to 2015 [5, 6]. During this period, it is estimated that Sub-Saharan Africa saved US$900 million in case management costs. In 2019, the governments of the endemic countries and their international partners invested funding estimated at US$ 3.0 billion for malaria control and elimination [2].

Early treatment of infected humans with effective antimalarial drugs gives complete recovery and prevents the transmission of infection to mosquitoes during a blood meal, recrudescence, severe malaria and even death [7]. Recrudescence is common in *Plasmodium falciparum* infection and may occur when parasites, which remain in the red blood cells after an episode of malaria, start multiplying and cause the recurrence of the clinical symptoms due to treatment failure in the patient [8]. *P. falciparum* is the most deadly species of malaria parasite globally and the most prevalent in Africa. In most Sub-Saharan countries, after *P. falciparum* resistance was identified, the treatment for uncomplicated malaria was changed to artemisinin-based combination therapy (ACT) [7, 9]. WHO recommends that an entire course of highly effective ACT must be used by both semi-immune and non-immune malaria patients to have a complete cure from both sexual and asexual forms of the parasites and partial immunity [5, 7].

The availability, distribution, trade and use of monotherapies and other substandard antimalarial drugs continue throughout most malaria-endemic countries [10–16]. It is estimated that about a third of antimalarial drugs that end up in Africa are counterfeit [13, 15]. These antimalarial drugs may contain too few or too many required active ingredients and may fail to be adequately absorbed by the body [17]. Recently, evidence has shown that counterfeit antimalarial drugs pose a public health threat of prolonging the illness, incomplete recovery, treatment failure, recrudescence, severe disease, spreading drug resistance and asymptomatic infection carriers, resulting in more than 122,000 deaths of African children under five years annually [7, 12, 15, 17, 18]. According to [4, 13], the use of these drugs may jeopardize the success made so far in controlling and eliminating malaria, particularly in Sub-Saharan Africa.

Several mathematical models have considered the effects of effective treatment [19–23], recovery or immunity [19, 24–28], reinfection [27, 29, 30] and age-structure [21, 22, 31, 32] on the dynamics of malaria. In particular, [19, 24–28, 33] incorporated into their models recovered or semi-immune humans, who are reservoirs of infection to mosquitoes. In addition, [27] assumed that the recovered humans could relapse. Evidence has shown that in most malaria-endemic areas in Sub-Saharan Africa, symptomatic humans often use counterfeit and effective drugs for treatment [4, 9, 11–16]. The aforementioned models did not consider the effect of both effective and counterfeit antimalarial drugs on the dynamics of malaria.

Many studies have also been carried out to examine the impact of control strategies on the transmission of malaria infection. The potential impact of personal protection, treatment and possible vaccination on the transmission dynamics of malaria was theoretically assessed in [20]. The optimal control theory has been successfully used in decisions concerning the cost minimization of several control intervention models after implementing Pontryagin's maximum principle [34]. The studies

[23, 24, 35–38] applied optimal control theory to determine the impact of control strategies on the transmission dynamics of malaria. The studies investigated optimal strategies for controlling the spread of malaria disease using treatment, treated bednets and spraying of mosquito insecticide in models with mass action [24], standard [23, 37] or non-linear [36] incidence rates and cost-effectiveness [23] of the controls. Other studies [38] used optimal control problem strategies to study how genetically modified mosquitoes should be introduced into the environment. The aforementioned studies did not consider optimal control in age-structured models, especially where the treatment can be either effective or ineffective due to using effective or counterfeit antimalarial drugs. Optimal control has, however, been applied to an age-structured model for HIV [39].

This paper seeks to answer the following question: What optimal control strategy best eliminates *P. falciparum* malaria infection in an age-structured population where counterfeit drug use persists? We do this by developing a deterministic model for malaria transmission incorporating the infant and adult populations, counterfeit drug use and three of the malaria control measures adopted by most endemic countries in Sub-Saharan Africa [4, 40], namely, use of highly effective antimalarial drugs (HEAs), insecticide-treated bednets (ITNs) and indoor residual spraying (IRS). The paper is organized as follows. Section 2 briefly describes the formulation of the model and its basic properties. In Section 3, the dynamics of the model is presented. The analysis of the reproduction number is done in Section 4. In Section 5, the analysis of the optimal control problem is undertaken to find the conditions for optimal malaria control using Pontryagin's maximum principle, and the numerical simulations of the model are illustrated. The discussion of results and conclusion are presented in Sections 6 and 7, respectively.

2. Model formulation

The transmission model for malaria in human and female anopheles mosquito populations is formulated with the total population sizes at time t given by $N_h(t)$ and $N_m(t)$, respectively. The human population is divided into two mutually exclusive age subgroups: infants aged 0–5 years and adults above five. Each age subgroup is divided into susceptible, infectious, counterfeit antimalarial drug users and effective antimalarial drug users epidemiological classes. The mosquito population is divided into susceptible and infectious epidemiological classes. Figure 1 shows the flows between the classes. We let $S_A(S_B)$, $I_A(I_B)$, $U_A(U_B)$ and $T_A(T_B)$ represent infants (adults) who are susceptible, infectious, counterfeit drug users and effective drug users, respectively. For the mosquito population, S_m and I_m denote the susceptibles and infectives, respectively. The total human population $N_h(t)$ at a time t is given by

$$N_h(t) = N_A(t) + N_B(t) = S_A(t) + I_A(t) + U_A(t) + T_A(t) + S_B(t) + I_B(t) + U_B(t) + T_B(t).$$

The total mosquito population $N_m(t)$ at a given time t is given by $N_m(t) = S_m(t) + I_m(t)$.

Susceptible humans are those with no merozoites or gametocytes in their bodies. Infectious humans show clinical symptoms of malaria and can infect feeding mosquitoes. Users of effective antimalarial drugs recover from malaria either naturally or due to using an effective antimalarial drug. These humans have partial immunity and become susceptible when this immunity wanes. Counterfeit drug users are humans who are removed from the infectious class due to using counterfeit drugs to treat malaria. They are asymptomatic, can infect mosquitoes (at a lower rate compared to the

infectious humans) and can recrudesce into the infectious class. Adult counterfeit drug users can become susceptible due to the high level of acquired immunity resulting from their repeated exposures to malaria [3]. The susceptible mosquitoes have no sporozoites in their body. Infective mosquitoes can infect humans during a blood meal. It is assumed that the infective stage of the mosquitoes ends with their death due to their short life cycle. Merozoites are the parasites released into the human bloodstream when a hepatic or erythrocytic schizont bursts, and gametocytes are the sexual stages of malaria parasites that infect anopheline mosquitoes when taken up during a blood meal. On the other hand, sporozoites are the motile malaria parasites inoculated by feeding female anopheline mosquitoes to invade the human hepatocytes [7].

The susceptible infants class, S_A, is generated by the recruitment of newborns at a birth rate α_h and the loss of post-treatment prophylaxis by effectively treated infants at a per capita rate ϕ_A. This class is decreased when infants in it die naturally, mature into susceptible adults or get infected, at a per capita natural death rate μ_h, per capita rate τ of maturing and per capita infection rate of infants $(1-u_1)\rho^n\lambda_A$, respectively. The control u_1 represents the effort of preventing malaria with insecticide-treated bednets (ITNs), so $(1-u_1)$ describes the failure probability of this prevention effort. The daily survival probability of a human is assumed to be $\rho_1 = e^{-\mu_h}$. The probability of survival of a human over the average latent period of length n_h to be infectious is given by $\rho^n = e^{-\mu_h n_h}$. λ_A is the force of infection in infants.

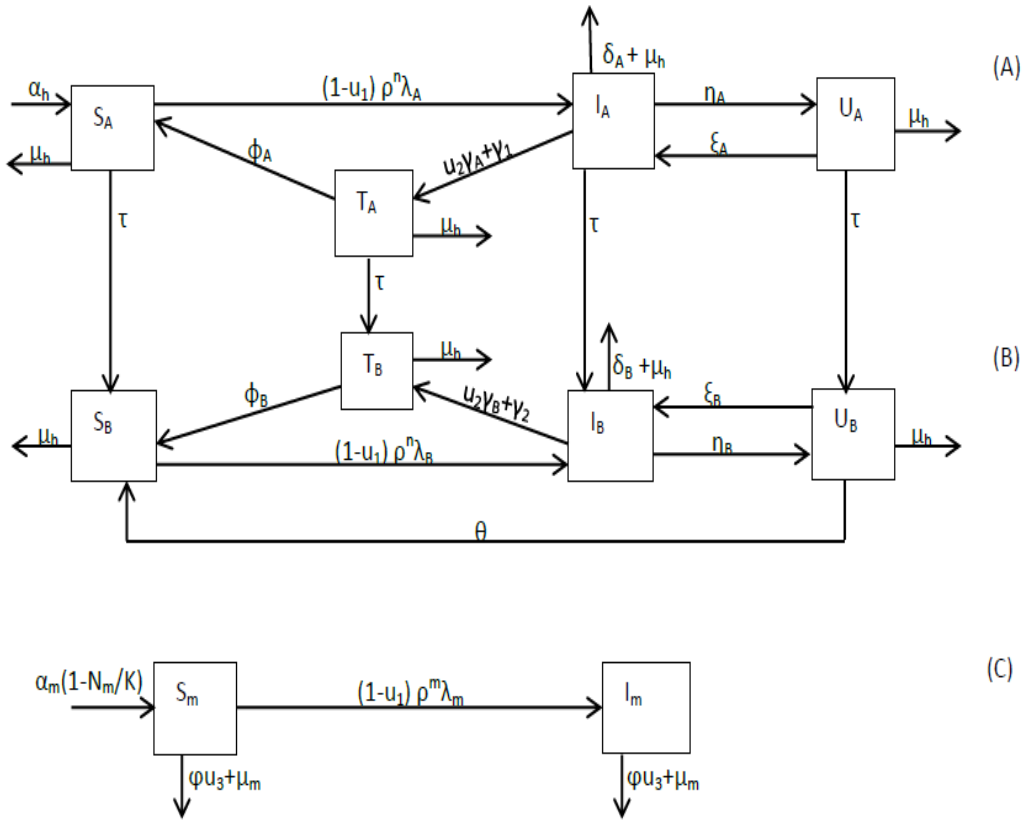

Figure 1. Schematic diagram of malaria transmission: (A) infants – humans five years old and younger, (B) adults – humans older than 5 years and (C) female *Anopheles* mosquitoes.

The infectious infants class, I_A, is generated by the per capita rate of acquiring infection $(1-u_1)\rho^n\lambda_A$ and per capita recrudescence rate, ξ_A, of infants who used counterfeit drugs. This class is reduced by the per capita natural death rate μ_h, per capita disease-induced death rate δ_A, per capita removal rate due to the use of counterfeit drugs η_A, per capita recovery rate due to the use of a highly effective antimalarial and natural recovery $u_2\gamma_A + \gamma_1$, and per capita rate of maturing into infectious adults τ of infants in it. The control u_2 represents the treatment efforts with highly effective antimalarials and involves diagnosing patients, administering drug intake and follow-up of drug management. The recovery rate in infants due to using a highly effective antimalarial drug is γ_A, and γ_1 is the natural recovery rate in infants.

The infant class of counterfeit drug users, U_A, increases at a per capita removal rate η_A of infectious infants due to counterfeit drug use and decreases at a per capita recrudescence rate ξ_A into infectious infants, per capita natural death rate μ_h and per capita rate of maturing into adults τ of infants who used counterfeit malaria drugs.

The infant class of effective drug users, T_A, increases with the per capita recovery rate $u_2\gamma_A + \gamma_1$ of infectious infants. This class decreases due to the loss of post-treatment prophylaxis at a per capita rate ϕ_A, natural death at a per capita natural death rate μ_h and maturing into adults at a per capita rate τ of infants in it.

The susceptible adults class, S_B, is generated when the susceptible infants mature above 5 years, recovered adults lose their partial immunity and post-treatment prophylaxis at a per capita rate ϕ_B, and counterfeit drug users become susceptible at a per capita rate θ. This class is decreased by natural death and infections, with, respectively, per capita natural death rate μ_h and per capita rate of acquiring infection from infectious mosquitoes $(1-u_1)\rho^n\lambda_B$, where λ_B is the force of infection in adults.

The infectious adults class, I_B, increases when infectious infants mature above 5 years, and adults recrudesce at per capita rate ξ_B and acquire infection at rate $(1-u_1)\rho^n\lambda_B$. The class is reduced at per capita natural death rate μ_h, per capita disease-induced death rate δ_B, per capita removal rate η_B due to counterfeit drugs use and recovery at per capita rate $u_2\gamma_B + \gamma_2$ of adults in it. The recovery rate of adults due to using an effective malarial drug is γ_B, and γ_2 is the natural recovery rate of adults.

The adult class of counterfeit drug users, U_B, increases when infants who used counterfeit drugs mature above 5 years and when the infectious adults who used counterfeit drugs are removed at a per capita rate η_B. This class decreases by natural death, recrudescence and reverting to the susceptible class of adults in it, with, respectively, per capita natural death rate μ_h, recrudescence rate ξ_B and susceptibility of adults θ.

The adult class of effective drug users, T_B, increases when infants in the infant class of effective drug users mature above 5 years and when the infectious adults recover at a per capita rate $u_2\gamma_B + \gamma_2$. This class decreases by natural death, loss of immunity and post-treatment prophylaxis of adults with, respectively, per capita natural death rate μ_h and per capita loss of partial immunity and post-treatment prophylaxis rate ϕ_B.

Susceptible female Anopheles mosquitoes are recruited at a per capita rate $\alpha_m(1-\frac{N_m}{K})$, where α_m is the birth rate of mosquitoes, and K is the environmental carrying capacity of pupa [41]. They die at a per capita natural death rate μ_m and a per capita indoor residual spraying (IRS) induced death rate φu_3. The control u_3 represents the prevention effort with the IRS and includes spraying with insecticide and surveillance. φ is the proportion of mortality induced by IRS. We assume that the mosquito population does not go extinct, and hence r_m=$\alpha_m - \mu_m - \varphi u_3 > 0$. Most of the analysis is redundant if $r_m < 0$.

The mosquitoes become infected by humans in the infectious and counterfeit drug users class at a rate $(1-u_1)\rho^m\lambda_m$, where λ_m is the force of infection rate in mosquitoes. The daily survival probability of a mosquito is assumed to be $\rho_2 = e^{-\mu_m}$. The probability of survival of a mosquito over the average latent period of length n_m and becoming infectious is given by $\rho^m = e^{-\mu_m n_m}$.

The infective mosquito population increases when mosquitoes acquire infection from humans at a per capita rate $(1-u_1)\rho^m\lambda_m$. It decreases with a per capita natural death rate μ_m and a per capita IRS-induced death rate φu_3.

Differences have been observed in malaria transmission rates, degree of infectivity, recovery and immunity due to strains, exposure, locality, age and treatment [3, 4, 7, 42, 43]. In humans, the gametocyte rate and density [42], as well as the parasite rate [42, 44], have been found to decrease with age. Thus, we assume that infants have higher infectiousness to mosquitoes than adults. The degree of infectivity in the human population is denoted by the parameter $\pi_i, i = 1, 2, 3$, where π_1, π_2 and π_3 are associated, respectively, with I_B, U_A and U_B such that $0 < \pi_3 < \pi_2 < \pi_1 < 1$. Further, the transmission probabilities in infants, adults and mosquitoes are denoted by β_A, β_B and β_m, respectively. The average numbers of mosquito bites per infant and adult per time unit are denoted by a and b, respectively, and c is the average number of bites given by a mosquito per time unit.

Usually, the recruitment of children is dependent on the adult population. At the same time, the children mature and move to the adult population. If the population of adults is much larger than that of children, we can assume that it is constant and not affected by the latter. In this case, the total birth rate α_h is just the per capita birth rate in the adult population α_B multiplied by N_B, $\alpha_h = \alpha_B N_B$.

The above formulations and assumptions give the following system of ordinary differential equations for the structured malaria model:

$$\frac{dS_A}{dt} = \alpha_h + \phi_A T_A - (e^{-\mu_h n_h}(1-u_1)\lambda_A + \tau + \mu_h)S_A, \tag{2.1}$$

$$\frac{dS_B}{dt} = \tau S_A + \phi_B T_B + \theta U_B - (e^{-\mu_h n_h}(1-u_1)\lambda_B + \mu_h)S_B, \tag{2.2}$$

$$\frac{dI_A}{dt} = e^{-\mu_h n_h}(1-u_1)\lambda_A S_A + \xi_A U_A - d_1 I_A, \tag{2.3}$$

$$\frac{dI_B}{dt} = \tau I_A + e^{-\mu_h n_h}(1-u_1)\lambda_B S_B + \xi_B U_B - d_2 I_B, \tag{2.4}$$

$$\frac{dU_A}{dt} = \eta_A I_A - d_3 U_A, \tag{2.5}$$

$$\frac{dU_B}{dt} = \tau U_A + \eta_B I_B - d_4 U_B, \tag{2.6}$$

$$\frac{dT_A}{dt} = (u_2\gamma_A + \gamma_1)I_A - (\phi_A + \tau + \mu_h)T_A, \tag{2.7}$$

$$\frac{dT_B}{dt} = \tau T_A + (u_2\gamma_B + \gamma_2)I_B - (\phi_B + \mu_h)T_B, \tag{2.8}$$

$$\frac{dS_m}{dt} = \alpha_m\left(1 - \frac{N_m}{K}\right)N_m - (e^{-\mu_m n_m}(1-u_1)\lambda_m + \mu_m + \varphi u_3)S_m, \tag{2.9}$$

$$\frac{dI_m}{dt} = e^{-\mu_m n_m}(1-u_1)\lambda_m S_m - (\mu_m + \varphi u_3)I_m, \tag{2.10}$$

with initial conditions

$$S_A(0) > 0, S_B(0) > 0, I_A(0) \geq 0, I_B(0) \geq 0, U_A(0) \geq 0, U_B(0) \geq 0, T_A(0) \geq 0, T_B(0) \geq 0, S_m(0) > 0, I_m(0) \geq 0,$$

where

$$\lambda_A = \frac{a\beta_A}{N_h} I_m, \quad \lambda_B = \frac{b\beta_B}{N_h} I_m, \quad \lambda_m = \frac{c\beta_m}{N_h}(I_A + \pi_1 I_B + \pi_2 U_A + \pi_3 U_B),$$

$$\begin{aligned} d_1 &= \delta_A + \eta_A + u_2\gamma_A + \gamma_1 + \tau + \mu_h, \quad d_2 = \delta_B + \eta_B + u_2\gamma_B + \gamma_2 + \mu_h, \\ d_3 &= \xi_A + \tau + \mu_h \quad \textit{and} \quad d_4 = \xi_B + \theta + \mu_h. \end{aligned}$$

The parameter values of the malaria control model are shown in Table 1 in Section 5. The age-structured models (2.1)–(2.10) is an extension of the malaria model developed in [45], by including differentiated susceptibility, infectivity and infectiousness of infant and adult populations and control measures to malaria.

