On a drug-resistant malaria model with susceptible individuals without access to basic amenities

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Abstract In this paper, a deterministic malaria transmission model in the presence of a drug-resistant strain is investigated. The model is studied using stability theory of differential equations, optimal control, and computer simulation. The threshold condition for disease-free equilibrium is found to be locally asymptotically stable and can only be achieved in the absence of a drug-resistant strain in the population. The existence of multiple endemic equilibria is also established. Both the Sensitivity Index (SI) of the model parameters and the Incremental Cost-Effectiveness Ratio (ICER) for all possible combinations of the disease-control measures are determined. Our results revealed among others that the most cost-effective strategy for drug-resistant malaria control is the combination of the provision of basic amenities (such as access to clean water, electricity, good roads, health care, and education) and treatment of infective individuals. Therefore, more efforts from policy-makers on the provisions of basic amenities and treatment of infectives would go a long way to combat the malaria epidemic.

Keywords Malaria · Drug-resistant strain · Stability · Optimality system · Sensitivity analysis

Mathematics Subject Classifications (2010) 92B05 · 93A30 · 93C15

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1 Introduction

Malaria disease incidence has been escalating at an alarming rate despite all efforts to combat the disease. Having more than 85% malaria cases occurring in Africa has generated an increasing research interest on predictive modeling of the distribution, intensity, and other factors responsible for malaria transmission. The existing methods for controlling the disease include insecticides, treated bednets, drugs for disease prevention, and treatment. However, despite all efforts, eradicating the disease has proved difficult and malaria disease still persists as a major public health problem until this moment. The inability to effectively control the disease is due to the cost associated with the interventions, availability of treatment, and the alarming rate of parasite drug-resistance and mosquito insecticide resistance.

The challenge posed by the resistance of parasites against drugs and insecticides used against mosquitoes calls for an urgent need for a better understanding of the important parameters in the disease transmission, and to develop effective and optimal strategies for the prevention and control of the spread of malaria disease.

Over the years, mathematical models have been used to provide important insights into disease behavior and intervention strategies. For instance, the study of an infectious disease model with population-dependent death rate using computer simulation was investigated by Greenhalgh [1]. To examine the impact of climate on disease spread, Ghosh et al. [2], studied the environmental effect on an SIS model for bacteria and the spread of carrier-dependent infectious diseases, like cholera and diarrhea. Anderson and May [3] derived a deterministic malaria model to investigate the effect of acquired immunity in malaria and different control measures on the transmission rate and on the disease prevalence. Hyun [4] studied a malaria-transmission model, incorporating different levels of acquired immunity and temperature-dependent parameters, also relating to global warming and local socioeconomic conditions. The authors in [5] proposed a model that accounts for acquired immunity in a mass action model.

Rafikov et al. [6] formulated a continuous model for malaria vector control with the aim of studying how genetically modified mosquitoes should be introduced in the environment using optimal control problem strategies. Kbenesh et al. [7] presented an autonomous ordinary differential equation model with vector control and treatment model and a time-dependent counter part of the model involving an optimal control of vector borne diseases with treatment and prevention as control measures. Okosun [8] and Okosun et al. [9] applied optimal control theory to a continuous malaria model that includes treatment and vaccination with waning immunity to study the impact of a possible vaccination with treatment strategies in controlling the spread of malaria. Makinde and Okosun [10] presented the impact of optimal control strategies on malaria spread with infective immigrants. None of these works considered the role of adequate provision of basic amenities on the spread of malaria and the challenge faced due to drug resistance.

The model we consider in this paper differs from those previous works because it incorporates the classes of individuals with drug-resistant strain parasites in both populations. The main question to be addressed is to what level is lack of basic amenities and drug-resistance strains influencing the spread of malaria disease.

In this study, we derive and analyze a malaria disease transmission mathematical model with individuals with drug-resistant strains. We study and determine the possible impact of control strategies on the spread of malaria. Theoretically, we analyze its stability properties and determine conditions on the parameters for the existence of equilibrium solutions. We also carried out detailed qualitative optimal control analysis of the resulting model and

we find the necessary conditions for optimal control of the disease using Pontryagin's maximum principle in order to determine optimal strategies for controlling the spread of the disease.

Our main goal is to develop a mathematical model of malaria transmission in the presence of drug-resistant strain parasites and lack of basic amenities in order to investigate the role of provision of basic amenities and drug-resistant strain parasites in malaria transmission. The paper is organized as follows, in Section 2, we derive a model consisting of ordinary differential equations (ODE) that describes the interactions between humans and mosquito populations and the underlying assumptions. In Section 3, we use Pontryagin's maximum principle to investigate analysis of control strategies and to find the necessary conditions for the optimal control of the disease. In Sections 4, we show the simulation results to illustrate the population dynamics with prevention and treatment as controls. Our conclusions are discussed in Section 5.