2.1. Basic properties of the structured model

The first step in showing that the malaria models (2.1)–(2.10) makes sense epidemiologically is to prove that the populations remain non-negative, that is, that all solutions of systems (2.1)–(2.10) with positive initial conditions will remain positive for all times $t > 0$. We define a feasible region Ω, such that

$$\Omega = \Big\{(S_A, S_B, I_A, I_B, U_A, U_B, T_A, T_B, S_m, I_m) \in \Re_+^{10} : 0 < N_h \leq \frac{\alpha_h}{\mu_h}; 0 < N_m \leq \frac{r_m K}{\alpha_m}\Big\}. \tag{2.11}$$

Theorem 2.1. *The feasible region Ω is positively invariant and attracting.*

Proof. The right-hand side of models (2.1)–(2.10) is continuous with continuous partial derivatives in Ω. Since $S_A(0) > 0$, $S_B(0) > 0$, the Picard theorem gives the existence of solutions at least on some (maximum) interval $[0, \omega)$. It can be seen that $S_A^{'} \geq 0$ if $S_A = 0$, $S_B^{'} \geq 0$ if $S_B = 0$, $I_A^{'} \geq 0$ if $I_A = 0$, $I_B^{'} \geq 0$ if $I_B = 0$, $U_A^{'} \geq 0$ if $U_A = 0$, $U_B^{'} \geq 0$ if $U_B = 0$, $T_A^{'} \geq 0$ if $T_A = 0$, $T_B^{'} \geq 0$ if $T_B = 0$, $S_m^{'} \geq 0$ if $S_m = 0$, and $I_m^{'} \geq 0$ if $I_m = 0$. Therefore, given the initial condition, the solutions $(S_A, S_B, I_A, I_B, U_A, U_B, T_A, T_B, S_m, I_m)$ are nonnegative on $[0, \omega)$. We let $0 < \delta_h = min\{\delta_A, \delta_B\}$. Adding the first eight and last two equations of (2.1)–(2.10) gives, respectively,

$$\frac{dN_h}{dt} = \alpha_h - \mu_h N_h - \delta_A I_A - \delta_B I_B \leq \alpha_h - \mu_h N_h, \tag{2.12}$$

that is,

$$\alpha_h - (\mu_h + \delta_h) N_h \leq \frac{dN_h}{dt} \leq \alpha_h - \mu_h N_h, \tag{2.13}$$

and

$$\frac{dN_m}{dt} = (\alpha_m - \mu_m - \varphi u_3) N_m - \frac{\alpha_m}{K} N_m^2 = r_m N_m - \frac{\alpha_m}{K} N_m^2. \tag{2.14}$$

Solving the inequality (2.13) and Eq (2.14) gives

$$N_h(0)e^{-(\mu_h+\delta_h)t} + \frac{\alpha_h}{(\mu_h+\delta_h)}(1-e^{-(\mu_h+\delta_h)t}) \leq N_h(t) \leq \frac{\alpha_h}{\mu_h} + \left(N_h(0) - \frac{\alpha_h}{\mu_h}\right)e^{-(\mu_h+\delta_h)t},$$

and

$$N_m(t) = \frac{r_m K N_m(0)}{\alpha_m N_m(0) + [r_m K - \alpha_m N_m(0)]e^{-r_m t}}. \tag{2.15}$$

Thus, we see that if $N_h(0) > 0$ and $N_m(0) > 0$, then neither N_h nor N_m can become 0 at any finite time (in particular, on $[0, \omega)$). Then, for $0 < N_h(0) \leq \frac{\alpha_h}{\mu_h}$ and $0 < N_m(0) \leq \frac{r_m K}{\alpha_m}$, we see that on $[0, \omega)$,

$$0 < N_h(t) \leq \frac{\alpha_h}{\mu_h}, \quad 0 < N_m(t) \leq \frac{r_m K}{\alpha_m},$$

and thus, by the nonnegativity, the solution (S_A,S_B,I_A,I_B,U_A,U_B,T_A,T_B,S_m,I_m) is a priori bounded, and hence it is defined for all $t \geq 0$ and stays in Ω. Thus, the region is positively invariant. Further, if $N_h(0) > \frac{\alpha_h}{\mu_h}$ or $N_m(0) > \frac{r_m K}{\alpha_m}$, then they are also isolated from zero, and $\limsup_{t\to\infty} N_h(t) \leq \frac{\alpha_h}{\mu_h}$, $\lim_{t\to\infty} N_m(t) = \frac{r_m K}{\alpha_m}$. Hence, $N_h(t)$ either becomes smaller than $\frac{\alpha_h}{\mu_h}$ or approaches $\frac{\alpha_h}{\mu_h}$, while $N_m(t)$ converges to $\frac{r_m K}{\alpha_m}$. Therefore, the region attracts the solutions in $\mathfrak{R}_+^{10}$ with $N_h(0) > \frac{\alpha_h}{\mu_h}$ and $N_m(0) > \frac{r_m K}{\alpha_m}$. □

Since the region Ω is positively invariant and attracting, it is sufficient to consider the dynamics of the flow generated by the model in Ω.

3. Model dynamics

3.1. Disease-free equilibrium

The disease-free equilibrium (DFE) of the models (2.1)–(2.10) is given by

$$E_0 = (S_A^*, S_B^*, I_A^*, I_B^*, U_A^*, U_B^*, T_A^*, T_B^*, S_m^*, I_m^*) = \left(\frac{\alpha_h}{\tau+\mu_h}, \frac{\tau\alpha_h}{\mu_h(\tau+\mu_h)}, 0, 0, 0, 0, 0, 0, \frac{r_m K}{\alpha_m}, 0\right). \tag{3.1}$$

The local stability of E_0 is established by applying the next generation matrix method [46] to (2.1)–(2.10). It follows that the basic reproduction number, R_0, of the age-structured malaria systems (2.1)–(2.10) is given by $R_0 = \rho(FV^{-1})$ where ρ represents the spectral radius. The associated matrices F, V and FV^{-1} are given in Appendix A.1. This way, we obtain

$$R_0 = \sqrt{R_A + R_B}, \tag{3.2}$$

where

$$\begin{aligned} R_A = {} & \frac{ac(1-u_1)^2 e^{-\mu_h n_h} e^{-\mu_m n_m} \beta_A \beta_m \mu_h^2 r_m K(d_3 + \pi_2 \eta_A)}{\alpha_h \alpha_m (\mu_m + \varphi u_3)(\tau + \mu_h)(d_1 d_3 - \eta_A \xi_A)} \\ & + \frac{ac(1-u_1)^2 e^{-\mu_h n_h} e^{-\mu_m n_m} \beta_A \beta_m \tau \mu_h^2 r_m K[\pi_1(d_3 d_4 + \eta_A \xi_B) + \pi_3(\eta_B d_3 + \eta_A d_2)]}{\alpha_h \alpha_m (\mu_m + \varphi u_3)(\tau + \mu_h)(d_1 d_3 - \eta_A \xi_A)(d_2 d_4 - \eta_B \xi_B)} \end{aligned} \tag{3.3}$$

and

$$R_B = \frac{bc(1-u_1)^2 e^{-\mu_h n_h} e^{-\mu_m n_m} \beta_B \beta_m \tau \mu_h r_m K(\pi_1 d_4 + \pi_3 \eta_B)}{\alpha_h \alpha_m (\mu_m + \varphi u_3)(\tau + \mu_h)(d_2 d_4 - \eta_B \xi_B)}. \tag{3.4}$$

We note that $d_1 d_3 - \eta_A \xi_A > 0$ and $d_2 d_4 - \eta_B \xi_B > 0$.

The result below follows from Theorem 2 of [46].

Lemma 1. *The DFE, E_0, of (2.1)–(2.10) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

3.2. Existence of endemic equilibrium

The conditions for the existence of an endemic equilibrium E_e for the model (2.1)-(2.10) are established in this section. Here, $E_e = (S_A^{**}, S_B^{**}, I_A^{**}, I_B^{**}, U_A^{**}, U_B^{**}, T_A^{**}, T_B^{**}, S_m^{**}, I_m^{**})$, and the forces of infection λ_A^*, λ_B^* and λ_A^* are non-zero. Expressing S_A^{**}, S_B^{**}, I_A^{**}, I_B^{**}, U_A^{**}, U_B^{**}, T_A^{**}, T_B^{**}, S_m^{**}, I_m^{**}, λ_m^* and λ_B^* in terms of λ_A^*, we get

$$S_A^{**} = \frac{C_7}{D_1\lambda_A^* + B_1 J_1 J_2}, \quad I_A^{**} = \frac{C_6\lambda_A^*}{D_1\lambda_A^* + B_1 J_1 J_2}, \quad U_A^{**} = \frac{\eta_A C_6 \lambda_A^*}{d_3(D_1\lambda_A^* + B_1 J_1 J_2)},$$

$$T_A^{**} = \frac{(u_2\gamma_A + \gamma_1)C_6\lambda_A^*}{J_2(D_1\lambda_A^* + B_1 J_1 J_2)}, \quad S_B^{**} = \frac{K_3{\lambda_A^*}^3 + K_2{\lambda_A^*}^2 + K_1\lambda_A^* + K_0}{K_4{\lambda_A^*}^4 + K_5{\lambda_A^*}^3 + K_6{\lambda_A^*}^2 + K_7\lambda_A^* + K_8},$$

$$I_B^{**} = \frac{C_1{\lambda_A^*}^2 + C_2\lambda_A^*}{C_3{\lambda_A^*}^2 + C_4\lambda_A^* + C_5}, \quad U_B^{**} = \frac{L_1{\lambda_A^*}^3 + L_2{\lambda_A^*}^2 + L_3\lambda_A^*}{d_3 d_4(E_4{\lambda_A^*}^3 + E_5{\lambda_A^*}^2 + E_6\lambda_A^* + E_7)},$$

$$T_B^{**} = \frac{L_4{\lambda_A^*}^3 + L_5{\lambda_A^*}^2 + L_6\lambda_A^*}{J_2 J_3(E_4{\lambda_A^*}^3 + E_5{\lambda_A^*}^2 + E_6\lambda_A^* + E_7)}, \quad \lambda_B^* = \sigma\lambda_A^*,$$

$$\begin{aligned} S_m^{**} &= \frac{K_m d_3 d_4 E_8 {\lambda_A^*}^3 + E_9{\lambda_A^*}^2 + E_{10}\lambda_A^* + \alpha_h E_7}{F_4{\lambda_A^*}^3 + F_5{\lambda_A^*}^2 + F_6\lambda_A^* + F_7}, \\ I_m^{**} &= \frac{F_1{\lambda_A^*}^3 + F_2{\lambda_A^*}^2 + F_3\lambda_A^*}{(\mu_m + \varphi u_3)(F_4{\lambda_A^*}^3 + F_5{\lambda_A^*}^2 + F_6\lambda_A^* + F_7)}, \\ \lambda_m^* &= \frac{\mu_h\beta_m(E_1{\lambda_A^*}^3 + E_2{\lambda_A^*}^2 + E_3\lambda_A^*)}{d_3 d_4(E_8{\lambda_A^*}^3 + E_9{\lambda_A^*}^2 + E_{10}\lambda_A^* + \alpha_h E_7)}, \end{aligned}$$

where $\sigma; B_1; C_i$ and $F_i, i = 1,2,3,4,5,6,7$; $D_i, i = 1,2,3,4,5$; $E_i, i = 1,2,3,4,5,6,7,8,9,10$; $G_i, i = 1,2,3$; $J_i, i = 1,2,3$; $K_i, i = 0,1,2,3,4,5,6,7,8$; $L_i, i = 1,2,3,4,5,6$ are shown in Appendices A.2 and A.3.

Substituting I_m^{**}, I_A^{**} and I_B^{**} into the expression for λ_A^*, we obtain the following equation for λ_A^*:

$$f(\lambda_A^*) = P_6{\lambda_A^*}^6 + P_5{\lambda_A^*}^5 + P_4{\lambda_A^*}^4 + P_3{\lambda_A^*}^3 + P_2{\lambda_A^*}^2 + P_1\lambda_A^* + P_0 = 0, \tag{3.5}$$

where $P_i, i = 0,1,2,3,4,5,6$, are given in Appendix A.3.

Lemma 2. *The malaria models (2.1)–(2.10) has at least one endemic equilibrium, E_e, when $R_0 > 1$.*

Proof. From Eq (3.5) we see that $f(\lambda_A^*)$ is continuous on $[0, \infty)$. We have that $\lim_{\lambda_A^* \to \infty} f(\lambda_A^*) = \infty$ (since $P_6 > 0$) and $f(0) = P_0 < 0$, when $R_0 > 1$. This implies that (3.5) admits at least one positive solution $\lambda_A^* > 0$. □

Lemma 2 ensures that there exists at least one endemic equilibrium provided $R_0 > 1$. There is also the possibility of multiple endemic equilibria when $R_0 > 1$ or $R_0 < 1$, as $f(\lambda_A^*)$ is a sextic polynomial. The maximum number of positive roots of Eq (3.5) can be identified using Descartes's rules of signs. It can be determined that when $R_0 > 1$, $f(\lambda_A^*)$ will have one, three or five positive roots. On the other hand, when $R_0 < 1$, there will be zero, two, four or six positive roots. The possibility of the existence of multiple endemic equilibria when $R_0 < 1$ suggests that a backward bifurcation may occur [29, 30, 36, 45].

3.3. Backward bifurcation

We explore the possibility and establish the conditions that ensure the existence of backward bifurcation in the systems (2.1)–(2.10) using the center manifold theory (Theorem 4.1, [47]). To do so, we introduce new variables and consider β_m as a bifurcation parameter with $\beta_m = \beta_m^*$ corresponding to $R_0 = 1$.

Let $x_1 = S_A, x_2 = S_A, x_3 = I_A, x_4 = I_B, x_5 = U_A, x_6 = U_B, x_7 = T_A, x_8 = T_B, x_9 = S_m, x_{10} = I_m$ so that $N_h = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8$ and $N_m = x_9 + x_{10}$. Let $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10})^T$ and $\frac{dX}{dt} = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10})^T$ so that (2.1)–(2.10) can be written in the form

$$\frac{dx_1}{dt} = f_1 = \alpha_h + \phi_A x_7 - \left[\frac{a(1-u_1)e^{-\mu_h n_h}\beta_A x_{10}}{\sum_{i=1}^{8} x_i} + \tau + \mu_h\right]x_1, \tag{3.6}$$

$$\frac{dx_2}{dt} = f_2 = \tau x_1 + \phi_B x_8 + \theta x_6 - \left[\frac{b(1-u_1)e^{-\mu_h n_h}\beta_B x_{10}}{\sum_{i=1}^{8} x_i} + \mu_h\right]x_2, \tag{3.7}$$

$$\frac{dx_3}{dt} = f_3 = \frac{a(1-u_1)e^{-\mu_h n_h}\beta_A x_{10}}{\sum_{i=1}^{8} x_i}x_1 + \xi_A x_5 - d_1 x_3, \tag{3.8}$$

$$\frac{dx_4}{dt} = f_4 = \tau x_3 + \frac{b(1-u_1)e^{-\mu_h n_h}\beta_B x_{10}}{\sum_{i=1}^{8} x_i}x_2 + \xi_B x_6 - d_2 x_4, \tag{3.9}$$

$$\frac{dx_5}{dt} = f_5 = \eta_A x_3 - d_3 x_5, \tag{3.10}$$

$$\frac{dx_6}{dt} = f_6 = \tau x_5 + \eta_B x_4 - d_4 x_6, \tag{3.11}$$

$$\frac{dx_7}{dt} = f_7 = (u_2\gamma_A + \gamma_1)x_3 - (\phi_A + \tau + \mu_h)x_7, \tag{3.12}$$

$$\frac{dx_8}{dt} = f_8 = \tau x_7 + (u_2\gamma_B + \gamma_2)x_4 - (\phi_B + \mu_h)x_8, \tag{3.13}$$

$$\frac{dx_9}{dt} = f_9 = \alpha_m\left(1 - \frac{(x_9 + x_{10})}{K}\right)(x_9 + x_{10}) - H_2 x_9, \tag{3.14}$$

$$\frac{dx_{10}}{dt} = f_{10} = (1-u_1)e^{-\mu_m n_m}H_1 x_9 - (\mu_m + \varphi u_3)x_{10}, \tag{3.15}$$

with $H_1 = \frac{c\beta_m(x_3 + \pi_1 x_4 + \pi_2 x_5 + \pi_3 x_6)}{\sum_{i=1}^{8} x_i}$ and $H_2 = (1-u_1)e^{-\mu_m n_m}H_1 + \mu_m + \varphi u_3$.

The bifurcation parameter β^* for which $R_0 = 1$ is given by

$$\beta_m^* = \frac{\alpha_h\alpha_m(\mu_m + \varphi u_3)(\tau + \mu_h)(d_1d_3 - \eta_A\xi_A)(d_2d_4 - \eta_B\xi_B)}{c(1-u_1)^2e^{-\mu_h n_h}e^{-\mu_m n_m}\mu_h r_m K(H_3 + H_4)},$$

where $H_3 = a\beta_A\mu_h[(d_2d_4 - \eta_B\xi_B)(d_3 + \pi_2\eta_A) + \tau(\pi_1(d_3d_4 + \eta_A\xi_B) + \pi_3(\eta_B d_3 + \eta_A d_2))]$,
and $H_4 = b\beta_B\tau(d_1d_3 - \eta_A\xi_A)(\pi_1 d_4 + \pi_3\eta_B)$.

The Jacobian matrix, J_{E_0}, of the transformed systems (2.1)–(2.10) evaluated at the DFE, E_0, with $\beta_m = \beta_m^*$, is given in Appendix A.2, where, in addition, explicit expressions are provided for the right and left eigenvectors, $w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10})^T$ and $v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10})$, respectively, corresponding to the zero eigenvalue of J_{E_0}. The associated non-zero partial derivatives of f evaluated at the DFE are also listed in Appendix A.2.

Using the approach in [47], we have the expressions for a_1 and b_1 as

$$a_1 = \sum_{k,i,j=1}^{10} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0) = \frac{2m\beta_m^*\mu_h}{\alpha_h} v_{10} g_1 \Big[-\frac{r_m K\mu_h}{\alpha_h\alpha_m} g_2 + w_9 \Big] \tag{3.16}$$

and

$$b_1 = \sum_{k,i=1}^{10} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_m^*}(E_0) = \frac{m r_m K\mu_h}{\alpha_h\alpha_m} v_{10} g_1, \tag{3.17}$$

where

$$w_1 < 0, w_2 < 0, w_9 < 0, \quad w_3 > 0, w_4 > 0, w_5 > 0, w_6 > 0, w_7 > 0, w_8 > 0, v_{10} > 0,$$

and

$$g_1 = w_3 + \pi_1 w_4 + \pi_2 w_5 + \pi_3 w_6 > 0, \quad g_2 = \sum_{i=1}^{8} w_i,$$

with $g_2 < 0$ if $w_1 + w_2 > w_3 + w_4 + w_5 + w_6 + w_7 + w_8$ or $g_2 \geq 0$ otherwise.

Clearly, $b_1 > 0$, and hence it follows from (Theorem 4.1, [47]) that the direction of the bifurcation of the transformed systems (3.6)–(3.15) at $R_0 = 1$ is determined by the sign of a_1 : if $a_1 > 0$, then it will be backward, and if $a_1 < 0$, then it will be forward.

To determine the sign of a_1, we expand the terms in parentheses in (3.16) and obtain

$$a_1 = \frac{r_m K\mu_h(w_1 + w_2) - (r_m K\mu_h(w_3 + w_4 + w_5 + w_6 + w_7 + w_8) + \alpha_h\alpha_m w_9)}{\alpha_h\alpha_m}. \tag{3.18}$$

We note that $a_1 > 0$ if

$$\alpha_h < \alpha_h^* = \frac{r_m K\mu_h(w_1 + w_2 - w_3 - w_4 - w_5 - w_6 - w_7 - w_8)}{\alpha_m w_9}. \tag{3.19}$$

The above result is summarized below.