2 Model formulation

The model sub-divides the total human population at time t , denoted by $N_h(t)$, into the following sub-populations of susceptible individuals with access to basic amenities (i.e., water, electricity, health care, road, and education): ($S_{h1}(t)$), susceptible individuals without access to basic amenities ($S_{h2}(t)$), those humans infected by malaria parasite sensitive to drugs ($I_{h1}(t)$), humans infected by malaria parasite with drug-resistant strain ($I_{h2}(t)$), and recovered humans ($R_h(t)$). So that

$$N_h(t) = S_{h1}(t) + S_{h2}(t) + I_{h1}(t) + I_{h2}(t) + R_h(t).$$

The total vector (mosquito) population at time t , denoted by $N_v(t)$, is sub-divided into susceptible mosquitoes ($S_v(t)$), mosquitoes infected by malaria parasites sensitive to drugs ($I_{v1}(t)$) and mosquitoes infected by malaria parasites with drug-resistant strain ($I_{v2}(t)$). Thus,

$$N_v(t) = S_v(t) + I_{v1}(t) + I_{v2}(t).$$

We assume that susceptible humans with access to basic amenities are recruited into the population at a constant rate $(1 - \rho)N_h$, while a proportion ρN_h are susceptible humans without access to basic amenities. Susceptible individuals with access to basic amenities acquire malaria infection following contact with infectious mosquitoes (at a rate $\eta\beta\epsilon\phi$), where $0 \leq \eta \leq 1$ is the modification parameter on susceptible with access to basic amenities and β is the transmission probability per bite and ϵ is the per capita biting rate of mosquitoes, ϕ is contact rate of vector per human per unit time. Susceptible individuals infected with malaria parasites sensitive to drugs are moved to the infected humans with malaria parasite sensitive to drugs (I_{h1}) class and the susceptible infected with malaria parasites with drug-resistant strain move to infected humans with drug-resistant strain at the rate $\beta\epsilon\phi$. A proportion of individuals with malaria parasites sensitive to drugs after treatment progress to the effectively treated class with temporary immunity (at a rate $(1 - b)\alpha$). The proportion $b\alpha$ of treated infected humans who develop drug-resistant strains are moved to the infected humans with drug-resistant strain class. Individuals infected with severe malaria suffer a disease-induced death (at a rate ψ). Upon recovery, the recovered individual loses immunity (at the rate κ) and becomes susceptible again. π is the proportion of recovered humans that becomes susceptible again with access to basic amenities. Also, ω is the proportion of

infected humans who after treatment becomes susceptible again (without partial immunity) with access to basic amenities.

Susceptible mosquitoes (S_v) are generated at rate Λ_v ; the susceptible mosquitoes acquire malaria infection (following effective contacts with humans infected with malaria parasites sensitive to drugs, infected humans with drug-resistant strains and recovered humans) at a rate $\lambda\phi\epsilon(I_{h1} + I_{h2} + qR_h)$, where λ is the probability of a vector getting infected through an infectious human and q is the modification parameter on recovered humans due to treatment. Mosquitoes are assumed to suffer natural death at a rate μ_v , regardless of their infection status. Susceptible mosquitoes infected with malaria parasites sensitive to drugs are moved to the class of infected mosquitoes with malaria parasite sensitive to drugs (I_{v1}) and those susceptible mosquitoes infected with malaria parasites with drug-resistant strain are moved to the class of infected mosquitoes with drug-resistant strain (I_{v2}).

Thus, putting the above formulations and assumptions together gives the following human-vector model, given by system of ordinary differential equations below as

$$\begin{aligned}
 \frac{dS_{h1}}{dt} &= (1 - \rho)N_h + \pi\kappa R_h + \omega\gamma I_{h1} - \frac{\eta\beta\epsilon\phi(I_{v1} + I_{v2})S_{h1}}{N_h} - \mu_h S_{h1} + \nu S_{h2}, \\
 \frac{dS_{h2}}{dt} &= \rho N_h + (1 - \pi)\kappa R_h + (1 - \omega)\gamma I_{h1} - \frac{\beta\epsilon\phi(I_{v1} + I_{v2})S_{h2}}{N_h} - \mu_h S_{h2} - \nu S_{h2}, \\
 \frac{dI_{h1}}{dt} &= \frac{\eta\beta\epsilon\phi I_{v1}S_{h1}}{N_h} + \frac{\beta\epsilon\phi I_{v1}S_{h2}}{N_h} - (\alpha + \mu_h + \gamma)I_{h1}, \\
 \frac{dI_{h2}}{dt} &= \frac{\eta\beta\epsilon\phi I_{v2}S_{h1}}{N_h} + \frac{\beta\epsilon\phi I_{v2}S_{h2}}{N_h} + b\alpha I_{h1} - (\psi + \mu_h)I_{h2}, \\
 \frac{dR_h}{dt} &= (1 - b)\alpha I_{h1} - (\kappa + \mu_h)R_h, \\
 \frac{dS_v}{dt} &= \Lambda_v - \frac{\lambda\phi\epsilon(I_{h1} + I_{h2} + qR_h)S_v}{N_h} - \mu_v S_v, \\
 \frac{dI_{v1}}{dt} &= \frac{\lambda\phi\epsilon(I_{h1} + qR_h)S_v}{N_h} - \mu_v I_{v1}, \\
 \frac{dI_{v2}}{dt} &= \frac{\lambda\phi\epsilon I_{h2}S_v}{N_h} - \mu_v I_{v2}.
 \end{aligned} \tag{1}$$

We normalize the variables, $s_{h1} = \frac{S_{h1}}{N_h}$, $s_{h2} = \frac{S_{h2}}{N_h}$, $i_{h1} = \frac{I_{h1}}{N_h}$, $i_{h2} = \frac{I_{h2}}{N_h}$, $r_h = \frac{R_h}{N_h}$, $s_v = \frac{S_v}{N_v}$, $i_{v1} = \frac{I_{v1}}{N_v}$, $i_{v2} = \frac{I_{v2}}{N_v}$ and $m = \frac{N_v}{N_h}$, $M_v = \frac{\Lambda_v}{N_v}$. For convenience we still use $s_{h1} = S_{h1}$, $s_{h2} = S_{h2}$, $i_{h1} = I_{h1}$, $i_{h2} = I_{h2}$, $r_h = R_h$, $s_v = S_v$, $i_{v1} = I_{v1}$, $i_{v2} = I_{v2}$. The system becomes

$$\begin{aligned}
 \frac{dS_{h1}}{dt} &= (1 - \rho) + \pi\kappa R_h + \omega\gamma I_{h1} - m\eta\beta\epsilon\phi(I_{v1} + I_{v2})S_{h1} - \mu_h S_{h1} \\
 &\quad + \psi S_{h1} I_{h2} + \nu S_{h2}, \\
 \frac{dS_{h2}}{dt} &= \rho + (1 - \pi)\kappa R_h + (1 - \omega)\gamma I_{h1} - m\beta\epsilon\phi(I_{v1} + I_{v2})S_{h2} \\
 &\quad - \mu_h S_{h2} + \psi S_{h2} I_{h2} - \nu S_{h2},
 \end{aligned}$$

$$\begin{aligned}
\frac{dI_{h1}}{dt} &= m\beta\epsilon\phi I_{v1}(\eta S_{h1} + S_{h2}) - (\alpha + \mu_h + \gamma)I_{h1} + \psi I_{h1}I_{h2}, \\
\frac{dI_{h2}}{dt} &= m\beta\epsilon\phi I_{v2}(\eta S_{h1} + S_{h2}) + b\alpha I_{h1} - (\psi + \mu_h)I_{h2} + \psi I_{h2}^2, \\
\frac{dR_h}{dt} &= (1 - b)\alpha I_{h1} - (\kappa + \mu_h)R_h + \psi R_h I_{h2}, \\
\frac{dS_v}{dt} &= M_v - \lambda\phi\epsilon(I_{h1} + I_{h2} + qR_h)S_v - \mu_v S_v, \\
\frac{dI_{v1}}{dt} &= \lambda\phi\epsilon(I_{h1} + qR_h)S_v - \mu_v I_{v1}, \\
\frac{dI_{v2}}{dt} &= \lambda\phi\epsilon I_{h2}S_v - \mu_v I_{v2}.
\end{aligned} \tag{2}$$

System (2) can be reduced further by setting $S_{h1}(t) + S_{h2}(t) = 1 - I_{h1}(t) - I_{h2}(t) - R_h(t)$, which implies that,

$$\eta_1 S_{h1}(t) + S_{h2}(t) \leq S_{h1}(t) + S_{h2}(t) := 1 - I_{h1}(t) - I_{h2}(t) - R_h(t)$$

and

$$S_v = 1 - I_{v1} - I_{v2}$$

to obtain,

$$\begin{aligned}
\frac{dI_{h1}}{dt} &= m\beta\epsilon\phi I_{v1}(1 - I_{h1} - I_{h2} - R_h) - (\alpha + \mu_h + \gamma)I_{h1} + \psi I_{h1}I_{h2}, \\
\frac{dI_{h2}}{dt} &= m\beta\epsilon\phi I_{v2}(1 - I_{h1} - I_{h2} - R_h) + b\alpha I_{h1} - (\psi + \mu_h)I_{h2} + \psi I_{h2}^2, \\
\frac{dR_h}{dt} &= (1 - b)\alpha I_{h1} - (\kappa + \mu_h)R_h + \psi R_h I_{h2}, \\
\frac{dI_{v1}}{dt} &= \lambda\phi\epsilon(I_{h1} + qR_h)(1 - I_{v1} - I_{v2}) - \mu_v I_{v1}, \\
\frac{dI_{v2}}{dt} &= \lambda\phi\epsilon I_{h2}(1 - I_{v1} - I_{v2}) - \mu_v I_{v2}.
\end{aligned} \tag{3}$$

2.1 Basic properties of the malaria model

2.1.1 Positivity and boundedness of solutions

For the malaria-transmission model (2) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all times. In other words, solutions of the model system (2) with non-negative initial data will remain non-negative for all times $t > 0$.

Theorem 1 *Let the initial data $S_{h1}(0) \geq 0$, $S_{h2}(0) \geq 0$, $I_{h1}(0) \geq 0$, $I_{h2}(0) \geq 0$, $R_h(0) \geq 0$, $S_v(0) \geq 0$, $I_{v1}(0) \geq 0$, $I_{v2}(0) \geq 0$. Then the solutions $(S_h, I_{h1}, I_{h2}, R_h, S_v, I_{v1}, I_{v2})$ of the malaria model (2) are non-negative for all $t > 0$. Furthermore,*

$$\limsup_{t \rightarrow \infty} N_h(t) \leq 1 \quad \text{and} \quad \limsup_{t \rightarrow \infty} N_v(t) \leq 1$$

with,

$$N_h = S_{h1} + S_{h2} + I_{h1} + I_{h2} + R_h; \text{ and } N_v = S_v + I_{v1} + I_{v2}.$$

Proof Let $t_1 = \sup\{t > 0 : S_{h1}(t) > 0, S_{h2}(t) > 0, I_{h1}(t) > 0, I_{h2}(t) > 0, R_h(t) > 0, S_v(t) > 0, I_{v1}(t) > 0, I_{v2}(t) > 0\}$. Since $S_{h1}(0) > 0, S_{h2}(0) > 0, I_{h1}(0) > 0, I_{h2}(0) > 0, R_h(0) > 0, S_v(0) > 0, I_{v1}(0) > 0, I_{v2}(0) > 0$, then, $t_1 > 0$. If $t_1 < \infty$, then $S_{h1}, S_{h2}, I_{h1}, I_{h2}, R_h, S_v, I_{v1}$ or I_{v2} is equal to zero at t_1 . It follows from the first equation of the system (2), that

$$\frac{dS_{h1}}{dt} = (1 - \rho) - m\eta\beta\epsilon\phi(I_{v1} + I_{v2})S_{h1} - \mu_h S_{h1} + \pi\kappa R_h + \omega\gamma I_{h1} + \nu S_{h2}$$