Theorem 3.1. *The models (2.1)–(2.10) exhibits backward bifurcation at $R_0 = 1$ when (3.19) holds.*

Remark 1. *We note that in this particular case, the existence of backward bifurcation can be proved in a more elementary way. Consider again*

$$f(\lambda_A^*, \beta_m) := P_6\lambda_A^{*6} + P_5\lambda_A^{*5} + P_4\lambda_A^{*4} + P_3\lambda_A^{*3} + P_2\lambda_A^{*2} + P_1\lambda_A^* + P_0. \tag{3.20}$$

We considered a bifurcation parameter β_m, such that R_0 and all coefficients P_i can be expressed as functions of this parameter. In particular, we defined β_m^* by $R_0(\beta_m^*) = 1$. Here, $P_0(\beta_m) = K_hE_7F_7(1 - R_0^2(\beta_m))$ ($K_hE_7F_7$ are independent of β_m) and $P_1 = F_7(K_hE_6 - G_3) + K_hE_7F_6 - ua\beta_A(E_7F_2 + E_6F_3)$. We see that the equation

$$f(\lambda_A^*, \beta_m^*) = 0$$

has an isolated single root $\lambda_A^* = \lambda_A(\beta_m^*) = 0$ as soon $P_1(\beta_m^*) \neq 0$. Using the implicit function theorem, for β_m close to β_m^* (that is, R_0 close to 1), there are differentiable solutions $\lambda_A(\beta_m)$, satisfying

$$f(\lambda_A(\beta_m), \beta_m) \equiv 0. \tag{3.21}$$

Indeed,

$$\left.\frac{\partial f(\lambda_A^*, \beta_m^*)}{\partial \lambda_A^*}\right|_{\lambda_A^*=0, \beta_m=\beta_m^*} = P_1(\beta_m^*) \neq 0.$$

Differentiating (3.21) with respect to β_m, we obtain

$$\begin{aligned}&\left.\frac{\partial f(\lambda_A^*, \beta_m)}{\partial \lambda_A^*}\frac{d\lambda_A(\beta_m)}{d\beta_m}\right|_{\lambda_A^*=0, \beta_m=\beta_m^*} + \left.\frac{\partial f(\lambda_A^*, \beta_m)}{\partial \beta_m}\right|_{\lambda_A^*=0, \beta_m=\beta_m^*}\\ &= P_1(\beta_m^*)\left.\frac{d\lambda_A(\beta_m)}{d\beta_m}\right|_{\lambda_A^*=0, \beta_m=\beta_m^*} - 2K_hE_7F_7R_0'(\beta_m^*) \equiv 0.\end{aligned}$$

Since, by (3.2)–(3.4), R_0 is an increasing function of β_m, if we assume that $P_1(\beta_m^*) < 0$, then $\frac{d\lambda_A}{d\beta_m}(\beta_m^*) < 0$, that is, $\beta_m \mapsto \lambda_A(\beta_m)$ is decreasing (in some neighborhood of $\beta_m = \beta_m^*$). Since $\lambda_A(\beta_m^*) = 0$, we see that $\lambda_A(\beta_m) > 0$ whenever $\beta_m < \beta_m^*$ is sufficiently close to β_m^*, that is, whenever $R_0 < 1$ is sufficiently close to 1. For such $\beta_m < \beta_m^*$ we have $f(0, \beta_m) > 0$, $f(\lambda_A(\beta_m), \beta_m) = 0$, and, from the above, we see that $\left.\frac{\partial f(\lambda_A^*, \beta_m)}{\partial \lambda_A^*}\right|_{\lambda_A^*=\lambda_A(\beta_m)} < 0$. Therefore, $f(\lambda_A^*, \beta_m) < 0$ for some $\lambda_A^* > \lambda_A(\beta_m)$. Since $\lim_{\lambda_A^*\to\infty} f(\lambda_A^*, \beta_m) = \infty$, it follows that there is another positive solution to $f(\lambda_A^*, \beta_m) = 0$, and consequently, we have backward bifurcation.

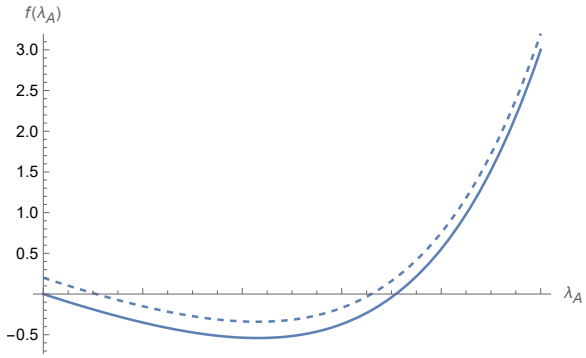

Figure 2. An illustration of the behavior of the function f when $P_0 = 0$ ($R_0 = 1$) (solid line) and $P_0 = 0.2$ ($R_0 < 1$) (dashed line). We see the emergence of a new positive solution, giving rise to at least two endemic equilibria for $R_0 < 1$ and hence to backward bifurcation.

Previous malaria studies [29, 30, 45] have shown the existence of backward bifurcation, with some attributing this to the use of the standard incidence function instead of mass action, and also to partial immunity, repeated infection and a high disease death rate. Our result in Theorem 3.1 indicates that increasing the birth rate of the population above the threshold (α_h^*) can remove the backward bifurcation.

4. Analysis of the reproduction number

The formula for R_0 in (3.2)–(3.4) can also be expressed in the form (4.1) given below to provide some insight into the adult, infant and mosquito malaria transmission and control. When a newly infected mosquito is introduced into a completely susceptible human population, during its average infectious period, $\frac{1}{(\mu_m+\varphi u_3)}$, it will infect humans (infants and adults) who are not using ITNs at the rate $\frac{(1-u_1)a\beta_A S_A^*}{N_h^*} + \frac{(1-u_1)b\beta_B S_B^*}{N_h^*}$. Humans survive the latent period with probability $e^{-\mu_h n_h}$ and become infectious. Thus, the total number of infants and adults who become infectious due to this mosquito during its entire infectious period is approximately equal to $R_{I_{mh}} = \frac{e^{-\mu_h n_h}(1-u_1)(a\beta_A\mu_h + b\beta_B\tau)}{(\mu_m+\varphi u_3)(\tau+\mu_h)}$.

Similarly, for humans, during the average infant's (adult's) infectious period, $\frac{d_3}{d_1d_3-\eta_A\xi_A}\left(\frac{d_4}{d_2d_4-\eta_B\xi_B}\right)$, the infant (adult) will infect mosquitoes at the rate $\frac{(1-u_1)c\beta_m S_m^*}{N_h^*}\left(\frac{(1-u_1)\pi_1 c\beta_m S_m^*}{N_h^*}\right)$. The mosquitoes survive the latent period with probability $e^{-\mu_m n_m}$ and become infective, and hence the total number of mosquitoes who become infective due to this infant (adult) during the infectious period is approximately equal to $R_{I_{Am}} = \frac{e^{-\mu_m n_m}(1-u_1)c\beta_m d_3\mu_h r_m K}{\alpha_h\alpha_m(d_1d_3-\eta_A\xi_A)}$ $\left(R_{I_{Bm}} = \frac{e^{-\mu_m n_m}(1-u_1)c\beta_m\pi_1 d_4\mu_h r_m K}{\alpha_h\alpha_m(d_2d_4-\eta_B\xi_B)}\right)$.

Additionally, when an infant (adult) who used a counterfeit drug is infectious with a degree $\pi_2(\pi_3)$, then he/she has a probability $\frac{\eta_A d_3}{d_1d_3-\eta_A\xi_A}$ $\left(\frac{\eta_B d_4}{d_2d_4-\eta_B\xi_B}\right)$ of surviving the infectious period using the counterfeit drug, and $\frac{1}{d_3}$ $\left(\frac{1}{d_4}\right)$ is the average time of using the drug. This infant (adult) will infect mosquitoes at the rate $\frac{(1-u_1)\pi_2 c\beta_m S_m^*}{N_h^*}\left(\frac{(1-u_1)\pi_3 c\beta_m S_m^*}{N_h^*}\right)$. The infected mosquitoes survive the latent period with probability $e^{-\mu_m n_m}$ and then become infective. Hence, the total number of mosquitoes that become infective due to the infant (adult) counterfeit drug user is approximately equal to $R_{U_{Am}} = \frac{e^{-\mu_m n_m}(1-u_1)c\beta_m\pi_2\eta_A\mu_h r_m K}{\alpha_h\alpha_m(d_1d_3-\eta_A\xi_A)}$ $\left(R_{U_{Bm}} = \frac{e^{-\mu_m n_m}(1-u_1)c\beta_m\pi_3\eta_B\mu_h r_m K}{\alpha_h\alpha_m(d_2d_4-\eta_B\xi_B)}\right)$.

Finally, when an infant who is infectious (or used a counterfeit drug) matures to an adult during the infectious period, the total number of mosquitoes that become infective due to it is approximately $R_{I_{ABm}} = \frac{e^{-\mu_m n_m}(1-u_1)c\beta_m\pi_1\tau\mu_h r_m K(d_3d_4+\eta_A\xi_B)}{\alpha_h\alpha_m(d_1d_3-\eta_A\xi_A)(d_2d_4-\eta_B\xi_B)}$ $\left(R_{U_{ABm}} = \frac{e^{-\mu_m n_m}(1-u_1)c\beta_m\pi_3\tau\mu_h r_m K(\eta_B d_3+\eta_A d_2)}{\alpha_h\alpha_m(d_1d_3-\eta_A\xi_A)(d_2d_4-\eta_B\xi_B)}\right)$. Therefore,

$$R_0^2 = (R_{I_{Am}} + R_{I_{Bm}} + R_{U_{Am}} + R_{U_{Bm}} + R_{I_{ABm}} + R_{U_{ABm}}) \times R_{I_{mh}} \tag{4.1}$$

represents the average number of secondary infections in a completely susceptible human population resulting from introducing one infective human who generates infections in a fully susceptible mosquito population [25].

4.1. Effects of control strategies on R_0

The effective use of the control measures by infants leads to a reduction in R_0 since all local reproduction numbers $R_{I_{Am}}$, $R_{U_{Am}}$, $R_{I_{ABm}}$ and $R_{U_{ABm}}$ will decrease. Similarly, adults using control measures will reduce R_0 because $R_{I_{Bm}}$ and $R_{U_{Bm}}$ will also decrease. We analyze the impact of insecticide-treated bednets (ITNs) on R_0 when highly effective antimalarial drugs (HEAs) and indoor residual spraying (IRS) are absent. Let us find the difference between the reproduction number with no control measure and with only ITNs as control, and the partial derivative with respect to u_1 of the reproduction number when ITNs are used. By (3.2)–(3.4), we obtain

$$R_0|_{u_1=u_2=u_3=0} - R_0|_{u_1\neq 0,u_2=u_3=0} = u_1 R_0|_{u_1=u_2=u_3=0}, \tag{4.2}$$

and

$$\frac{\partial R_0|_{u_1\neq 0,u_2=u_3=0}}{\partial u_1} = -\frac{R_0|_{u_1\neq 0,u_2=u_3=0}}{(1-u_1)}. \tag{4.3}$$

We find that $R_0|_{u_1=u_2=u_3=0} - R_0|_{u_1\neq 0,u_2=u_3=0} > 0$ and $\frac{\partial R_0|_{u_1\neq 0,u_2=u_3=0}}{\partial u_1} < 0$ for all $u_1 \in [0,1)$. Hence, if humans sleep under the ITNs, contact between mosquitoes and humans will become difficult, reducing transmission to and from mosquitoes and hence R_0.

On the other hand, treating infectious humans (infants and adults) will decrease the average length of the infection period and transmission period, causing decreases in R_0 and the disease incidence. The duration of the infection can be reduced if a highly effective antimalarial drug is used [7,48] and also if the recovery rate due to using an effective antimalarial drug is increased [19,45]. Even though using counterfeit drugs for treatment reduces disease symptoms and may prevent death, it creates and increases a reservoir of infection. This is because humans who use such drugs can still transmit parasites (gametocytes) to feeding mosquitoes and also can recrudesce. Hence, if more humans opt for counterfeit drugs, then it will be difficult to control malaria transmission. On the other hand, if both infants and adults use only highly effective antimalarial drugs for the treatment of malaria, then $R_{U_{Am}}$, $R_{U_{Bm}}$ and $R_{U_{ABm}}$ will equal zero, and R_0 will be vastly reduced.

Lastly, the effects of the IRS on R_0 are considered. We let $R_{I_{mh}}$ denote the local reproduction number from mosquitoes to humans. Taking the difference between this reproduction number without control and with the IRS control only, and the partial derivative with respect to u_3 of this reproduction number with the IRS control, yields

$$R_{I_{mh}}|_{u_1=u_3=0} - R_{I_{mh}}|_{u_1=0,u_3\neq 0} = \frac{e^{-\mu_h n_h}(a\beta_A\mu_h + b\beta_B\tau)}{(\tau+\mu_h)}\frac{\varphi u_3}{(\mu_m+\varphi u_3)\mu_m} \tag{4.4}$$

and

$$\frac{\partial R_{I_{mh}}|_{u_1=0,u_3\neq 0}}{\partial u_3} = -\frac{e^{-\mu_h n_h}(a\beta_A\mu_h + b\beta_B\tau)\varphi}{(\mu_m + \varphi u_3)^2(\tau + \mu_h)}. \tag{4.5}$$

Since $R_{I_{mh}}|_{u_1=u_3=0} - R_{I_{mh}}|_{u_1=0,u_3\neq 0} > 0$ and $\frac{\partial R_{I_{mh}}}{\partial u_3} < 0$ for all $\varphi > 0$ and $u_3 > 0$, using IRS also reduces R_0.

5. Application of optimal control

This section uses control theory to derive optimal prevention and treatment methods to curtail malaria infection in an endemic area while minimizing the implementation cost. We apply Pontryagin's maximum principle to determine the necessary conditions for the optimal control of the age-structured model. The controls used are based on treatment and preventive tools adopted by most endemic countries in Sub-Saharan Africa [4, 40].

5.1. Analysis of optimal control

Together with the malaria models (2.1)–(2.10), we consider an optimal control problem with the objective (cost) functional given by

$$J(u_1, u_3, u_3) = \int_0^{t_f} [z_1 I_A + z_2 I_B + z_3 U_A + z_4 U_B + z_5 N_m + Y_1 {u_1}^2 + Y_2 {u_2}^2 + Y_3 {u_3}^2]dt, \tag{5.1}$$

where t_f is the final time, and the coefficients z_1, z_2, z_3, z_4 and z_5 represent, respectively, the positive weight constants of the infectious infants and adults, infants and adults who used counterfeit drugs, and the total mosquito population. On the other hand, the coefficients Y_1, Y_2 and Y_3 are positive constant weights for prevention efforts with insecticide-treated bednets (ITNs), treatment efforts with highly effective antimalarial drugs (HEAs) and prevention effort with indoor residual spraying (IRS), respectively, which regularize the optimal control. The terms $z_1 I_A, z_2 I_B, z_3 U_A, z_4 U_B$ and $z_5 N_m$ are the costs of infection in infants, adults and in the total mosquito population. It is assumed that the cost of prevention and treatment, given in the quadratic form in (5.1), that is, $Y_1 {u_1}^2, Y_3 {u_3}^2$ and $Y_2 {u_2}^2$, are the costs of prevention with ITNs, IRS and treatment with HEAs, respectively. The cost of prevention is associated with the purchase and use of ITNs and IRS. Similarly, the cost of treatment is the cost associated with the diagnosis or medical examination, HEAs and hospitalization.

Note that for bounded Lebesgue measurable controls and non-negative initial conditions, non-negative bounded solutions to the state system exist [49]. Our goal is to minimize the number of infectious humans, counterfeit drug users, the total number of mosquitoes and the cost of implementing the controls $u_1(t), u_2(t)$ and $u_3(t)$. Hence, we seek to find optimal controls ${u_1}^*, {u_2}^*$ and ${u_3}^*$ such that

$$J(u_1^*, u_2^*, u_3^*) = min\{J(u_1, u_2, u_3)|u_1, u_2, u_3 \in \Gamma\} \tag{5.2}$$

where the control set is $\Gamma = \{(u_1, u_2, u_3)$ such that u_1, u_2, u_3 are Lebesgue measurable with $0 \leq u_1 \leq 1$, $0 \leq u_2 \leq 1, 0 \leq u_3 \leq 1$ for $t \in [0, t_f]\}$.

The necessary conditions that an optimal solution must satisfy come from the Pontryagin maximum principle [34]. This principle converts (2.1)–(2.10) and (5.1) into a problem of minimizing pointwise the Hamiltonian H, given below, with respect to u_1, u_2 and u_3.

$$H = z_1 I_A + z_2 I_B + z_3 U_A + z_4 U_B + z_5 N_m + Y_1 {u_1}^2 + Y_2 {u_2}^2 + Y_3 {u_3}^2$$

$$
\begin{aligned}
&+ \quad \lambda_{S_A}\{\alpha_h + \phi_A T_A - (S_1 + \tau + \mu_h)S_A\} + \lambda_{S_B}\{\tau S_A + \phi_B T_B + \theta U_B - (S_3 + \mu_h)S_B\} \\
&+ \quad \lambda_{I_A}\{S_1 S_A + \xi_A U_A - d_1 I_A\} + \lambda_{I_B}\{\tau I_A + S_3 S_B + \xi_B U_B - d_2 I_B\} \\
&+ \quad \lambda_{U_A}\{\eta_A I_A - d_3 U_A\} + \lambda_{U_B}\{\tau U_A + \eta_B I_B - d_4 U_B\} \\
&+ \quad \lambda_{T_A}\{(u_2\gamma_A + \gamma_1)I_A - (\phi_A + \tau + \mu_h)T_A\} + \lambda_{T_B}\{\tau T_A + (u_2\gamma_B + \gamma_2)I_B - (\phi_B + \mu_h)T_B\} \\
&+ \quad \lambda_{S_m}\{\alpha_m N_m - \frac{\alpha_m}{K}N_m^2 - (S_5 + \mu_m + \varphi u_3)S_m\} + \lambda_{I_m}\{S_5 S_m - (\mu_m + \varphi u_3)I_m\}, \qquad (5.3)
\end{aligned}
$$

where $S_1 = e^{-\mu_h n_h}(1-u_1)\frac{a\beta_A}{N_h}I_m$, $\quad S_3 = e^{-\mu_h n_h}(1-u_1)\frac{b\beta_B}{N_h}I_m$, $\quad S_5 = e^{-\mu_m n_m}(1-u_1)\frac{c\beta_m}{N_h}(I_A + \pi_1 I_B + \pi_2 U_A + \pi_3 U_B)$, and λ_{S_A}, λ_{S_B}, λ_{I_A}, λ_{I_B}, λ_{U_A}, λ_{U_B}, λ_{T_A}, λ_{T_B}, λ_{S_m} and λ_{I_m} are the adjoint variables.