Thus,

$$\begin{aligned} \frac{d}{dt} \{S_{h1}(t) \exp[(m\eta\beta\epsilon\phi(I_{v1} + I_{v2}) + \mu_h)t]\} &= (\mu_h + \pi\kappa R_h + \omega\gamma I_{h1} + \nu S_{h2}) \\ &\quad \times \exp[(m\eta\beta\epsilon\phi(I_{v1} + I_{v2}) - \mu_h)t] \end{aligned}$$

Hence,

$$\begin{aligned} S_{h1}(t_1) \exp[(m\eta\beta\epsilon\phi(I_{v1} + I_{v2}) + \mu_h)t_1] &- S_{h1}(0) \\ &= \int_0^{t_1} (\mu_h + \pi\kappa R_h + \omega\gamma I_{h1} + \nu S_{h2}) \exp[(m\eta\beta\epsilon\phi(I_{v1} + I_{v2}) + \mu_h)p] dp \end{aligned}$$

so that,

$$\begin{aligned} S_{h1}(t_1) &= S_{h1}(0) \exp[-(m\eta\beta\epsilon\phi(I_{v1} + I_{v2}) + \mu_h)t_1] + \exp[-(m\eta\beta\epsilon\phi(I_{v1} + I_{v2}) + \mu_h)t_1] \\ &\quad \times \int_0^{t_1} (\mu_h + \pi\kappa R_h + \omega\gamma I_{h1}) \exp[(m\eta\beta\epsilon\phi(I_{v1} + I_{v2}) + \mu_h)p] dp > 0. \end{aligned}$$

and

$$\begin{aligned} R_h(t_1) &= R_h(0) \exp[-(\mu_h + \kappa)t_1] + \exp[(\mu_h + \kappa)t_1] \\ &\quad \times \int_0^{t_1} \alpha(1 - b)I_h \exp[(\mu_h + \kappa)p] dp > 0. \end{aligned}$$

It can similarly be shown that $S_{h2} > 0, I_{h1} > 0, I_{h2} > 0, S_v > 0, I_{v1} > 0$ and $I_{v2} > 0$ for all $t > 0$. For the second part of the proof, it should be noted that $0 < I_{h1}(t) \leq N_h(t)$ and $0 < I_{v1}(t) \leq N_v(t)$.

Adding the first four equations and the last three equations of the model (2) gives

$$\begin{aligned} \frac{dN_h(t)}{dt} &= \mu_h - \mu_h N_h(t) - \psi I_{h2}(t), \\ \frac{dN_v(t)}{dt} &= \mu_v - \mu_v N_v(t). \end{aligned} \quad (4)$$

Thus,

$$\begin{aligned} \mu_h - (\mu_h + \psi)N_h(t) &\leq \frac{dN_h(t)}{dt} \leq \mu_h - \mu_h N_h(t), \\ \mu_v - \mu_v N_v(t) &\leq \frac{dN_v(t)}{dt} \leq \mu_v - \mu_v N_v(t). \end{aligned}$$

Hence, respectively

$$\frac{\mu_h}{\mu_h + \psi} \leq \liminf_{t \rightarrow \infty} N_h(t) \leq \limsup_{t \rightarrow \infty} N_h(t) \leq \frac{\mu_h}{\mu_h},$$

and,

$$\frac{\mu_v}{\mu_v} \leq \liminf_{t \rightarrow \infty} N_v(t) \leq \limsup_{t \rightarrow \infty} N_v(t) \leq \frac{\mu_v}{\mu_v},$$

as required. $\square$

2.1.2 Invariant regions

The malaria model (2) will be analyzed in a biologically feasible region as follows. The system (2) is split into two parts, namely the human population (N_h ; with $N_h = S_{h1} + S_{h2} + I_{h1} + I_{h2} + R_h$) and the vector population (N_v ; with $N_v = S_v + I_{v1} + I_{v2}$). Consider the feasible region

$$\mathcal{D} = \mathcal{D}_h \cup \mathcal{D}_v \subset \mathbb{R}_+^5 \times \mathbb{R}_+^3$$

with,

$$\mathcal{D}_h = \{(S_{h1}, S_{h2}, I_{h1}, I_{h2}, R_h) \in \mathbb{R}_+^5 : S_{h1} + S_{h2} + I_{h1} + I_{h2} + R_h \leq 1\},$$

and

$$\mathcal{D}_v = \{(S_v, I_{v1}, I_{v2}) \in \mathbb{R}_+^3 : S_v + I_{v1} + I_{v2} \leq 1\}.$$

The following steps are followed to establish the positive invariance of $\mathcal{D}$ (i.e., solutions in $\mathcal{D}$ remain in $\mathcal{D}$ for all $t > 0$). The rate of change of the human and mosquito populations is given in Eq. (4); it follows that

$$\begin{aligned} \frac{dN_h(t)}{dt} &\leq \mu_h - \mu_h N_h(t), \\ \frac{dN_v(t)}{dt} &\leq \mu_v - \mu_v N_v(t). \end{aligned} \quad (5)$$

A standard comparison theorem [11] can then be used to show that $N_h(t) \leq N_h(0)e^{-\mu_h t} + (1 - e^{-\mu_h t})$ and $N_v(t) \leq N_v(0)e^{-\mu_v t} + (1 - e^{-\mu_v t})$. In particular, $N_h(t) \leq 1$ and $N_v(t) \leq 1$ if $N_h(0) \leq 1$ and $N_v(0) \leq 1$ respectively. Thus, the region $\mathcal{D}$ is positively invariant. Hence, it is sufficient to consider the dynamics of the flow generated by (2) in $\mathcal{D}$. In this region, the model can be considered as being epidemiologically and mathematically well posed [12]. Thus, every solution of the basic model (2) with initial conditions in $\mathcal{D}$ remains in $\mathcal{D}$ for all $t > 0$. Therefore, the ω -limit sets of the system (2) are contained in $\mathcal{D}$. This result is summarized below.