Theorem 5.1. *Given the solutions S_A, S_B, I_A, I_B, U_A, U_B, T_A, T_B, S_m and I_m of the state system (2.1)–(2.10) and optimal controls u_1^*, u_2^*, u_3^* that minimize $J(u_1, u_2, u_3)$ over Γ, there exist adjoint variables λ_{S_A}, λ_{S_B}, λ_{I_A}, λ_{I_B}, λ_{U_A}, λ_{U_B}, λ_{T_A}, λ_{T_B}, λ_{S_m} and λ_{I_m} satisfying*

$$
\begin{aligned}
\frac{d\lambda_{S_A}}{dt} &= -(\lambda_{S_A}[-S_1 + S_2 - (\tau + \mu_h)] + \lambda_{S_B}[\tau + S_4] + \lambda_{I_A}[S_1 - S_2] \\
&+ \lambda_{I_B}[-S_3] + (\lambda_{S_m} - \lambda_{I_m})[S_6]), \\
\frac{d\lambda_{S_B}}{dt} &= -(\lambda_{S_A}[S_2] + \lambda_{S_B}[S_4 - S_3 - \mu_h] + \lambda_{I_A}[-S_2] + \lambda_{I_B}[S_3 - S_4] \\
&+ (\lambda_{S_m} - \lambda_{I_m})[S_6]), \\
\frac{d\lambda_{I_A}}{dt} &= -(z_1 + \lambda_{S_A}[S_2] + \lambda_{S_B}[S_4] + \lambda_{I_A}[-S_2 - d_1] + \lambda_{I_B}[\tau - S_4] + \lambda_{U_A}[\eta_A] \\
&+ \lambda_{T_A}[u_2\gamma_A + \gamma_1] + (\lambda_{S_m} - \lambda_{I_m})[S_6] + (\lambda_{S_m} - \lambda_{I_m})[-S_7]), \\
\frac{d\lambda_{I_B}}{dt} &= -(z_2 + \lambda_{S_A}[S_2] + \lambda_{S_B}[S_4] + \lambda_{I_A}[-S_2] + \lambda_{I_B}[-S_4 - d_2] + \lambda_{U_B}[\eta_B] \\
&+ \lambda_{T_B}[u_2\gamma_B + \gamma_2] + (\lambda_{S_m} - \lambda_{I_m})[S_6] + (\lambda_{S_m} - \lambda_{I_m})[-\pi_1 S_7]), \\
\frac{d\lambda_{U_A}}{dt} &= -(z_3 + \lambda_{S_A}[S_2] + \lambda_{S_B}[S_4] + \lambda_{I_A}[-S_2 + \xi_A] + \lambda_{I_B}[-S_4] + \lambda_{U_A}[-d_3] \\
&+ \lambda_{U_B}[\tau] + (\lambda_{S_m} - \lambda_{I_m})[S_6] + (\lambda_{S_m} - \lambda_{I_m})[-\pi_2 S_7]), \\
\frac{d\lambda_{U_B}}{dt} &= -(z_4 + \lambda_{S_A}[S_2] + \lambda_{S_B}[S_4 + \theta] + \lambda_{I_A}[-S_2] + \lambda_{I_B}[-S_4 + \xi_B] + \lambda_{U_B}[-d_4] \\
&+ (\lambda_{S_m} - \lambda_{I_m})[S_6] + (\lambda_{S_m} - \lambda_{I_m})[-\pi_3 S_7]), \\
\frac{d\lambda_{T_A}}{dt} &= -(\lambda_{S_A}[\phi_A + S_2] + \lambda_{S_B}[S_4] + \lambda_{I_A}[-S_2] + \lambda_{I_B}[-S_4] + \lambda_{T_A}[-(\phi_A + \tau + \mu_h)] \\
&+ \lambda_{T_B}[\tau] + (\lambda_{S_m} - \lambda_{I_m})[S_6]), \\
\frac{d\lambda_{T_B}}{dt} &= -(\lambda_{S_A}[S_2] + \lambda_{S_B}[\phi_B + S_4] + \lambda_{I_A}[-S_2] + \lambda_{I_B}[-S_4] + \lambda_{T_B}[-(\phi_B + \mu_h)] \\
&+ (\lambda_{S_m} - \lambda_{I_m})[S_6]), \\
\frac{d\lambda_{S_m}}{dt} &= -(z_5 + \lambda_{S_m}[\alpha_m - 2\frac{\alpha_m}{K}N_m - (\mu_m + \varphi u_3)] + (\lambda_{S_m} - \lambda_{I_m})[-S_5]), \\
\frac{d\lambda_{I_m}}{dt} &= -(z_5 + \lambda_{S_A}[-\frac{S_1 S_A}{I_m}] + \lambda_{S_B}[-\frac{S_3 S_B}{I_m}] + \lambda_{I_A}[\frac{S_1 S_A}{I_m}] + \lambda_{I_B}[\frac{S_3 S_B}{I_m}] \\
&+ \lambda_{S_m}[\alpha_m - 2\frac{\alpha_m}{K}N_m] + \lambda_{I_m}[-(\mu_m + \varphi u_3)]),
\end{aligned}
$$

where

$$S_2 = \frac{S_1 S_A}{N_h}, \quad S_4 = \frac{S_3 S_B}{N_h}, \quad S_6 = \frac{S_5 S_m}{N_h} \quad \textit{and} \quad S_7 = \frac{S_5 S_m}{(I_A + \pi_1 I_B + \pi_2 U_A + \pi_3 U_B)},$$

with transversality conditions

$$\lambda_i(t_f) = 0, \tag{5.4}$$

for $i = S_A, S_B, I_A, I_B, U_A, U_B, T_A, T_B, S_m$ *and* I_m. *Furthermore, the controls* u_1^*, u_2^*, u_3^* *satisfy the optimality condition*

$$\begin{aligned}
u_1^* &= max\Big\{0, min\Big\{1, \frac{e^{-\mu_h n_h} a\beta_A I_m S_A(\lambda_{I_A} - \lambda_{S_A}) + e^{-\mu_h n_h} b\beta_B I_m S_B(\lambda_{I_B} - \lambda_{S_B})}{2Y_1 N_h} \\
&+ \frac{e^{-\mu_m n_m} c\beta_m (I_A + \pi_1 I_B + \pi_2 U_A + \pi_3 U_B) S_m(\lambda_{I_m} - \lambda_{S_m})}{2Y_1 N_h}\Big\}\Big\}, \\
u_2^* &= max\Big\{0, min\Big\{1, \frac{\gamma_A I_A(\lambda_{I_A} - \lambda_{T_A}) + \gamma_B I_B(\lambda_{I_B} - \lambda_{T_B})}{2Y_2}\Big\}\Big\}, \\
u_3^* &= max\Big\{0, min\Big\{1, \frac{\varphi(S_m \lambda_{S_m} + I_m \lambda_{I_m})}{2Y_3}\Big\}\Big\}.
\end{aligned} \tag{5.5}$$

Proof. Corollary 4.1 in [50] gives the existence of an optimal control on account of the convexity of the integrand of J with respect to u_1, u_2, u_3, a priori boundedness of the state solutions and the Lipschitz property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by differentiating the Hamiltonian, evaluated at the optimal control. Then, the adjoint system can be written as

$$\frac{d\lambda_i}{dt} = -\frac{\partial H}{\partial i}, \tag{5.6}$$

for $i = S_A, S_B, I_A, I_B, U_A, U_B, T_A, T_B, S_m$ and I_m. To obtain the optimality conditions (5.5), we also differentiate the Hamiltonian with respect to $(u_1, u_2, u_3) \in \Gamma$ and set it equal to zero. Thus,

$$\begin{aligned}
\frac{\partial H}{\partial u_1} &= 2Y_1 u_1 + e^{-\mu_h n_h} \frac{a\beta_A}{N_h} I_m S_A(\lambda_{S_A} - \lambda_{I_A}) + e^{-\mu_h n_h} \frac{b\beta_B}{N_h} I_m S_B(\lambda_{S_B} - \lambda_{I_B}) \\
&\quad + e^{-\mu_m n_m} \frac{c\beta_m}{N_h} (I_A + \pi_1 I_B + \pi_2 U_A + \pi_3 U_B) S_m(\lambda_{S_m} - \lambda_{I_m}), \\
\frac{\partial H}{\partial u_2} &= 2Y_2 u_2 - \gamma_A I_A \lambda_{I_A} + \gamma_A I_A \lambda_{T_A} - \gamma_B I_B \lambda_{I_B} + \gamma_B I_B \lambda_{T_B}, \\
\frac{\partial H}{\partial u_3} &= 2Y_3 u_3 - \varphi(S_m \lambda_{S_m} + I_m \lambda_{I_m}).
\end{aligned}$$

Solving for the optimal control, we obtain

$$\begin{aligned}
u_1^* &= \frac{e^{-\mu_h n_h} a\beta_A I_m S_A(\lambda_{I_A} - \lambda_{S_A}) + e^{-\mu_h n_h} b\beta_B I_m S_B(\lambda_{I_B} - \lambda_{S_B})}{2Y_1 N_h} \\
&\quad + \frac{e^{-\mu_m n_m} c\beta_m (I_A + \pi_1 I_B + \pi_2 U_A + \pi_3 U_B) S_m(\lambda_{I_m} - \lambda_{S_m})}{2Y_1 N_h},
\end{aligned}$$

$$
\begin{aligned}
u_2^* &= \frac{\gamma_A I_A(\lambda_{I_A} - \lambda_{T_A}) + \gamma_B I_B(\lambda_{I_B} - \lambda_{T_B})}{2Y_2}, \\
u_3^* &= \frac{\varphi(S_m \lambda_{S_m} + I_m \lambda_{I_m})}{2Y_3}.
\end{aligned}
$$

By standard control arguments involving the controls' bounds, we conclude that

$$
u_1^* = \begin{cases} 0 & \text{if } X_1^* \le 1 \\ X_1^* & \text{if } 0 < X_1^* < 1 \\ 1 & \text{if } X_1^* \ge 1 \end{cases}, \quad
u_2^* = \begin{cases} 0 & \text{if } X_2^* \le 1 \\ X_2^* & \text{if } 0 < X_2^* < 1 \\ 1 & \text{if } X_2^* \ge 1 \end{cases}, \quad
u_3^* = \begin{cases} 0 & \text{if } X_3^* \le 1 \\ X_3^* & \text{if } 0 < X_3^* < 1 \\ 1 & \text{if } X_3^* \ge 1 \end{cases},
$$

where

$$
\begin{aligned}
X_1^* &= \frac{e^{-\mu_h n_h} a\beta_A I_m S_A(\lambda_{I_A} - \lambda_{S_A}) + e^{-\mu_h n_h} b\beta_B I_m S_B(\lambda_{I_B} - \lambda_{S_B})}{2Y_1 N_h} \\
&+ \frac{e^{-\mu_m n_m} c\beta_m (I_A + \pi_1 I_B + \pi_2 U_A + \pi_3 U_B) S_m(\lambda_{I_m} - \lambda_{S_m})}{2Y_1 N_h}, \\
X_2^* &= \frac{\gamma_A I_A(\lambda_{I_A} - \lambda_{T_A}) + \gamma_B I_B(\lambda_{I_B} - \lambda_{T_B})}{2Y_2}, \\
X_3^* &= \frac{\varphi(S_m \lambda_{S_m} + I_m \lambda_{I_m})}{2Y_3}.
\end{aligned}
$$

□

The optimality system consists of the state systems (2.1)–(2.10) with initial conditions, the adjoint system (5.4) with transversality conditions (5.4) and the optimality condition (5.5).

Table 1. Parameter values for the age-structured malaria models (2.1)–(2.10).

Parameter	Value/Range	Unit	References	Parameter	Value/Range	Unit	References
α_h	0.3002	day^{-1}	Estimated	π_1	0.5/[0,1]		Assumed
α_m	0.2	day^{-1}	Estimated	π_2	0.2/[0,1]		Assumed
τ	$\frac{1}{5\times365}$	day^{-1}	Estimated	π_3	0.1/[0,1]		Assumed
a	11/[1-34]	day^{-1}	[52–55]	η_A	$[\frac{1}{7}\text{-}\frac{1}{30}]$	day^{-1}	[7,9,48]
b	5/[1-34]	day^{-1}	[52–55]	η_B	$[\frac{1}{7}\text{-}\frac{1}{30}]$	day^{-1}	[7]
c	3	day^{-1}	[35]	γ_A	$\frac{1}{4}/[\frac{1}{3}\text{-}\frac{1}{30}]$	day^{-1}	[7,9]
β_A	0.0005		Estimated	γ_B	$\frac{1}{4}/[\frac{1}{3}\text{-}\frac{1}{30}]$	day^{-1}	[7]
β_B	0.0005		Estimated	ξ_A	$[\frac{1}{7}\text{-}\frac{1}{30}]$	day^{-1}	[7]
β_m	0.1		Estimated	ξ_B	$[\frac{1}{7}\text{-}\frac{1}{30}]$	day^{-1}	[7]
n_h	$12/[9-17]$	$days$	[24,25]	ϕ_A	$\frac{1}{30}/[\frac{1}{14}\text{-}\frac{1}{180}]$	day^{-1}	[7]
n_m	11	$days$	[25]	ϕ_B	$\frac{1}{180}/[\frac{1}{14}\text{-}\frac{1}{730}]$	day^{-1}	[7]
γ_1	$\frac{1}{365}$	day^{-1}	Assumed	γ_2	$\frac{1}{180}/[\frac{1}{58}\text{-}\frac{1}{714}]$	day^{-1}	[20,25]
δ_A	1.476×10^{-5}	day^{-1}	[56]	θ	$\frac{1}{365}$	day^{-1}	Assumed
δ_B	8.209×10^{-5}	day^{-1}	[5]	μ_h	$\frac{1}{64\times365}$	day^{-1}	[57]
φ	0.09	day^{-1}	Estimated	μ_m	$\frac{1}{30}$	day^{-1}	[25]
K	17500		Estimated				

5.2. Numerical simulation

As mentioned in the introduction, our next objective is to investigate numerically the optimal control strategies that can eliminate malaria infection in the age-structured population using two main scenarios, namely, the population without counterfeit drug use, i.e., $\eta_A = \eta_B = \xi_A = \xi_B = \theta = 0$, and the population with counterfeit drugs. For the first scenario, we use the following control strategies: (i.) insecticide-treated bednets only, $(u_1, 0, 0)$, (ii.) highly effective antimalarial drugs only, $(0, u_2, 0)$, (iii.) indoor residual spraying only, $(0, 0, u_3)$, (iv.) insecticide-treated bednets and highly effective antimalarial drugs only, $(u_1, u_2, 0)$, (v.) insecticide-treated bednets and indoor residual spraying only, $(u_1, 0, u_3)$, (vi.) highly effective antimalarial drugs and indoor residual spraying, $(0, u_2, u_3)$ and (vii.) insecticide-treated bednets, highly effective antimalarial drugs and indoor residual spraying, (u_1, u_2, u_3). For the second scenario, we shall use the best control strategy results from the first scenario and incorporate the effects of counterfeit drug use considering the following sub-categories: (i) high removal rate and high recrudescence rate using $\eta_A = \frac{1}{7}$, $\eta_B = \frac{1}{7}$, $\xi_A = \frac{1}{7}$, $\xi_B = \frac{1}{7}$, (ii) high removal rate and low recrudescence rate using $\eta_A = \frac{1}{7}$, $\eta_B = \frac{1}{7}$, $\xi_A = \frac{1}{30}$, $\xi_B = \frac{1}{30}$, (iii) low removal rate and high recrudescence rate using $\eta_A = \frac{1}{30}$, $\eta_B = \frac{1}{30}$, $\xi_A = \frac{1}{7}$, $\xi_B = \frac{1}{7}$ and (iv) low removal rate and low recrudescence rate using $\eta_A = \frac{1}{30}$, $\eta_B = \frac{1}{30}$, $\xi_A = \frac{1}{30}$, $\xi_B = \frac{1}{30}$. A fourth-order Runge-Kutta iterative scheme is used to solve the optimality system. The state system is solved forward in time with initial conditions $(S_A, S_B, I_A, I_B, U_A, U_B, T_A, T_B, S_m, I_m)$=$(508, 6505, 100, 300, 0, 0, 0, 0, 14583, 300)$, and the adjoint system is solved backwards in time with transversality conditions (5.4). The initial total populations are estimated using (2.15) and the parameter values in Table 1. At first, the state system and the adjoint system are solved with an initial guess for the control $(u_1(t), u_2(t), u_3(t)) = (0, 0, 0)$. The control functions are updated using the optimality conditions given by (5.5), and the process is repeated. This iterative process terminates when the values converge sufficiently: the differences between the current state, adjoint and control values and the previous state, adjoint and control values are negligibly small [51]. The current values are then taken as the solution. The numerical values of the parameters used for solving the optimality system to obtain the optimal solution are given in Table 1. Most of the parameter values are taken from the literature on Ghana. Other parameter values not directly found in the literature were estimated using the assumptions made during the model formulation and following literature indications. The following weight constants were used: $Y_1 = 20, Y_2 = 40, Y_3 = 25$ and $z_1 = 30, z_2 = 25, z_3 = 20, z_4 = 15, z_5 = 20$. The control is applied over 5 years (1825 days).

5.3. Simulation results

5.3.1. The control strategies without counterfeit antimalarial drug use

We investigate the effect of each of the seven control strategies mentioned above on the dynamics of the population when no counterfeit antimalarial drugs are used (i.e., $\eta_A = \eta_B = \xi_A = \xi_B = \theta = 0$).

1) Insecticide-treated bednets only:

The strategy considers insecticide-treated bednets (u_1) as the only control. The highly effective antimalarial drugs (u_2) and indoor residual spraying (u_3) are set to zero to optimize the objective function (5.1). The benefits of using ITNs are seen in the reduction of the number of infectious individuals in both mosquito and human populations, as compared to when there is no control, as

shown in Figure 3(a)–(c). Also, the number of susceptible mosquitoes is higher than when no control is used (Figure 3(d)). The control profile in Figure 3(e) indicates that, in this case, the coverage of insecticide-treated bednets (u_1) should be maintained at 75% for the entire duration of the intervention.

2) Highly effective antimalarial drugs only:

Here, only highly effective antimalarial drugs (u_2) are used to optimize the objective function (5.1), while the insecticide-treated bednets (u_1) and indoor residual spraying (u_3) are absent. From the results in Figure 4(a)–(c), we observe a significant decrease in the numbers of the infectious human and mosquito populations as compared to when no control is used. The results also show an increase in the susceptible mosquito population. (Figure 4(d)). From the control profile shown in Figure 4(e), we observe that strategy (u_2) should be maintained at coverage of 75% for 148 days, then gradually reduced to 25% by day 350 and maintained at this level for the remaining intervention period.

3) Indoor residual spraying only:

We use indoor residual spraying (u_3) to optimize the objective function (5.1), while insecticide-treated bednets (u_1) and highly effective antimalarial drugs (u_2) are absent. The results reveal a reduction in the number of infectious humans I_A, I_B and mosquitoes I_A when the control is applied as compared to the case without control, as observed in Figure 5(a)–(c). The graph in Figure 5(d) also shows an increase in the susceptible mosquito population. We observe from the control profile shown in Figure 5(e) that the IRS (u_3) only strategy should be maintained at coverage of 75% for the total duration of the intervention.

4) Insecticide-treated bednets and highly effective antimalarial drugs:

We use the strategy which has both insecticide-treated nets (u_1) and highly effective antimalarial drugs (u_2) as controls while setting the indoor residual spraying to zero ($u_3 = 0$) and optimize the objective function (5.1). Figure 6(a)–(d) shows a significant decrease in the number of infectious humans and mosquitoes and a considerable increase in the number of susceptible mosquitoes due to the application of this control. Its profile in Figure 6(e) also reveals that to be optimal, the highly effective antimalarial drugs coverage should be at 75% for 74 days, and then gradually be reduced to 25% on day 230 for the rest of the duration, while the insecticide-treated net's coverage should begin at 44%, then increase to 45% from day 91 to day 1735 and finally be reduced gradually to 25% by the end of the intervention.

5) Insecticide-treated bednets and indoor residual spraying:

When the insecticide-treated bednets (u_1) and indoor residual spraying (u_3) are used to optimize the objective function (5.1) without highly effective antimalarial drugs ($u_2 = 0$), we observe a reduced number of infectious humans I_A, I_B and mosquitoes I_m and an increased number of susceptible mosquitoes (Figure 7(a)–(d)) as compared to the populations with no control. The control profile in Figure 7(e) shows that for this strategy to be optimal, the insecticide-treated bednets and the indoor residual spraying must both be maintained at 75% coverage for the total duration of the intervention.

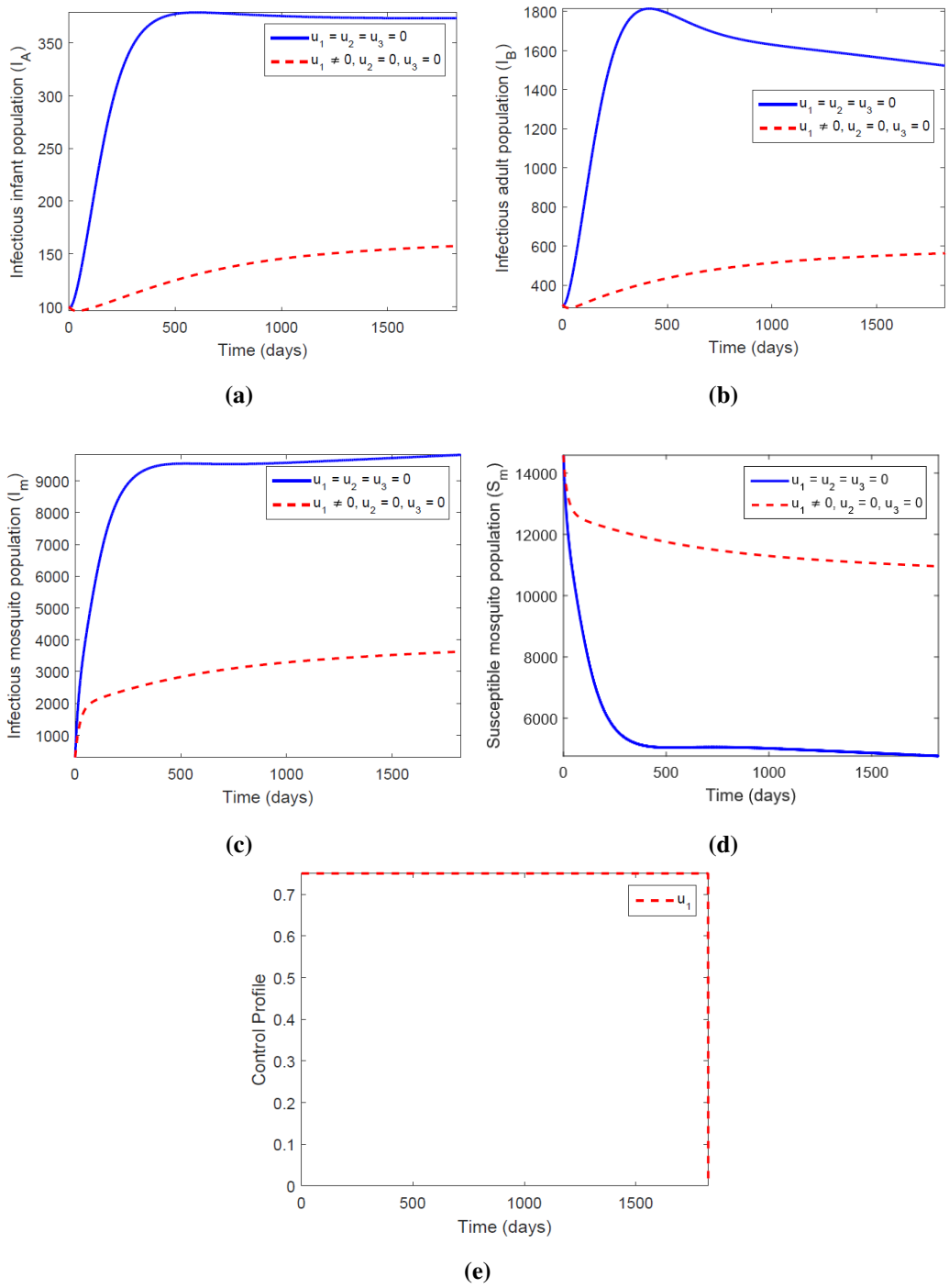

Figure 3. Numerical simulation of the dynamics of (a) infectious infants, (b) infectious adults, (c) infectious mosquitoes, (d) susceptible mosquito population and (e) control profile when the optimal strategy (insecticide-treated nets only) is used without counterfeit drugs. The parameter values used are shown in Table 1.

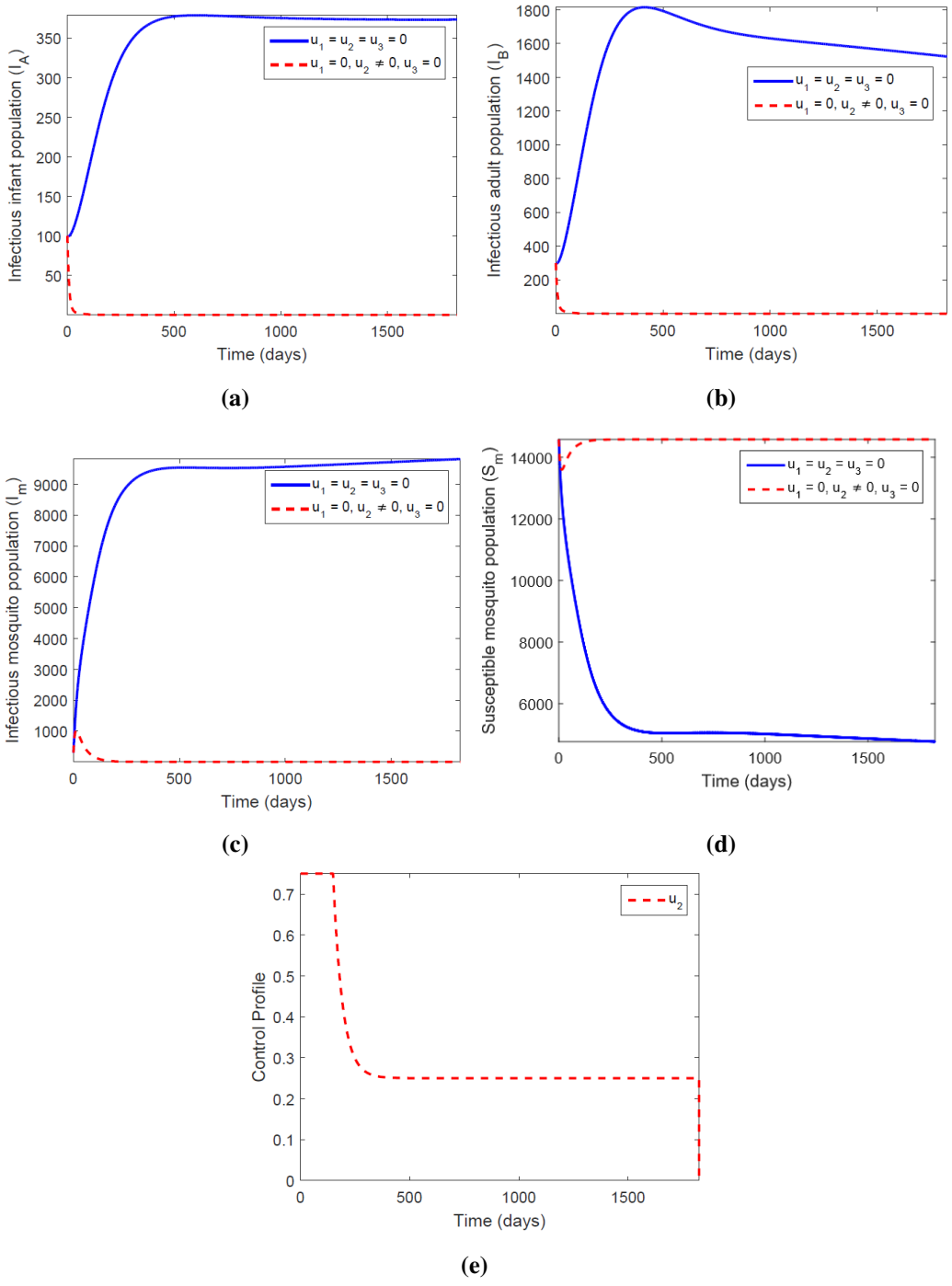

Figure 4. Graphs showing the effect of the optimal strategy (highly effective antimalarial drugs only) on the dynamics of the (a) infectious infants, (b) infectious adults, (c) infectious mosquitoes, (d) susceptible mosquitoes and (e) the control profile, in the absence of counterfeit antimalarial drug use. The parameter values used are shown in Table 1.

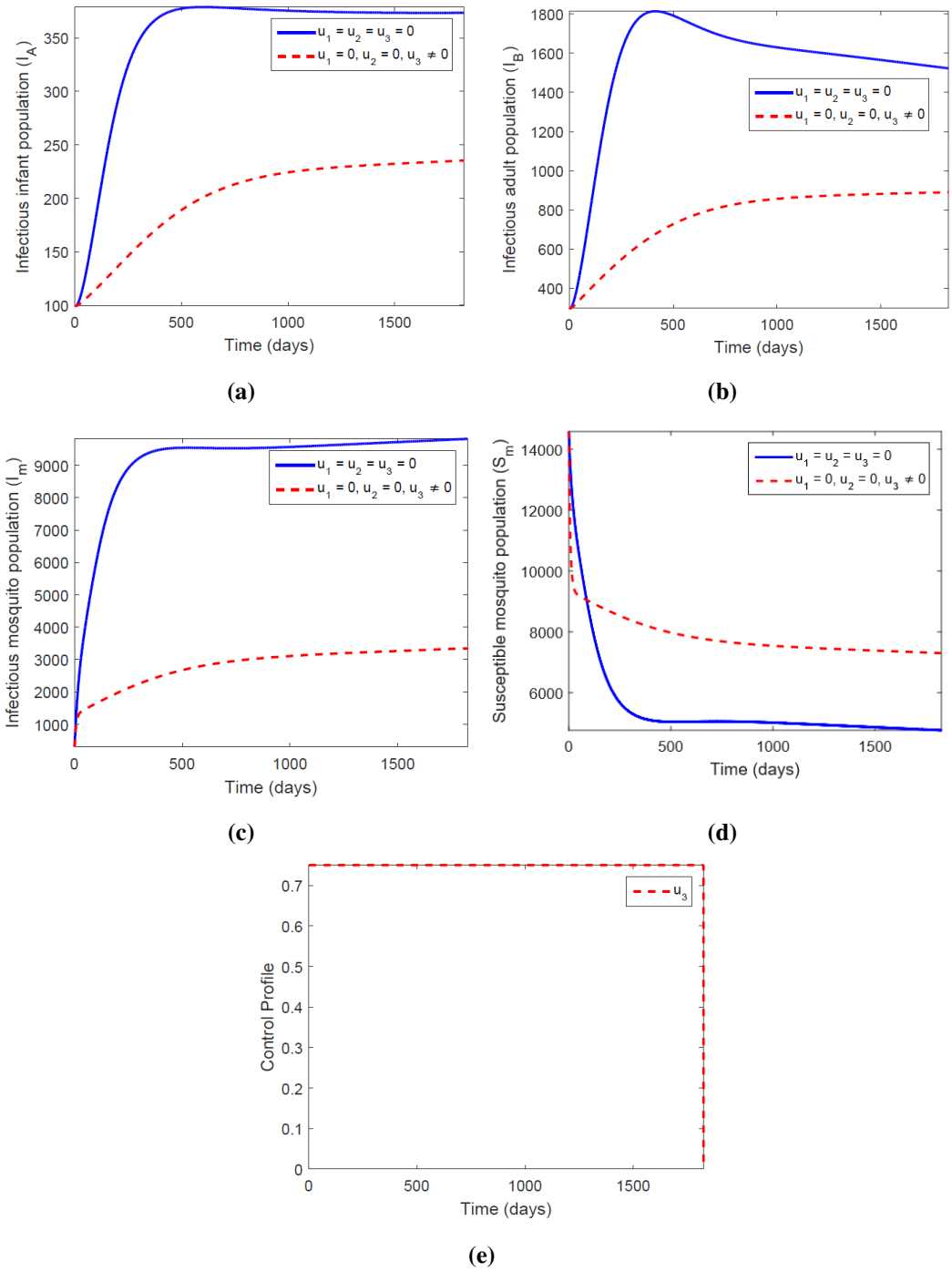

Figure 5. Graphs showing the effect of the optimal strategy (indoor residual sprayig only), in the absence of counterfeit antimalarial drug use, on the dynamics of (a) infectious infants, (b) infectious adults, (c) infectious mosquitoes, (d) susceptible mosquitoes and (e) the control profile. The parameter values used are shown in Table 1.

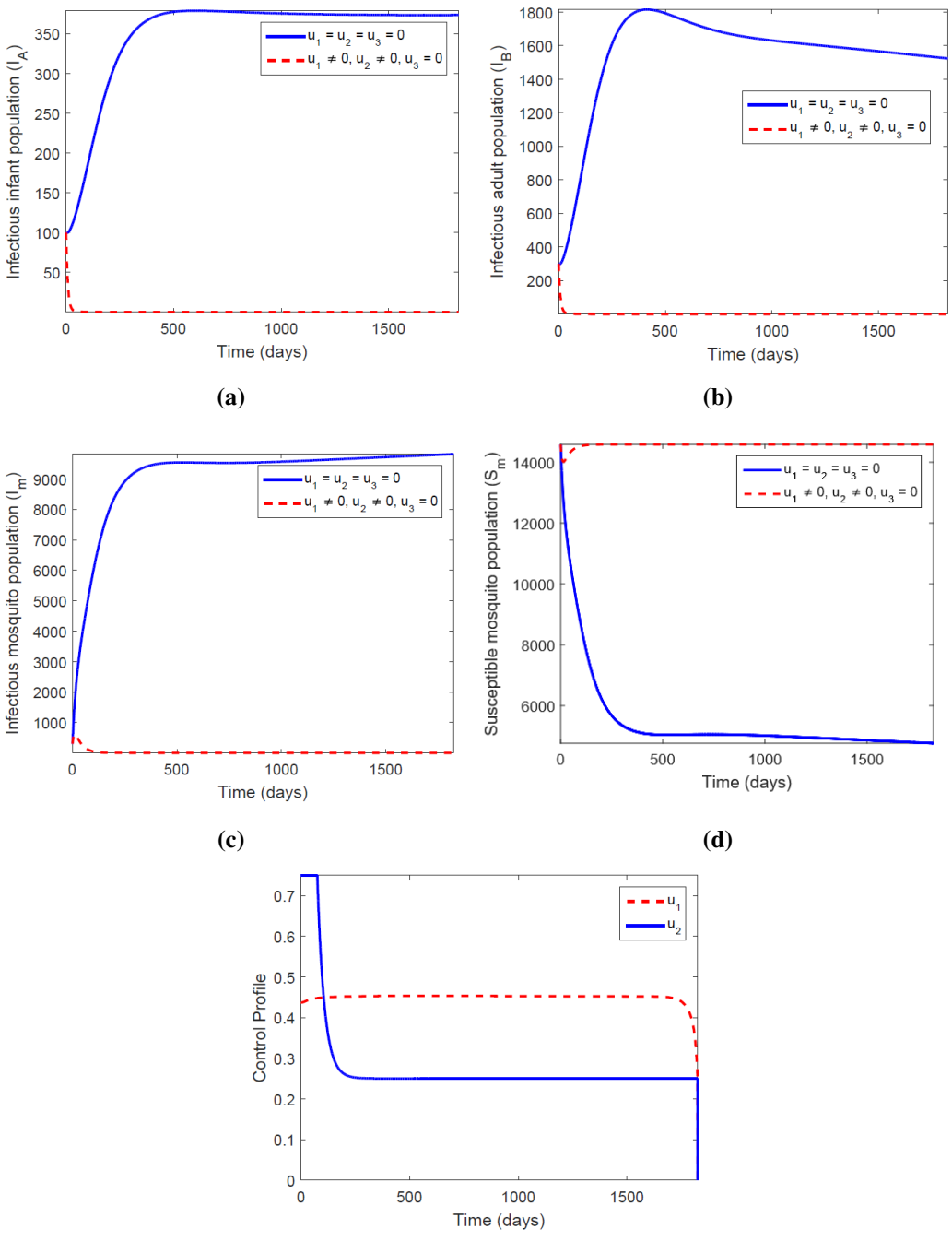

Figure 6. The graphs show the effect of the optimal strategy (both insecticide-treated nets and highly effective antimalarial drugs) in the absence of counterfeit antimalarial drug use on (a) infectious infants, (b) infectious adults, (c) infectious mosquitoes, (d) susceptible mosquitoes and (e) the control profile. The parameter values are given in Table 1.

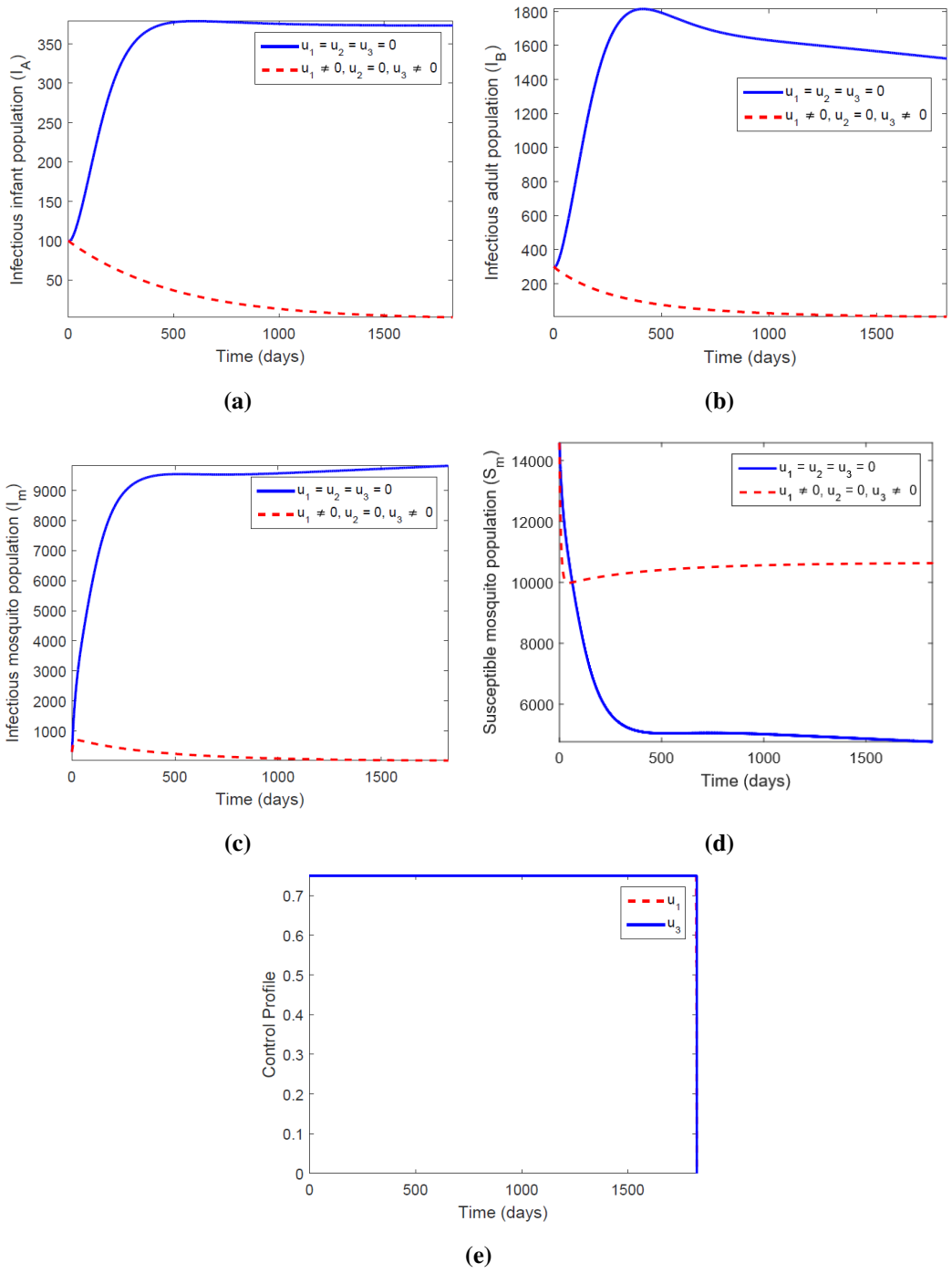

Figure 7. Simulation results of the optimal strategy (both insecticide-treated bednets and indoor residual spraying) in the absence of counterfeit drugs on the transmission of malaria on (a) infectious infants, (b) infectious adults, (c) infectious mosquitoes, (d) susceptible mosquitoes and (e) the control profile. The parameter values used are shown in Table 1.