Lemma 1 *The region $\mathcal{D} = \mathcal{D}_h \cup \mathcal{D}_v \subset \mathbb{R}_+^5 \times \mathbb{R}_+^3$ is positively invariant for the basic model (2) with non-negative initial conditions in $\mathbb{R}_+^8$*

2.2 Stability of the disease-free equilibrium (DFE)

The malaria model (2) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\mathcal{E}_0 = (S_{h1}^*, S_{h2}^*, I_{h1}^*, I_{h2}^*, R_h^*, S_v^*, I_{v1}^*, I_{v2}^*) = \left(\frac{v + \mu_h(1 - \rho)}{(\mu_h + v)}, \frac{\rho}{(\mu_h + v)}, 0, 0, 0, 1, 0, 0 \right).$$

The linear stability of $\mathcal{E}_0$ can be established using the next-generation operator method [13] on the system (2), the matrices F and V , for the new infection terms and the remaining transfer terms, are, respectively, given by

$$F = \begin{pmatrix} 0 & 0 & 0 & m\beta\epsilon\phi(\eta S_{h1}^* + S_{h2}^*) & 0 \\ 0 & 0 & 0 & 0 & m\beta\epsilon\phi(\eta S_{h1}^* + S_{h2}^*) \\ 0 & 0 & 0 & 0 & 0 \\ \lambda\epsilon\phi S_v^* & 0 & q\lambda\epsilon\phi S_v^* & 0 & 0 \\ 0 & \lambda\epsilon\phi S_v^* & 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 \\ -b\alpha & k_2 & 0 & 0 & 0 \\ -(1-b)\alpha & 0 & k_3 & 0 & 0 \\ 0 & 0 & 0 & \mu_v & 0 \\ 0 & 0 & 0 & 0 & \mu_v \end{pmatrix},$$

where $k_1 = \alpha + \gamma + \mu_h$, $k_2 = \psi + \mu_h$, $k_3 = \kappa + \mu_h$. It follows that the drug-resistance free reproduction number of the malaria system (2), denoted by $\mathcal{R}_s$, is given by

$$\mathcal{R}_s = \sqrt{\frac{m\lambda\beta\phi^2\epsilon^2(\eta v + \rho + (1 - \rho)\eta\mu_h)}{(v + \mu_h)(\psi + \mu_h)\mu_v}}, \quad (6)$$

and the drug resistance reproductive number is

$$\mathcal{R}_r = \sqrt{\mathcal{R}_s^2 \frac{(\psi + \mu_h)}{(\alpha + \gamma + \mu_h)} \left(1 + \frac{(1 - b)q\alpha}{\kappa + \mu_h} \right)}. \quad (7)$$

Further, using Theorem 2 in [13], the following result is established.

Theorem 2 *The DFE of the model (2), given by $\mathcal{R}_s$, is locally asymptotically stable (LAS) if $\mathcal{R}_s < 1$, and unstable if $\mathcal{R}_s > 1$.*

2.3 Sensitivity analysis of model parameters

We carried out the sensitivity analysis to determine the model robustness to parameter values, that is, to help us know the parameters that have a high impact on the reproduction number ($\mathcal{R}_r$). Using the approach in [10, 14], we analyzed the reproduction number to

determine whether the treatment of infectives and mortality can lead to the effective elimination or control of the disease in the population.

Definition 1 The normalized forward-sensitivity index of a variable, h , that depends differentially on a parameter, l , is defined as:

$$\Upsilon_l^h := \frac{\partial h}{\partial l} \times \frac{l}{h}. \quad (8)$$

2.3.1 Sensitivity indices of $\mathcal{R}_r$

We therefore derive the sensitivity of $\mathcal{R}_r$ to each of the 13 different parameters described in Table 3. However, the expression for sensitivity indices for human natural death (μ_h), progression from susceptible without basic amenities humans (α), κ , ρ , η and progression from S_n to S_p (ν), are complex, hence we evaluate the sensitivity indices of these parameters at the baseline parameter values as given in Table 3. The sensitivity index of $\mathcal{R}_r$ with respect to β , for example is,

$$\Upsilon_\beta^{\mathcal{R}_r} := \frac{\partial \mathcal{R}_r}{\partial \beta} \times \frac{\beta}{\mathcal{R}_r} = 0.5 \quad (9)$$

The detail sensitivity indices of $\mathcal{R}_r$ resulting from the evaluation to the other parameters of the model are shown below.

$$\Upsilon_\gamma^{\mathcal{R}_r} := \frac{\partial \mathcal{R}_r}{\partial \gamma} \times \frac{\gamma}{\mathcal{R}_r} = -\frac{\gamma}{2(\alpha + \gamma + \mu_h)} \quad (10)$$

Equation (10) and Table 1 above implies that an increase in treatment γ or increase in the mosquito mortality μ_v have a positive impact in controlling malaria in the community. The parameters are arranged from the most sensitive to the least sensitive, the most sensitive parameters are the proportion of mosquitoes biting and contact rates ϵ , ϕ . Since $\Upsilon_\epsilon^{\mathcal{R}_r} = 1$,