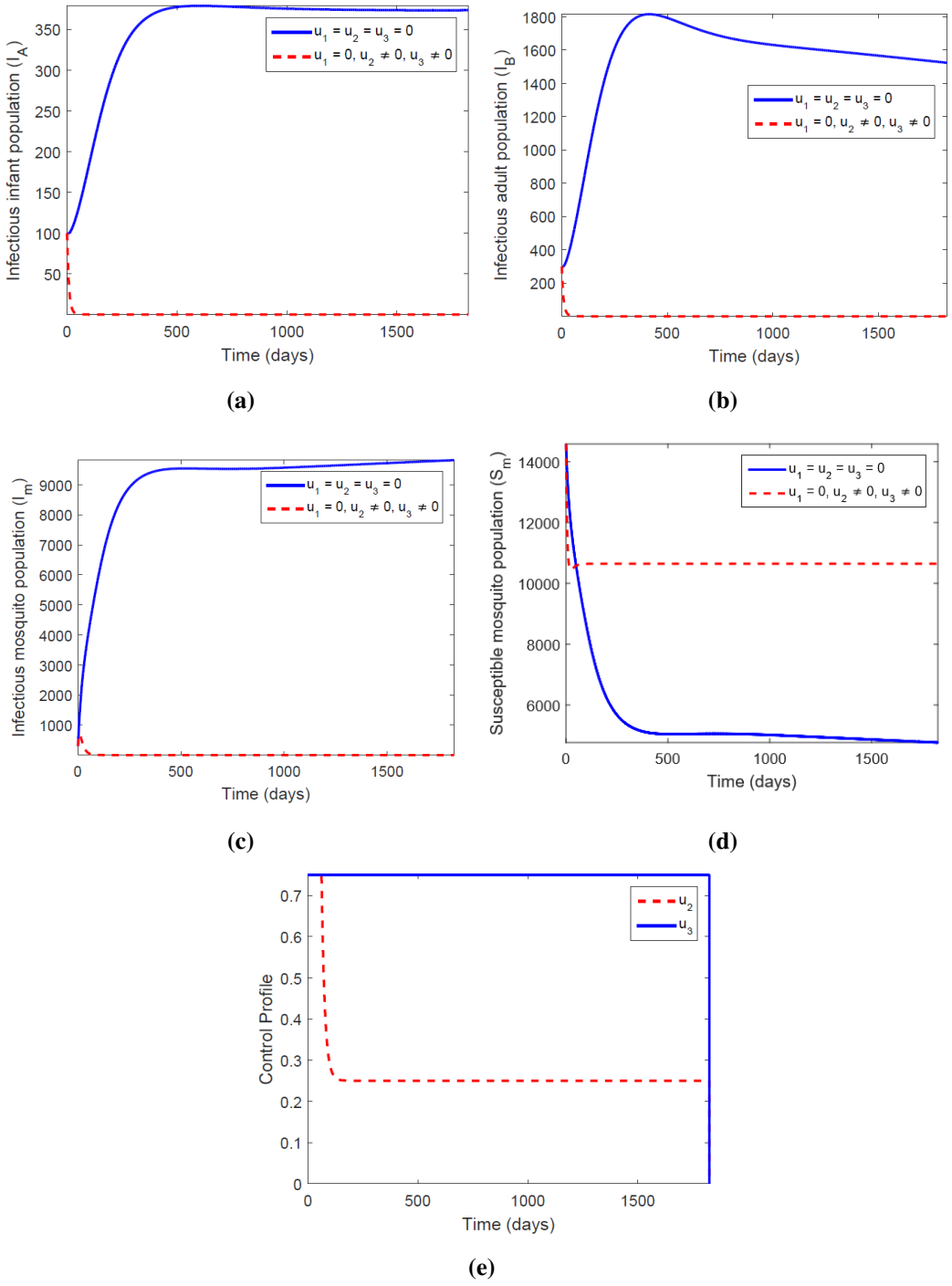

Figure 8. Simulation results of the effect of the optimal strategy (highly effective antimalarial drugs and indoor residual spraying), in the absence of counterfeit antimalarial drug use, on the transmission of malaria in (a) infectious infants, (b) infectious adults, (c) infectious mosquitoes, (d) susceptible mosquitoes and (e) the control profile. The parameter values used are shown in Table 1.

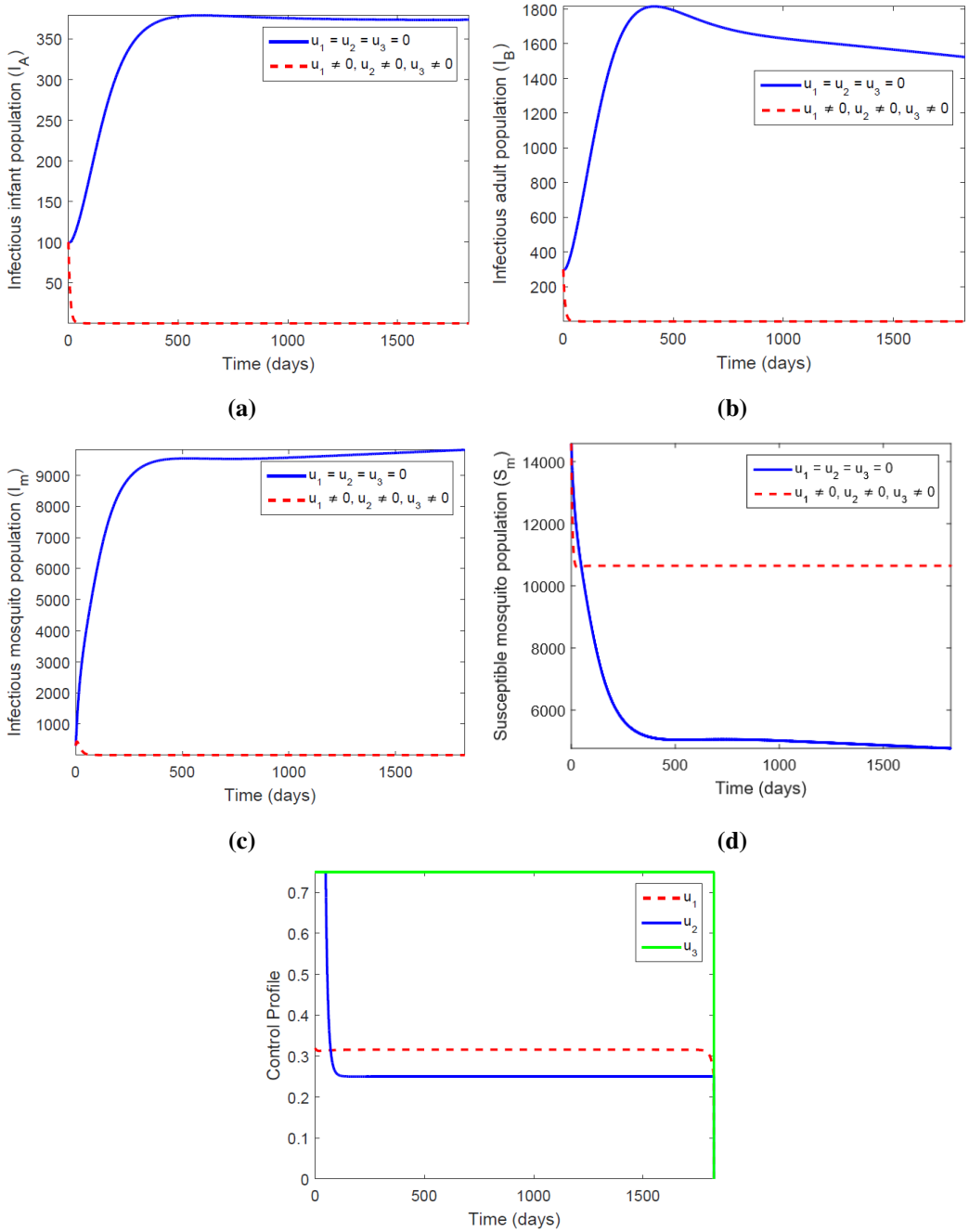

Figure 9. Simulation results of the optimal strategy (insecticide-treated bednets, highly effective antimalarial drugs and indoor residual spraying), in the absence of counterfeit drug use, on the transmission of malaria on (a) infectious infants (b) infectious adults (c) infectious mosquitoes (d) susceptible mosquitoes and (e) the control profile. The parameter values used are shown in Table 1.

6) Highly effective antimalarial drugs and indoor residual spraying:

Here, we use highly effective antimalarial drugs (u_2) and indoor residual spraying (u_3) while setting the control on insecticide-treated bednets to zero ($u_1 = 0$) to optimize the objective function (5.1). As shown in Figure 8(a)–(d), with this control, the infectious populations I_A, I_B and I_m are significantly smaller, and the susceptible mosquitoes population S_m is larger, as compared to the populations without control. The control profile in Figure 8(e) shows that the coverage of indoor residual spraying should be maintained at 75% for the whole duration of the intervention. At the same time, administration of highly effective antimalarial drugs should begin with 75% coverage for 61 days before being reduced to 25% by day 132 and maintained at this level for the remaining treatment time.

7) Insecticide-treated bednets, highly effective antimalarial drugs and indoor residual spraying:

We explore the combination of all three controls by using insecticide-treated bednets (u_1), highly effective antimalarial drugs (u_2) and indoor residual spraying (u_3) to optimize the objective function (5.1). The benefits of this strategy are a significant decrease in the populations of infectious humans and mosquitoes and a significant increase in the number of susceptible mosquitoes in comparison to when no controls are used (Figure 9(a)–(d)). The control profile indicates that for the strategy to be optimal, the indoor residual spraying coverage at 75% should be maintained for the entire intervention period, the insecticide-treated bednets should be applied with coverage of 32% between day 1 to day 1769 and then reduced gradually to 25%, and, lastly, highly effective antimalarial drugs should be administered with coverage of 75% for the first 47 days and then reduced to 25% by day 105 and maintained at this level to the end of the period (Figure 9(e)).

5.3.2. The effect of counterfeit drugs on the best control strategy

In this section, we examine the impact of four possible cases resulting from counterfeit drug use on the performance of the best control strategies discussed in Section 5.3.1, i.e., the insecticide-treated bednets, highly effective antimalarial drugs and indoor residual spraying.

1) Counterfeit drug with high removal rate and high recrudescence rate:

As the control we use insecticide-treated bednets (u_1), highly effective antimalarial drugs (u_2) and indoor residual spraying (u_3) and set the per capita removal rates $\eta_A = \frac{1}{7}$ and $\eta_B = \frac{1}{7}$ and the per capita recrudescence rate $\xi_A = \frac{1}{7}$ and $\xi_B = \frac{1}{7}$ for both infants and adults. Figures 10(a)–(g) show significant increases in the populations of susceptible humans S_A and S_B and significant decreases in the numbers of infectious individuals I_A, I_B, I_m and counterfeit antimalarial drug users U_A, U_B when the control is used. The control profile in Figure 10(h) shows that maintaining indoor residual spraying coverage at 75% for the whole intervention period, highly effective antimalarial drugs coverage at 75% for the first 94 days and gradually reduced to 25% by day 191, and, lastly, the insecticide-treated bednets coverage at 36%, reduced to 35% on day 1744 and then gradually to 25%, is optimal.

2) Counterfeit drug with high removal and low recrudescence rates:

Similarly, we use the insecticide-treated bednets (u_1), highly effective antimalarial drugs (u_2) and indoor residual spraying (u_3) control to optimize the objective function (5.1) and take the per capita

removal rates $\eta_A = \frac{1}{7}$ and $\eta_B = \frac{1}{7}$ and the per capita recrudescence rates $\xi_A = \frac{1}{30}$ and $\xi_B = \frac{1}{30}$ for both infants and adults. We observe in Figure 11(a)–(g) that the control strategy causes a significant difference in the populations. Namely, the number of susceptibles increases while that of the infectious and counterfeit drug users decreases, as compared to when no control is used. The control profile in Figure 11(h) shows that it is optimal to use the indoor residual spraying coverage at 75% for the entire intervention period, the insecticide-treated bednets coverage at 60%, reduced to 55% by day 27, increased to 57% until day 1532 and again gradually reduced to 25%, and, lastly, starting with highly effective antimalarial drugs coverage at 75% for 258 days and then gradually reducing it to 25% on day 575 and maintaining this level to the end of the period.

3) Counterfeit drug with low removal and high recrudescence rates:

We use insecticide-treated bednets (u_1), highly effective antimalarial drugs (u_2) and indoor residual spraying (u_3) to optimize the objective function (5.1) and take the per capita removal rates $\eta_A = \frac{1}{30}$, $\eta_B = \frac{1}{30}$ and the per capita recrudescence rates $\xi_A = \frac{1}{7}$, $\xi_B = \frac{1}{7}$. The control produces an increase in the susceptible population compared to when no control is applied (Figure 12(a),(b)). Also, the infectious and counterfeit antimalarial drug users populations are observed to decrease (Figure 12(c)–(g)). Figure 12(h) illustrates that indoor residual spraying with coverage of 75% for the entire intervention period, insecticide-treated bednets coverage at 33% at the beginning, then reduced and maintained at 32% for 1794 days and reduced again to 25%, and, lastly, highly effective antimalarial drugs coverage at 75% for the first 61 days and reduced to 25% by day 127 is optimal for disease control.

4) Counterfeit drug with low removal and low recrudescence rates:

Finally, we use insecticide-treated bednets (u_1), highly effective antimalarial drugs (u_2) and indoor residual spraying (u_3) to optimize the objective function (5.1) and take the per capita removal rates $\eta_A = \frac{1}{30}$ and $\eta_B = \frac{1}{30}$ and the per capita recrudescence rates $\xi_A = \frac{1}{30}$ and $\xi_B = \frac{1}{30}$. The control produces significant decreases in the infectious classes I_A, I_B, I_m and also in the number of counterfeit antimalarial users in the classes U_A, U_B (Figure 13(c)–(g)) in comparison with the populations without control. The control profile indicates that maintaining the indoor residual spraying coverage at 75% for the entire intervention period, beginning with the insecticide-treated bednets coverage of 37%, then reducing it and maintaining it at 36% from day 4 to day 1735 and reducing it to 25% by the end of the intervention period, and lastly, administering the highly effective antimalarial drugs with coverage of 75% for 127 days before reducing it to 25% by day 308 is optimal for disease control (Figure 13(h)).

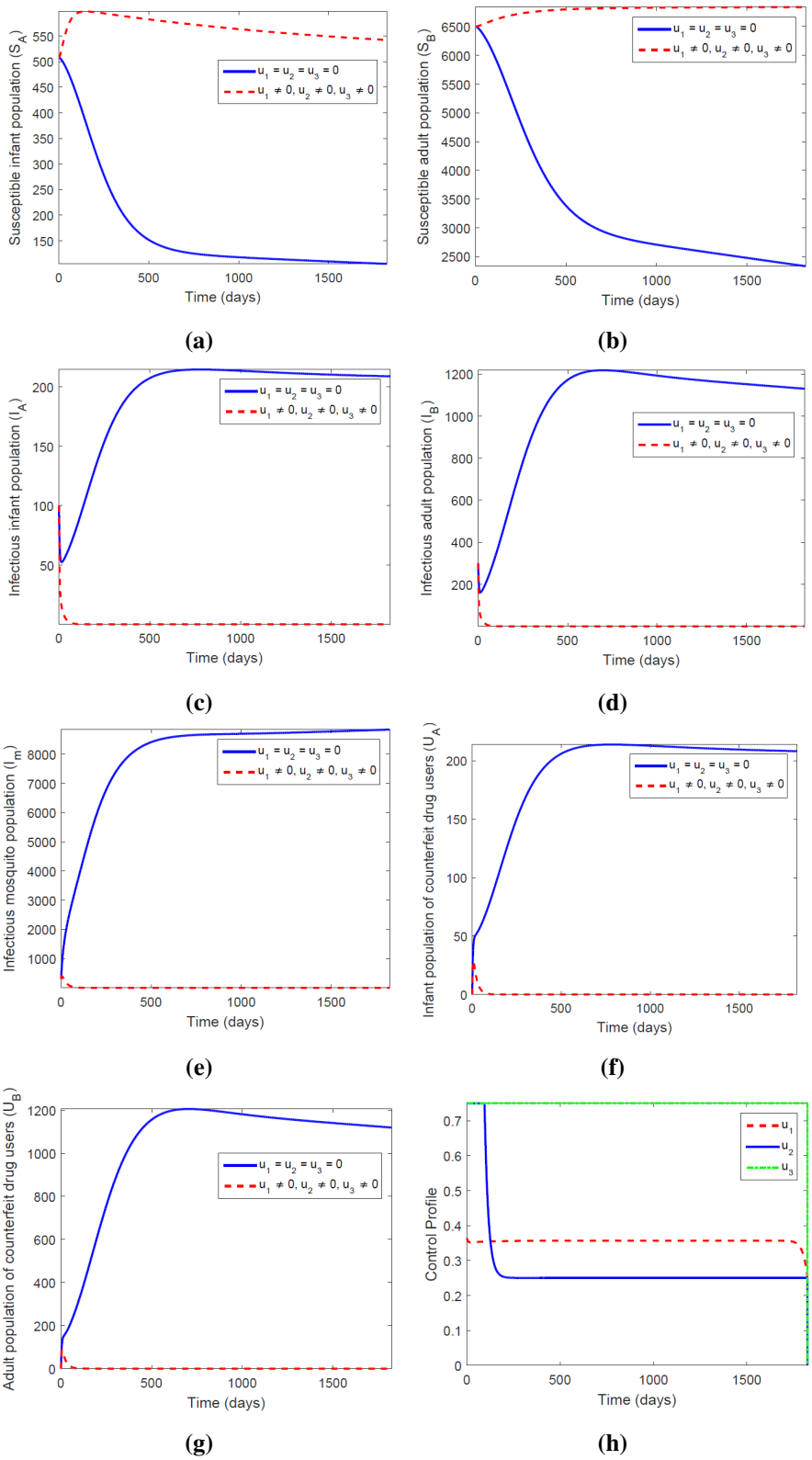

Figure 10. Simulation of the optimal strategy (ITN, highly effective antimalarial drugs and IRS) with parameters values in Table 1, when counterfeit antimalarial drugs have high removal rate and high recrudescence rate – (a) S_A, (b) S_B, (c) I_A, (d) I_B, (e) I_m, (f) U_A, (g) U_B and (h) the control profile.