Table 1 Sensitivity indices of model parameters to $\mathcal{R}_r$

	Parameter	Description	Sensitivity index
1	ϵ	Mosquito biting rate	1
2	ϕ	Contact rate/human/time	1
3	μ_v	Mosquito death rate	-0.5
4	β	Human rate of infection	0.5
5	λ	Mosquito rate of infection	0.5
6	ρ	Recruitment rate of S_{h2}	0.4895
7	ν	Prop of S_{h2} gaining access to amenities	-0.4894
8	γ	Treatment rate from infectious	-0.4553
9	b	Prop that develops resistance	-0.1169
10	q	Modification parameter on recovered humans	0.0971
11	κ	Recovery lose of immunity rate	-0.0612
12	α	Recovery rate from I_{h1}	0.01833
13	η	Modification parameter on susceptible	0.0105
14	μ_h	Human mortality rate	-0.001839

increasing (or decreasing) the biting rate ϵ by 10%, increases (or decreases) the $\mathcal{R}_r$ by 10%, similarly increasing (or decreasing) the contact rate, ϕ , by 10%, increases (or decreases) the $\mathcal{R}_r$ by 10%. In the same way, increasing (or decreasing) the mosquitoes' death rates μ_v , decreases (or increases) $\mathcal{R}_r$, by 5.0% and in a like manner increasing (or decreasing) the progression from S_{h2} to S_{h1} rate ν , decreases (or increases) $\mathcal{R}_r$, by 4.9%.

Reducing the number of contacts between humans and mosquitoes, through a reduction in either or both, the frequency of mosquito contact, and the mosquitoes' biting rate, would have the largest effect on disease transmission. Also, shortening the lifespan of the mosquitoes reduces the basic reproductive number because more infected mosquitoes die before they become infectious.

In the next section, we apply optimal control method using Pontryagin's maximum principle to determine the necessary conditions for the optimal control of the impact of control measures on malaria disease.

2.3.2 Existence of endemic equilibrium

Case 1 Calculating the endemic equilibrium point of the reduced system (3), we first consider the case when there is drug-resistant-induced death ($\psi \neq 0$). We obtain,

$$\begin{cases} I_{v1}^* = \frac{(1 - I_{v2}^*)(\epsilon\lambda\phi I_{h1}^* + q\epsilon\lambda\phi R_h^*)}{\mu_v + \epsilon\lambda\phi I_{h1}^* + q\epsilon\lambda\phi R_h^*}, \\ I_{v2}^* = \frac{\epsilon\lambda\phi I_{h2}^*}{\epsilon\lambda\phi(I_{h1}^* + I_{h2}^* + qR_h^*) + \mu_v}, \\ R_h^* = \frac{\alpha(1 - b)I_{h1}^*}{\kappa + \mu_h}, \end{cases} \quad (11)$$

and endemic equilibrium satisfies the following polynomial

$$P(I_{h1}^*) = AI_{h1}^* + B = 0, \quad (12)$$

where,

$$\begin{aligned} A &= a_1 I_{h2}^{*3} + a_2 I_{h2}^{*2} + a_3 I_{h2}^* + a_4, \\ B &= b_1 I_{h2}^{*4} + b_2 I_{h2}^{*3} + b_3 I_{h2}^{*2} + b_4 I_{h2}^* + b_5. \end{aligned} \quad (13)$$

Here,

$$\begin{aligned} a_1 &= -\phi\lambda\epsilon\psi^3, \\ a_2 &= m\beta\lambda\epsilon^2\phi^2\psi^2 + \epsilon\phi\lambda\psi^2((\alpha + q(1 - b)\alpha) + \gamma + 2\kappa + 3\mu_h), \\ a_3 &= -m\beta\lambda\epsilon^2\phi^2\psi((1 - b)(1 + q)\alpha + 2(\kappa + \mu_h)) - \epsilon\phi\lambda\psi((1 - b)q\alpha(\alpha + \gamma + \kappa) \\ &\quad - (2(1 + (1 - b)q)\alpha + 2(\gamma + 2\kappa) + 3\mu_h)\mu_h), \\ a_4 &= \mu_v\epsilon\phi\lambda((1 - b)q\alpha + \kappa + \mu_h)(\alpha + \gamma + \mu_h)(\kappa + \mu_h)(H\mathcal{R}_0^2 + 1), \end{aligned} \quad (14)$$

and

$$\begin{aligned}
 b_1 &= \epsilon\phi\lambda\psi^3, \\
 b_2 &= -\psi^2(\epsilon\phi\lambda(\alpha + \gamma + 2\kappa + 3\mu_h + m\beta\epsilon\phi) - \psi\mu_v), \\
 b_3 &= \mu_v\psi(\kappa + \mu_h)^2(\alpha + \gamma + \mu_h)(\mathcal{R}_v^2 + \mathcal{R}_0^2(\kappa + \mu_h + \psi) + K), \\
 b_4 &= -\mu_v(\kappa + \mu_h)^2(\alpha + \gamma + \mu_h)(\mathcal{R}_v^2(\kappa + \psi + \mu_h) + \mathcal{R}_0^2\psi(\kappa + \mu_h) - G), \\
 b_5 &= \mu_v(\kappa + \mu_h)^2(\alpha + \gamma + \mu_h)(\mathcal{R}_v^2 - 1),
 \end{aligned} \tag{15}$$

with

$$\begin{aligned}
 H &= \frac{((1-b)\alpha + \kappa + \mu_h)}{\epsilon\phi\lambda(\alpha + \gamma + \mu_h)(\kappa + \mu_h)}, \\
 G &= \frac{\psi(2(\alpha + \gamma) + \kappa + 3\mu_h)\mu_h - \epsilon\phi\lambda(\alpha + \gamma + \mu_h)(\kappa + \mu_h)}{\mu_v(\alpha + \mu_h + \gamma)(\kappa + \mu_h)^2}, \\
 K &= \frac{\psi\mu_v(\alpha + \gamma + 2\kappa + 3\mu_h) + \epsilon\phi\lambda(\kappa + \mu_h)(2(\alpha + \gamma) + \kappa + 3\mu_h)}{\mu_v(\kappa + \mu_h)^2(\alpha + \gamma + \mu_h)}, \\
 \mathcal{R}_0^2 &= \frac{m\beta\lambda\epsilon^2\phi^2}{\mu_v(\kappa + \mu_h)^2(\alpha + \gamma + \mu_h)}, \\
 \mathcal{R}_v^2 &= \mathcal{R}_0^2\left(1 + \frac{(1-b)q\alpha}{\kappa + \mu_h}\right).
 \end{aligned} \tag{16}$$