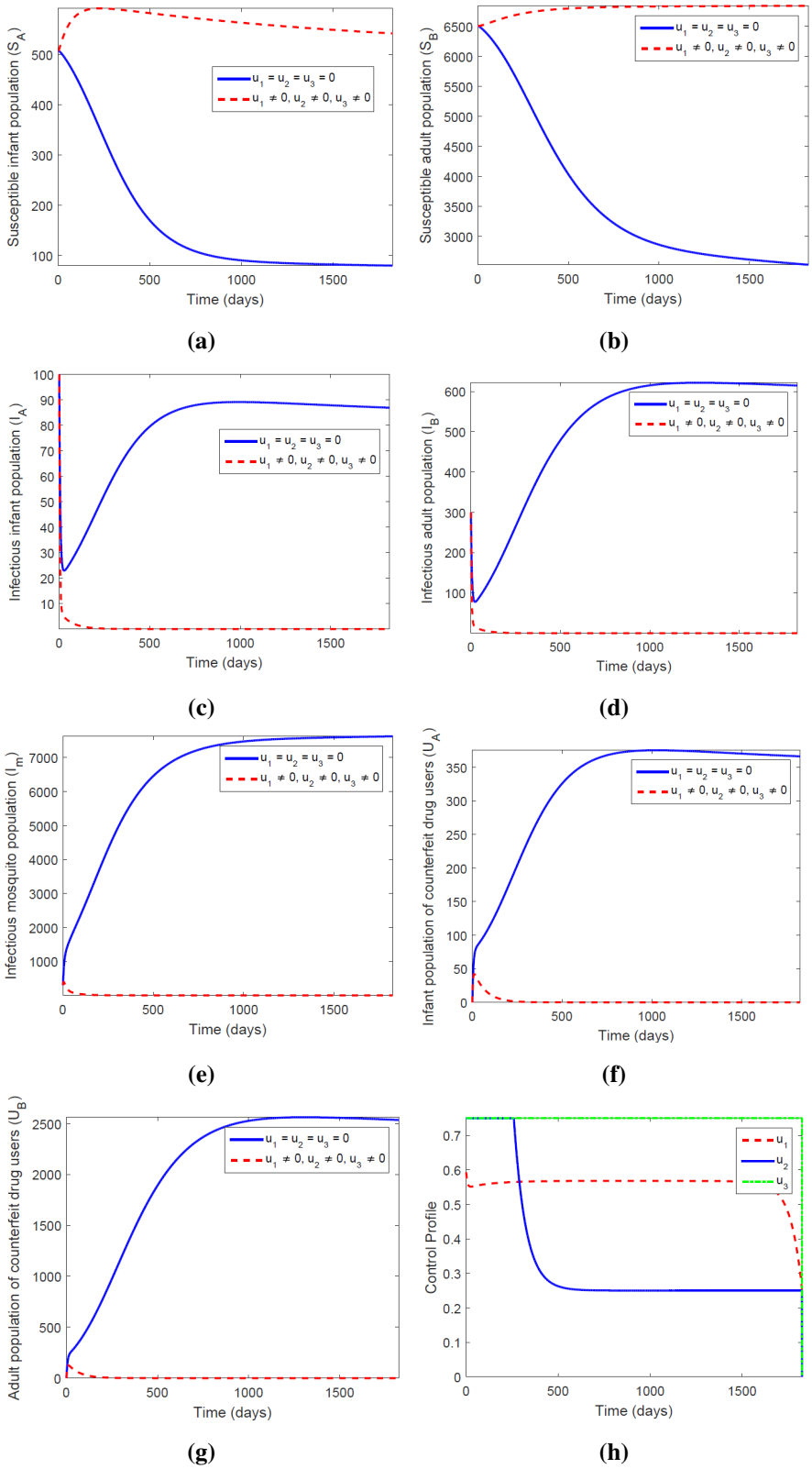

Figure 11. Simulations of counterfeit antimalarial drugs with high removal and low recrudescence rates, the optimal strategy (ITN, highly effective antimalarial drugs and IRS), and values in Table 1 – (a) S_A, (b) S_B, (c) I_A, (d) I_B, (e) I_m, (f) U_A, (g) U_B and (h) control profile.

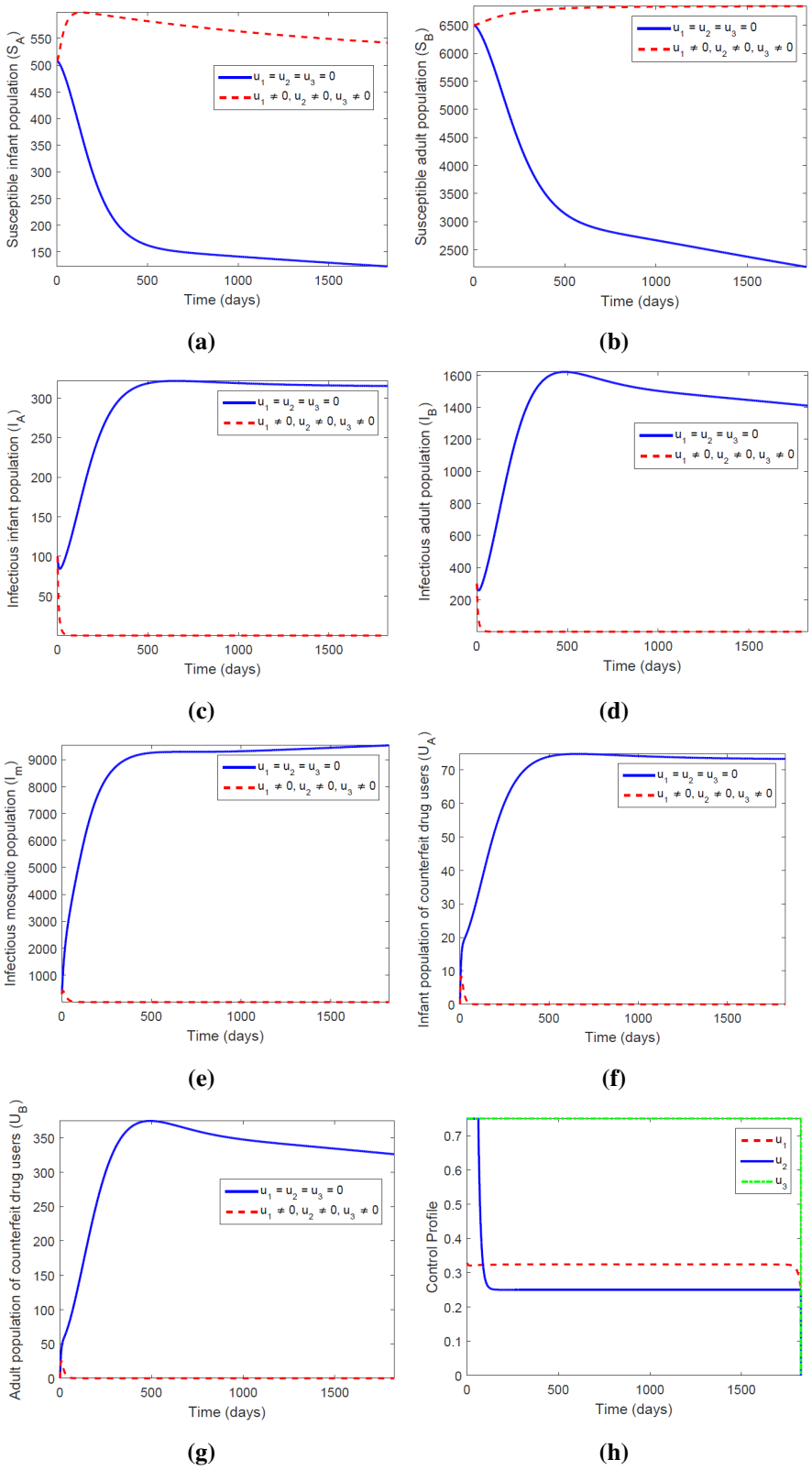

Figure 12. Simulation of the optimal strategy (ITN, highly effective antimalarial drugs and IRS) and counterfeit drugs with low removal rate and high recrudescence rate – (a) S_A, (b) S_B, (c) I_A, (d) I_B, (e) I_m, (f) U_A, (g) U_B and (h) the control profile. The parameter values are in Table 1.

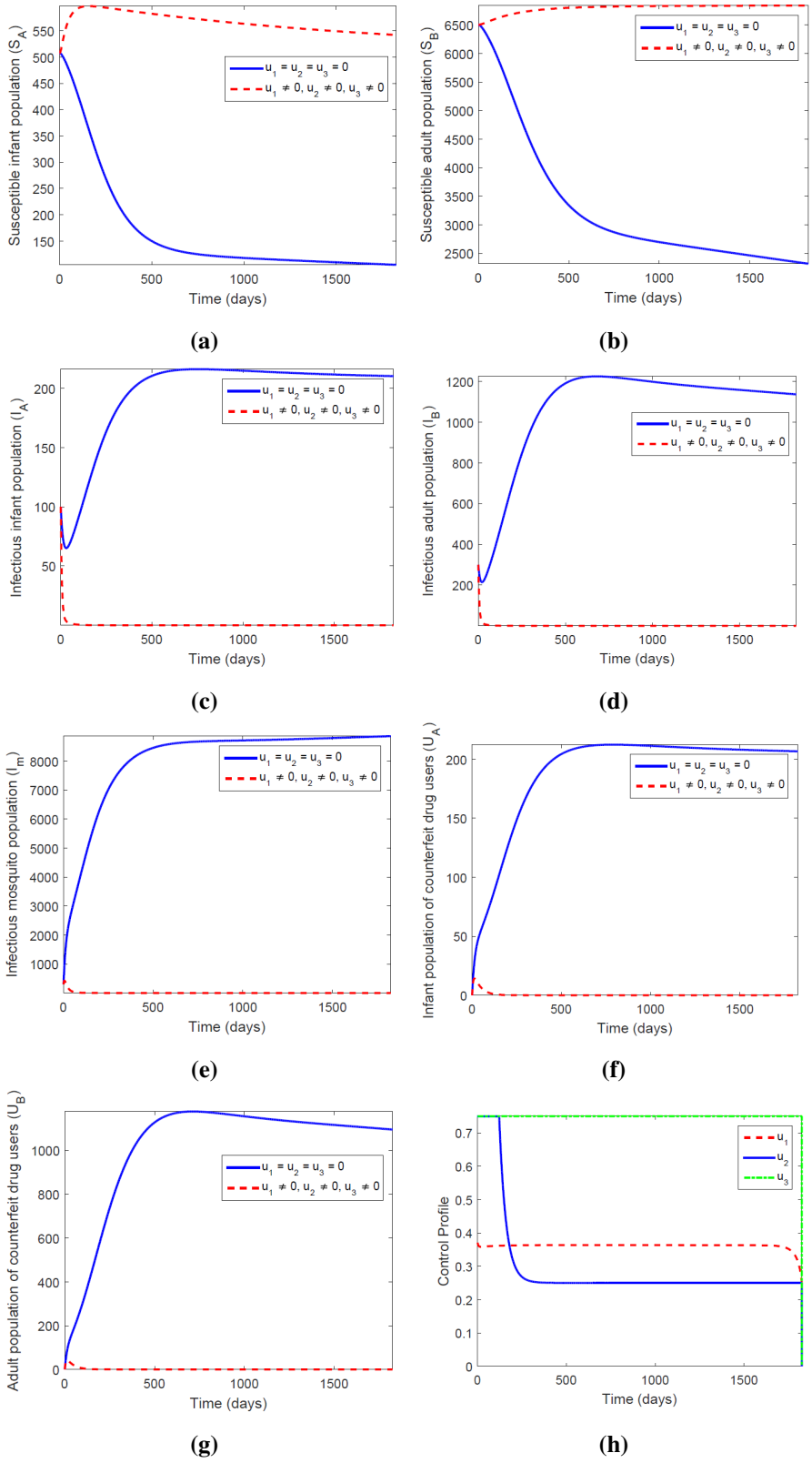

Figure 13. Simulations of low removal and recrudescence rates due to the counterfeit drugs in the scenario of the optimal strategy (ITN, highly effective antimalarial drugs and IRS) with values in Table 1 – (a) S_A, (b) S_B, (c) I_A, (d) I_B, (e) I_m (f) U_A, (g)U_B and (h) the control profile.

5.3.3. Comparison of control strategies

The simulation results from all seven control strategies without counterfeit drugs (in Figures 3–9) reveal that all the strategies reduce the populations of infectious humans and infectious mosquitoes and increase the susceptible populations.

When counterfeit drug use is absent in the population, we observe that any strategy with highly effective antimalarial drugs achieves a 100% reduction in the infectious population. Still, any strategy without highly effective antimalarial drugs reduces the numbers of infectious adults and infectious mosquitoes significantly more than the number of infectious infants. Also, a strategy with only one prevention control measure, either IRS or ITNs, may be insufficient to reduce the disease burden in humans and to control malaria unless they are combined with the other controls.

Comparing the four strategies with highly effective antimalarial drugs, we observe similar benefits of the 100% reduction in the infectious populations (Figures 4, 6, 8 and 9). However, the four strategies differ in the increase in the susceptible mosquito population and the control profiles. The two strategies, (I) highly effective antimalarial drugs and indoor residual spraying and (II) insecticide-treated bednets, highly effective antimalarial drugs and indoor residual spraying, give the smallest increases in the susceptible mosquitoes numbers, which is a part of the objective of our optimal control problem. From the control profiles, the duration of the coverage of highly effective antimalarial drugs in (I) must be longer than in (II) (Figures 8(e) and 9(e)).

We observe that using the different sub-categories of counterfeit drugs without control significantly reduces the population of susceptible infants (in Figures 10–13). However, when the combination of insecticide-treated bednets, highly effective antimalarial drugs and indoor residual spraying is used as control, we observe a considerable increase in that population. We also observe that a combination of insecticide-treated bednets, highly effective antimalarial drugs and indoor residual spraying achieves a 100% reduction in the infectious population even when counterfeit drug use persists. From the control profiles in Figures 9(e), 10–13(h), we observe that the required intervention periods with high coverage are more extended when there is counterfeit drug use. This is particularly visible when applying highly effective antimalarial drugs or insecticide-treated bednets as controls. On the other hand, the rates of removal or recrudescence of counterfeit drugs seem to have no impact on the increases in the susceptible population.

Ranking the effect of the four subcategories of counterfeit drugs on the performances of the best control strategy, we see that when the counterfeit drugs used have a high removal rate and low recrudescence rate, then the control strategy has to be applied for the most extended period to achieve the elimination; this is followed by counterfeit drugs with low removal and recrudescence rates, then counterfeit drugs with high removal and recrudescence rates and, finally, counterfeit drugs with low removal rate and high recrudescence rate. Thus, counterfeit drugs with low removal and high recrudescence rates are the easiest to deal with using the considered control strategies (Figure 12(h)).

6. Discussion

A deterministic model for *P. falciparum* malaria infection in a structured human population that uses counterfeit drugs was developed. The model incorporates the infant and adult populations, users of counterfeit drugs and three malaria control measures adopted by most endemic countries in Sub-Saharan Africa, namely, highly effective antimalarial drugs (HEAs), insecticide-treated bednets (ITNs)

and indoor residual spraying (IRS). The model was developed to comprehensively understand disease transmission dynamics in children under five years, adults and mosquitoes and identify the best control strategy for disease elimination. We performed a standard analysis of the reproduction number R_0 and the equilibria. Our model revealed the possible existence of a backward bifurcation.

The R_0 and bifurcation analysis indicate that to control malaria transmission from the infectious population to others, it is necessary to reduce the value of R_0 below 1. However, this approach may not be sufficient for elimination when backward bifurcation is present. We found that a backward bifurcation occurs in our model when the birth rate of humans is lower than a determined threshold. Further, the analysis of R_0 showed that the control measures negatively impact malaria transmission. Thus, increasing coverage of the three control measures in the endemic setting through easy access, affordable pricing and individual adherence will reduce R_0 and hence the malaria burden.

Also, the optimal control analysis revealed that using any strategy without counterfeit drugs reduces the size of the infectious populations while increasing the susceptible populations, especially infants. For infectious diseases, when the infectious population is reduced, there is a reduction in the disease and the value of R_0. We also found that the ITNs-only or IRS-only strategy was less effective than the highly effective antimalarial drugs-only strategy for reducing disease in humans and mosquitoes. Thus, the ITNs-only and IRS-only strategies are only effective when used together or with highly effective antimalarial drugs. This result is supported by the evidence from previous studies [6, 7, 26], which showed that in an endemic region, where *P. falciparum* malaria infection is common, intervention strategies that involve highly effective antimalarial drugs are very effective in reducing the disease burden. In particular, our results suggest that the combination of highly effective antimalarial drugs and indoor residual spraying, and the combination of insecticide-treated bednets, highly effective antimalarial drugs and indoor residual spraying, have the best impact on malaria control and elimination. These strategies eliminate the infection from the population of infants, adults and mosquitoes, giving the highest increase in the susceptible human population and the smallest increase in the susceptible mosquito population. The study in [24] also confirmed that the combination of the three controls was the most effective, and the study in [23] even proved that the combination of highly effective antimalarial drugs and indoor residual spraying was the most cost-effective. Considering which of these two strategies should be adopted must be guided by the availability of resources, possible levels of coverage and their cost.

Finally, we observed that using the combination of insecticide-treated bednets, highly effective antimalarial drugs and indoor residual spraying as a control strategy, where counterfeit drugs persist, requires an increase in the duration of the coverage, especially for highly effective antimalarial drugs and insecticide-treated bednets, to achieve elimination. This increase is the highest when counterfeit drugs have high removal and low recrudescence rates. Since the counterfeit drug users remain asymptomatically infectious and may not seek further treatment, if many people in a community are using counterfeit drugs as an alternative to highly effective antimalarial drugs, then more resources, effort, time and funds will be required to control and possibly eliminate the disease [2]. Efforts to determine the level of use of counterfeit drugs are thus necessary to decide how an intervention can be properly implemented, especially when resources are scarce [58].

Our results exposed the negative impact of counterfeit drugs, even when the best control strategies were used. Hence, we conjecture that the effects will worsen when other strategies are used. The counterfeit drug effects could also be further compounded when factors such as the effects of

environment, weather and movement of both humans and mosquitoes [25, 33, 54, 59, 60] on the disease dynamics and control are considered.

7. Conclusions

The control and possible elimination of malaria can be achieved if the existing control strategies of insecticide-treated bednets, vector control methods and prompt treatment of infected humans with highly effective antimalarial drugs are accessible, affordable and duly implemented. This will also relieve infants under five years of the burden of the disease. However, the widespread use of counterfeit drugs may jeopardize the timely achievement of the malaria elimination milestones, especially in endemic areas.

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Conflict of interest

The authors declare there is no conflict of interest.

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Appendix

A.1.

The associated non-negative matrix F and the non-singular M-matrix V of (2.1)–(2.10) are, respectively, given by

$$\mathbf{F} = \begin{pmatrix} 0 & 0 & 0 & 0 & q_1 \\ 0 & 0 & 0 & 0 & q_2 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ q_3 & \pi_1 q_3 & \pi_2 q_3 & \pi_3 q_3 & 0 \end{pmatrix}, \mathbf{V} = \begin{pmatrix} d_1 & 0 & -\xi_A & 0 & 0 \\ -\tau & d_2 & 0 & -\xi_B & 0 \\ -\eta_A & 0 & d_3 & 0 & 0 \\ 0 & -\eta_B & -\tau & d_4 & 0 \\ 0 & 0 & 0 & 0 & \mu_m + \varphi u_3 \end{pmatrix},$$

where

$$q_1 = a(1-u_1)e^{-\mu_h n_h}\beta_A \frac{\mu_h}{(\tau+\mu_h)}, q_2 = b(1-u_1)e^{-\mu_h n_h}\beta_B \frac{\tau}{(\tau+\mu_h)}, q_3 = c(1-u_1)e^{-\mu_m n_m}\beta_m^* \frac{r_m K \mu_h}{\alpha_h \alpha_m},$$
$$d_1 = \delta_A + \eta_A + u_2\gamma_A + \gamma_1 + \tau + \mu_h, d_2 = \delta_B + \eta_B + u_2\gamma_B + \gamma_2 + \mu_h, d_3 = \xi_A + \tau + \mu_h, d_4 = \xi_B + \theta + \mu_h.$$

Further calculation gives V^{-1}, FV^{-1} and $\rho(FV^{-1})$ as follows:

$$V^{-1} = \begin{pmatrix} \frac{d_3}{d_1d_3 - \xi_A\eta_A} & 0 & \frac{\xi_A}{d_1d_3 - \xi_A\eta_A} & 0 & 0 \\ \frac{\tau(\xi_B\eta_A + d_3d_4)}{(d_1d_3 - \xi_A\eta_A)(d_2d_4 - \xi_B\eta_B)} & \frac{d_4}{d_2d_4 - \xi_B\eta_B} & \frac{\tau(d_1\xi_B + d_4\xi_A)}{(d_1d_3 - \xi_A\eta_A)(d_2d_4 - \xi_B\eta_B)} & \frac{\xi_B}{d_2d_4 - \xi_B\eta_B} & 0 \\ \frac{\eta_A}{d_1d_3 - \xi_A\eta_A} & 0 & \frac{d_1}{d_1d_3 - \xi_A\eta_A} & 0 & 0 \\ \frac{\tau(d_2\eta_A + d_3\eta_B)}{(d_1d_3 - \xi_A\eta_A)(d_2d_4 - \xi_B\eta_B)} & \frac{\eta_B}{d_2d_4 - \xi_B\eta_B} & \frac{\tau(\xi_A\eta_B + d_1d_2)}{(d_1d_3 - \xi_A\eta_A)(d_2d_4 - \xi_B\eta_B)} & \frac{d_2}{d_2d_4 - \xi_B\eta_B} & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{\mu_m + \varphi u_3} \end{pmatrix},$$

and

$$FV^{-1} = \begin{pmatrix} 0 & 0 & 0 & 0 & Z_1 \\ 0 & 0 & 0 & 0 & Z_2 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ Z_3 & Z_4 & Z_5 & Z_6 & 0 \end{pmatrix},$$

with

$Z_1 = \frac{q_1}{\mu_m + \varphi u_3}$, $Z_2 = \frac{q_2}{\mu_m + \varphi u_3}$, $Z_3 = \frac{q_3d_3 + q_3\pi_2\eta_A}{d_1d_3 - \xi_A\eta_A} + \frac{q_3\pi_1\tau(d_3d_4 + \xi_B\eta_A) + q_3\pi_3\tau(d_2\eta_A + d_3\eta_B)}{(d_1d_3 - \xi_A\eta_A)(d_2d_4 - \xi_B\eta_B)}$,

$Z_4 = \frac{q_3\pi_1d_4 + q_3\pi_3\eta_B}{d_2d_4 - \xi_B\eta_B}$, $Z_5 = \frac{q_3\xi_A + q_3\pi_2}{d_1d_3 - \xi_A\eta_A} + \frac{q_3\pi_1\tau(d_1\xi_B + d_4\xi_A) + q_3\pi_3\tau(d_1d_2 + \xi_A\eta_B))}{(d_1d_3 - \xi_A\eta_A)(d_2d_4 - \xi_B\eta_B)}$

and $Z_6 = \frac{q_3\pi_1d_2 + q_3\pi_3\eta_B}{d_2d_4 - \xi_B\eta_B}$.

The spectral radius of $FV^{-1} = \sqrt{Z_1Z_3 + Z_2Z_4}$.

A.2.

The Jacobian matrix of the transformed systems (3.6)–(3.15) evaluated at the DFE, E_0, with $\beta_m = \beta_m^*$, is given by

$$J_{E_0} = \begin{pmatrix} -J_1 & 0 & 0 & 0 & 0 & 0 & \phi_A & 0 & 0 & -q_1 \\ \tau & -\mu_h & 0 & 0 & 0 & \theta & 0 & \phi_B & 0 & -q_2 \\ 0 & 0 & -d_1 & 0 & \xi_A & 0 & 0 & 0 & 0 & q_1 \\ 0 & 0 & \tau & -d_2 & 0 & \xi_B & 0 & 0 & 0 & q_2 \\ 0 & 0 & \eta_A & 0 & -d_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \eta_B & \tau & -d_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & u_2\gamma_A + \gamma_1 & 0 & 0 & 0 & -J_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & u_2\gamma_B + \gamma_2 & 0 & 0 & \tau & -J_3 & 0 & 0 \\ 0 & 0 & -q_3 & -\pi_1q_3 & -\pi_2q_3 & -\pi_3q_3 & 0 & 0 & -r_m & \alpha_m - 2r_m \\ 0 & 0 & q_3 & \pi_1q_3 & \pi_2q_3 & \pi_3q_3 & 0 & 0 & 0 & -(\mu_m + \varphi u_3) \end{pmatrix},$$

where $r_m = \alpha_m - \mu_m - \varphi u_3$, $J_1 = \tau + \mu_h$, $J_2 = \phi_A + \tau + \mu_h$, $J_3 = \phi_B + \mu_h$.

The right eigenvector corresponding to the zero eigenvalue of J_{E_0} is given by

$$w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10})^T,$$

where

$$w_1 = \frac{\phi_A(u_2\gamma_A + \gamma_1)d_3 - J_2B_1}{J_1J_2\eta_A}w_5 < 0, \quad w_3 = \frac{d_3}{\eta_A}w_5, \quad w_4 = \frac{\tau q_1B_4 + q_2d_4B_1}{q_1\eta_AB_2}w_5,$$
$$w_5 = w_5, \quad w_6 = \frac{\tau q_1B_5 + q_2\eta_BB_1}{q_1\eta_AB_2}w_5, \quad w_7 = \frac{(u_2\gamma_A + \gamma_1)d_3}{J_2\eta_A}w_5, \quad w_{10} = \frac{B_1}{q_1\eta_A}w_5,$$
$$w_2 = \frac{\tau q_1(B_6 - J_2J_3B_1B_2) + q_2J_2B_1(B_7 - J_3B_2)}{q_1\eta_AB_2J_1J_2J_3\mu_h}w_5 < 0,$$
$$w_8 = \frac{q_2(u_2\gamma_B + \gamma_2)d_4J_2B_1 + \tau q_1((u_2\gamma_A + \gamma_1)d_3B_2 + (u_2\gamma_B + \gamma_2)J_2B_4)}{q_1\eta_AJ_2J_3B_2}w_5$$

and

$$w_9 = -\left[\frac{B_8 + (2r_m - \alpha_m)B_1B_2}{r_mq_1\eta_AB_2}\right]w_5 < 0,$$

with $B_1 = d_1d_3 - \xi_A\eta_A$, $B_2 = d_2d_4 - \xi_B\eta_B$, $B_4 = d_3d_4 + \xi_B\eta_A$, $B_5 = d_3\eta_B + d_2\eta_A$, $B_6 = (u_2\gamma_A + \gamma_1)d_3B_2(J_3\phi_A + J_1\phi_B) + J_1J_2(J_3\theta B_5 + \phi_B(u_2\gamma_B + \gamma_2)B_4)$, $B_7 = J_3\eta_B\theta + \phi_B(u_2\gamma_B + \gamma_2)d_4$ and $B_8 = q_1q_3[B_2(d_3 + \pi_2\eta_A) + \tau(\pi_1B_4 + \pi_3B_5)] + q_2q_3B_1(\pi_1d_4 + \pi_3\eta_B)$.

We note that $B_6 - J_2J_3B_1B_2 < 0$, $B_7 - J_3B_2 < 0$, and $B_8 > (\alpha_m - 2r_m)B_1B_2$.
Similarly, the left eigenvector corresponding to the zero eigenvalue of J_{E_0} is given by

$$v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}),$$

where

$$v_3 = \frac{(\mu_m + \varphi u_3)B_2 - q_2q_3(\pi_1d_4 + \pi_3\eta_B)}{q_1B_2}v_{10}, \quad v_4 = \frac{q_3(\pi_1d_4 + \pi_3\eta_B)}{B_2}v_{10},$$
$$v_5 = \frac{\xi_A((\mu_m + \varphi u_3)B_2 - q_2q_3(\pi_1d_4 + \pi_3\eta_B)) + \tau q_1q_3(\pi_1\xi_B + \pi_3d_2) + \pi_2q_1q_3B_2}{q_1d_3B_2}v_{10},$$
$$v_6 = \frac{q_3(\pi_1\xi_B + \pi_3d_2)}{B_2}v_{10}, \quad v_{10} = v_{10} \quad \textit{and} \quad v_1 = v_2 = v_7 = v_8 = v_9 = 0.$$

For the transformed systems (3.6)–(3.15), the associated non-zero partial derivatives of f (evaluated at the DFE), which are needed in the computation of a_1 and b_1, are given by

$$\frac{\partial^2 f_{10}}{\partial x_3^2} = -\frac{2m\beta_mr_mK\mu_h^2}{\alpha_h^2\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_3\partial x_4} = \frac{\partial^2 f_{10}}{\partial x_4\partial x_3} = -\frac{m\beta_m(1+\pi_1)r_mK\mu_h^2}{\alpha_h^2\alpha_m},$$
$$\frac{\partial^2 f_{10}}{\partial x_3\partial x_5} = \frac{\partial^2 f_{10}}{\partial x_5\partial x_3} = -\frac{m\beta_m(1+\pi_2)r_mK\mu_h^2}{\alpha_h^2\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_3\partial x_9} = \frac{\partial^2 f_{10}}{\partial x_9\partial x_3} = \frac{m\beta_m\mu_h}{\alpha_h},$$
$$\frac{\partial^2 f_{10}}{\partial x_3\partial x_6} = \frac{\partial^2 f_{10}}{\partial x_6\partial x_3} = -\frac{m\beta_m(1+\pi_3)r_mK\mu_h^2}{\alpha_h^2\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_4^2} = -\frac{2m\beta_m\pi_1r_mK\mu_h^2}{\alpha_h^2\alpha_m},$$

$$\frac{\partial^2 f_{10}}{\partial x_4 \partial x_5} = \frac{\partial^2 f_{10}}{\partial x_5 \partial x_4} = -\frac{m\beta_m(\pi_1+\pi_2)r_m K\mu_h^2}{\alpha_h^2\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_4 \partial x_9} = \frac{\partial^2 f_{10}}{\partial x_9 \partial x_4} = \frac{m\beta_m\pi_1\mu_h}{\alpha_h},$$
$$\frac{\partial^2 f_{10}}{\partial x_4 \partial x_6} = \frac{\partial^2 f_{10}}{\partial x_6 \partial x_4} = -\frac{m\beta_m(\pi_1+\pi_3)r_m K\mu_h^2}{\alpha_h^2\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_5^2} = -\frac{2m\beta_m\pi_2 r_m K\mu_h^2}{\alpha_h^2\alpha_m},$$
$$\frac{\partial^2 f_{10}}{\partial x_5 \partial x_6} = \frac{\partial^2 f_{10}}{\partial x_6 \partial x_5} = -\frac{m\beta_m(\pi_2+\pi_3)r_m K\mu_h^2}{\alpha_h^2\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_5 \partial x_9} = \frac{\partial^2 f_{10}}{\partial x_9 \partial x_5} = \frac{m\beta_m\pi_2\mu_h}{\alpha_h},$$
$$\frac{\partial^2 f_{10}}{\partial x_6^2} = -\frac{2m\beta_m\pi_3 r_m K\mu_h^2}{\alpha_h^2\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_6 \partial x_9} = \frac{\partial^2 f_{10}}{\partial x_9 \partial x_6} = \frac{m\beta_m\pi_3\mu_h}{\alpha_h},$$
$$\frac{\partial^2 f_{10}}{\partial x_3 \partial \beta_m^*} = \frac{m r_m K\mu_h}{\alpha_h\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_4 \partial \beta_m^*} = \frac{m\pi_1 r_m K\mu_h}{\alpha_h\alpha_m},$$
$$\frac{\partial^2 f_{10}}{\partial x_5 \partial \beta_m^*} = \frac{m\pi_2 r_m K\mu_h}{\alpha_h\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_6 \partial \beta_m^*} = \frac{m\pi_3 r_m K\mu_h}{\alpha_h\alpha_m},$$

where $m = c(1-u_1)e^{-\mu_m n_m}$. For $i = 1, 2, 7, 8$,

$$\frac{\partial^2 f_{10}}{\partial x_3 \partial x_i} = \frac{\partial^2 f_{10}}{\partial x_i \partial x_3} = -\frac{m\beta_m r_m K\mu_h^2}{\alpha_h^2\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_4 \partial x_i} = \frac{\partial^2 f_{10}}{\partial x_i \partial x_4} = -\frac{m\beta_m\pi_1 r_m K\mu_h^2}{\alpha_h^2\alpha_m},$$
$$\frac{\partial^2 f_{10}}{\partial x_5 \partial x_i} = \frac{\partial^2 f_{10}}{\partial x_i \partial x_5} = -\frac{m\beta_m\pi_2 r_m K\mu_h^2}{\alpha_h^2\alpha_m}, \frac{\partial^2 f_{10}}{\partial x_6 \partial x_i} = \frac{\partial^2 f_{10}}{\partial x_i \partial x_6} = -\frac{m\beta_m\pi_3 r_m K\mu_h^2}{\alpha_h^2\alpha_m}.$$

A.3.

The parameters in the endemic equilibrium, E_e, and (3.5) are defined as follows:

$$\begin{aligned}
u &= a(1-u_1)e^{-\mu_h n_h}, \quad \sigma = \frac{b\beta_B}{a\beta_A}, \quad K_h = \frac{\alpha_h}{\mu_h}, \quad K_m = \frac{r_m K}{\alpha_m},\\
C_1 &= \tau\alpha_h\sigma D_4 u, \quad C_2 = \tau\alpha_h(\sigma D_2 + D_5), \quad C_3 = D_1 D_3\sigma, \quad C_4 = B_2 J_3 D_1\mu_h\\
&\quad +B_1 J_1 J_2 D_3\sigma, \quad C_5 = B_1 B_2 J_1 J_2 J_3\mu_h, \quad C_6 = \alpha_h d_3 J_2 u, \quad C_7 = \alpha_h B_1 J_2,\\
D_1 &= (B_1 J_2 - \phi_A(u_2\gamma_A+\gamma_1)d_3)u, \quad D_2 = B_1 J_2 J_3 d_4 u, \quad D_3 = [B_2 J_3 - (\phi_B(u_2\gamma_B+\gamma_2)d_4\\
&\quad +\eta_B\theta J_3)]u, \quad D_4 = [J_2 J_3(B_4+\theta\eta_A) + d_3 d_4\phi_B(u_2\gamma_A+\gamma_1)]u, \quad D_5 = J_2 J_3 B_4\mu_h u,\\
E_1 &= C_3 C_6(d_4(d_3+\pi_2\eta_A)+\tau\pi_3\eta_A) + C_1 D_1(d_3(\pi_1 d_4+\pi_3\eta_B)), \quad E_2 = C_4 C_6(d_4(d_3+\pi_2\eta_A)+\\
&\quad \tau\pi_3\eta_A) + (C_2 D_1 + B_1 J_1 J_2 C_1)(d_3(\pi_1 d_4+\pi_3\eta_B)), \quad E_3 = C_5 C_6(d_4(d_3+\pi_2\eta_A)+\\
&\quad \tau\pi_3\eta_A) + B_1 J_1 J_2 C_2(d_3(\pi_1 d_4+\pi_3\eta_B)), \quad E_4 = C_3 D_1, \quad E_5 = C_4 D_1 + B_1 J_1 J_2 C_3,\\
E_6 &= C_5 D_1 + B_1 J_1 J_2 C_4, \quad E_7 = B_1 J_1 J_2 C_5, \quad E_8 = \alpha_h E_4 - (\delta_A C_3 C_6 + \delta_B C_1 D_1),\\
E_9 &= \alpha_h E_5 - (\delta_A C_4 C_6 + \delta_B(C_2 D_1 + B_1 J_1 J_2 C_1)), \quad E_{10} = \alpha_h E_6 - (\delta_A C_5 C_6 + \delta_B B_1 J_1 J_2 C_2),\\
F_1 &= mK_m\mu_h\beta_m E_1, \quad F_2 = mK_m\mu_h\beta_m E_2, \quad F_3 = mK_m\mu_h\beta_m E_3,\\
F_4 &= m\mu_h\beta_m E_1 + (\mu_m+\varphi u_3)d_3 d_4 E_8, \quad F_5 = m\mu_h\beta_m E_2 + (\mu_m+\varphi u_3)d_3 d_4 E_9,\\
F_6 &= m\mu_h\beta_m E_3 + (\mu_m+\varphi u_3)d_3 d_4 E_{10}, \quad F_7 = \alpha_h(\mu_m+\varphi u_3)d_3 d_4 E_7,\\
G_1 &= \delta_A C_3 C_6 + \delta_B C_1 D_1, G_2 = \delta_A C_4 C_6 + \delta_B(C_2 D_1 + B_1 C_1 J_1 J_2), G_3 = \delta_A C_5 C_6 + \delta_B B_1 C_2 J_1 J_2,\\
K_0 &= \tau d_3 d_4 J_2 J_3 C_5 C_7, K_1 = \tau d_3 d_4 J_2 J_3 C_4 C_7 + \theta J_2 J_3 L_3 + d_3 d_4\phi_B L_6,
\end{aligned}$$

$$
\begin{aligned}
K_2 &= \tau d_3 d_4 J_2 J_3 C_3 C_7 + \theta J_2 J_3 L_2 + d_3 d_4 \phi_B L_5, \quad K_3 = \theta J_2 J_3 L_1 + d_3 d_4 \phi_B L_4, \quad K_4 = u\sigma E_4,\\
K_5 &= u\sigma E_5 + \mu_h E_4, \quad K_6 = u\sigma E_6 + \mu_h E_5, \quad K_7 = u\sigma E_7 + \mu_h E_6, \quad K_8 = \mu_h E_7,\\
L_1 &= \tau\eta_A C_3 C_6 + d_3\eta_B C_1 D_1, L_2 = \tau\eta_A C_4 C_6 + d_3\eta_B B_1 C_1 J_1 J_2 + d_3\eta_B C_2 D_1,\\
L_3 &= \tau\eta_A C_5 C_6 + d_3\eta_B B_1 C_2 J_1 J_2, L_4 = \tau(u_2\gamma_A + \gamma_1) C_3 C_6 + J_2(u_2\gamma_B + \gamma_2) C_1 D_1,\\
L_5 &= \tau(u_2\gamma_A + \gamma_1) C_5 C_6 + J_2(u_2\gamma_B + \gamma_2) C_2 D_1 + (u_2\gamma_B + \gamma_2) B_1 C_1 J_1 J_2^2,\\
L_6 &= \tau(u_2\gamma_A + \gamma_1) C_5 C_6 + (u_2\gamma_B + \gamma_2) B_1 C_2 J_1 J_2^2.
\end{aligned}
$$

The coefficients of (3.5) are defined as

$$
\begin{aligned}
P_6 &= F_4(K_h E_4 - G_1), \quad P_5 = F_5(K_h E_4 - G_1) + F_4(K_h E_5 - G_2) - ua\beta_A E_4 F_1,\\
P_4 &= F_6(K_h E_4 - G_1) + F_5(K_h E_5 - G_2) + F_4(K_h E_6 - G_3) - ua\beta_A(E_4 F_2 + E_5 F_1),\\
P_3 &= F_7(K_h E_4 - G_1) + F_6(K_h E_5 - G_2) + F_5(K_h E_6 - G_3) + K_h E_7 F_4 - ua\beta_A(E_4 F_3\\
&\quad + E_5 F_2 + E_6 F_1), \quad P_2 = F_7(K_h E_5 - G_2) + F_6(K_h E_6 - G_3) + K_h E_5 F_7 - ua\beta_A(E_5 F_3\\
&\quad + E_6 F_2 + E_7 F_1), \quad P_1 = F_7(K_h E_6 - G_3) + K_h E_7 F_6 - ua\beta_A(E_7 F_2 + E_6 F_3),\\
P_0 &= K_h E_7 F_7 - ua\beta_A E_7 F_3 = K_h E_7 F_7(1 - R_0^2).
\end{aligned}
$$

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