So for $\psi \neq 0$

$$I_{h1}^* = \frac{-(b_1 I_{h2}^{*4} + b_2 I_{h2}^{*3} + b_3 I_{h2}^{*2} + b_4 I_{h2}^* + b_5)}{a_1 I_{h2}^{*3} + a_2 I_{h2}^{*2} + a_3 I_{h2}^* + a_4}. \tag{17}$$

It is clear that there would exist a non-linear relationship between I_{h1}^* and I_{h2}^* , for this, the system (3) exhibits multiple endemic equilibria. This is further illustrated in Fig. 1b–d

Case 2 For the case where there is no drug-resistant-induced death ($\psi = 0$), the coefficient of A and B reduces a_4 , b_4 and b_5 , respectively

$$\begin{aligned}
 a_4 &= \mu_v((1-b)q\alpha + \kappa + \mu_h)(\alpha + \gamma + \mu_h)(\kappa + \mu_h)(H\mathcal{R}_0^2 + 1), \\
 b_4 &= -\mu_v(\kappa + \mu_h)^3(\alpha + \gamma + \mu_h)\left(\mathcal{R}_v^2 + \frac{\epsilon\phi\lambda}{\mu_v(\kappa + \mu_h)^2}\right), \\
 b_5 &= \mu_v(\kappa + \mu_h)^2(\alpha + \gamma + \mu_h)(\mathcal{R}_v^2 - 1).
 \end{aligned} \tag{18}$$

Hence,

$$I_{h1}^* = \frac{-(b_4 I_{h2}^* + b_5)}{a_4}, \tag{19}$$

It is clear that there is a linear relationship between I_{h1} and I_{h2} . From the above, we also see that $a_4 > 0$, implying that $A > 0$, for $\mathcal{R}_v < 1$, $B = b_4 I_{h2}^* + b_5 < 0$ the system (3) has a unique endemic equilibrium and when $\mathcal{R}_v > 1$, $B = b_4 I_{h2}^* + b_5 < 0$ whenever $\mathcal{R}_v^2 - 1 < \mathcal{R}_v^2 + \frac{\epsilon\phi\lambda}{\mu_v(\kappa + \mu_h)^2}$ the endemic equilibrium of system (3) exists and it is unique. Otherwise for $\mathcal{R}_v > 1$, the system (3) has no endemic equilibrium. This shows that the malaria model

Fig. 1 Simulations of the drug-resistant malaria model using the following parameter values, $b = 0.13$, $\mu_v = 0.1429$, $q = 0.01$, $\beta = 0.030$, $\mu_h = 0.4$, $\alpha = 0.82$, $\gamma = 0.7$, $\lambda = 0.09$, $\kappa = 0.7902$, $\phi = 0.502$, $\epsilon = 0.01$, $m = 0.1$, $\psi = 0.02$. **a** and **b** illustrates the relationship between I_{h1} and I_{h2} when the parameter $\psi = 0$ and $\psi \neq 0$, respectively. **c** The numerical simulation of Eq. (12), when there are no infected individuals sensitive to drug (i.e., $I_{h1} = 0$), with four (4) endemic solutions, (two (2) positive and stable endemic equilibrium and two (2) unstable endemic equilibrium). **d** The numerical simulation of Eq. (12) when there is at least one (1) infected individual sensitive to drug (i.e., $I_{h1} = 1$), with four (4) endemic solutions, (one (1) positive and stable endemic equilibrium, three (1) unstable endemic equilibrium)

with the drug-resistant strain has no disease-free equilibrium (DFE). The relationship is illustrated in Fig. 1a.

3 Analysis of optimal control

We introduce into the model (2), time-dependent control efforts on provisions of basic amenities (u_1), preventive (treated bednet) u_2 , and treatments of infected u_3 efforts as controls to curtail the spread of malaria. The malaria model (2) becomes

$$\begin{aligned} \frac{dS_{h1}}{dt} &= (1 - u_1\rho) + \pi\kappa R_h + \omega\gamma I_{h1} - (1 - u_2)m\eta\beta\epsilon\phi(I_{v1} + I_{v2})S_{h1} \\ &\quad - \mu_h S_{h1} + \psi S_{h1} I_{h2} + u_1\nu S_{h2}, \\ \frac{dS_{h2}}{dt} &= u_1\rho + (1 - \pi)\kappa R_h + (1 - \omega)\gamma I_{h1} - (1 - u_2)m\beta\epsilon\phi(I_{v1} + I_{v2})S_{h2} \\ &\quad - \mu_h S_{h2} + \psi S_{h2} I_{h2} - u_1\nu S_{h2}, \end{aligned}$$

$$\begin{aligned}
\frac{dI_{h1}}{dt} &= (1 - u_2)m\beta\epsilon\phi I_{v1}(\eta S_{h1} + S_{h2}) - (u_3\alpha + \mu_h + \gamma)I_{h1} + \psi I_{h1}I_{h2}, \\
\frac{dI_{h2}}{dt} &= (1 - u_2)m\beta\epsilon\phi I_{v2}(\eta S_{h1} + S_{h2}) + u_3b\alpha I_{h1} - (\psi + \mu_h)I_{h2} + \psi I_{h2}^2, \\
\frac{dR_h}{dt} &= (1 - b)u_3\alpha I_{h1} - (\kappa + \mu_h)R_h + \psi R_h I_{h2}, \\
\frac{dS_v}{dt} &= \mu_v - (1 - u_2)\lambda\phi\epsilon(I_{h1} + I_{h2} + qR_h)S_v - \mu_v S_v, \\
\frac{dI_{v1}}{dt} &= (1 - u_2)\lambda\phi\epsilon(I_{h1} + qR_h)S_v - \mu_v I_{v1}, \\
\frac{dI_{v2}}{dt} &= (1 - u_2)\lambda\phi\epsilon I_{h2}S_v - \mu_v I_{v2}.
\end{aligned} \tag{20}$$

For this, we consider the objective functional

$$J = \min_{u_1, u_2, u_3} \int_0^{t_f} (A_0 I_{h2} + A_1 I_{h1} + A_2 S_{h2} + A_3 u_1^2 + A_4 u_2^2 + A_5 u_3^2) dt \tag{21}$$

where A_1, A_2, A_3, A_4, A_5 are positive weights. The term $A_3 u_1^2$ is the cost of control efforts on provisions of basic amenities to minimizing the population of susceptibles without basic amenities, $A_4 u_2^2$ is the cost of control efforts on reducing human contact rate with mosquito, $A_5 u_3^2$ is the cost of control efforts on treatment of infected individuals. We choose a quadratic cost on the controls, this is similar with what is in other literature on epidemic controls [15–19]. With the given objective function $J(u_1, u_2, u_3)$, our goal is to minimize the number of carefree susceptible S_t , while minimizing the cost of control $u_1(t)$, $u_2(t)$ and $u_3(t)$. We seek an optimal control triple u_1^*, u_2^* and u_3^* such that

$$J(u_1^*, u_2^*, u_3^*) = \min\{J(u_1, u_2, u_3) | u_1, u_2, u_3 \in \mathcal{U}\} \tag{22}$$

where $\mathcal{U} = \{(u_1, u_2, u_3) \text{ such that } u_1, u_2, u_3 \text{ measurable with } 0 \leq u_1 \leq 1, 0 \leq u_2 \leq 1 \text{ and } 0 \leq u_3 \leq 1 \text{ for } t \in [0, t_f]\}$ is the control set. The necessary conditions that an optimal must satisfy come from the Pontryagin's maximum principle [20]. This principle converts (20)–(21) into a problem of minimizing point-wise a Hamiltonian H , with respect to u_1, u_2 and u_3 .

$$\begin{aligned}
H &= A_0 I_{h2} + A_1 I_{h1} + A_2 S_{h2} + A_3 u_1^2 + A_4 u_2^2 + A_5 u_3^2 \\
&\quad + \lambda_{S_{h1}}((1 - u_1)\rho) + \pi\kappa R_h + \omega\gamma I_{h1} - (1 - u_2)m\eta\beta\epsilon\phi(I_{v1} + I_{v2})S_{h1} \\
&\quad - \mu_h S_{h1} + \psi S_{h1}I_{h2} + u_1 v S_{h2}) \\
&\quad + \lambda_{S_{h2}}(u_1\rho + (1 - \pi)\kappa R_h + (1 - \omega)\gamma I_{h1} - (1 - u_2)m\beta\epsilon\phi(I_{v1} + I_{v2})S_{h2} \\
&\quad - \mu_h S_{h2} + \psi S_{h2}I_{h2} - u_1 v S_{h2} \\
&\quad + \lambda_{I_{h1}}((1 - u_2)m\beta\epsilon\phi I_{v1}(\eta S_{h1} + S_{h2}) - (u_3\alpha + \mu_h + \gamma)I_{h1} + \psi I_{h1}I_{h2}) \\
&\quad + \lambda_{I_{h2}}((1 - u_2)m\beta\epsilon\phi I_{v2}(\eta S_{h1} + S_{h2}) + u_3b\alpha I_{h1} - (\psi + \mu_h)I_{h2} + \psi I_{h2}^2 \\
&\quad + \lambda_{R_h}((1 - b)u_3\alpha I_{h1} - (\kappa + \mu_h)R_h + \psi R_h I_{h2})
\end{aligned}$$

$$\begin{aligned}
& + \lambda_{S_v} (\mu_v - (1 - u_2) \lambda \phi \epsilon (I_{h1} + I_{h2} + q R_h) S_v - \mu_v S_v) \\
& + \lambda_{I_{v1}} ((1 - u_2) \lambda \phi \epsilon (I_{h1} + q R_h) S_v - \mu_v I_{v1}) \\
& + \lambda_{I_{v2}} ((1 - u_2) \lambda \phi \epsilon I_{h2} S_v - \mu_v I_{v2})
\end{aligned} \tag{23}$$

where the $\lambda_{S_{h1}}, \lambda_{S_{h2}}, \lambda_{I_{h1}}, \lambda_{I_{h2}}, \lambda_{R_h}, \lambda_{S_v}, \lambda_{I_{v1}}$ and $\lambda_{I_{v2}}$ are the adjoint variables or shadow price. By applying Pontryagin's maximum principle [20], and the existence result for the optimal control from [21] we obtain

Theorem 3 For the optimal control triple u_1^*, u_2^* and u_3^* that minimizes $J(u_1, u_2, u_3)$ over $\mathcal{U}$, then there exist adjoint variables $\lambda_{S_{h1}}, \lambda_{S_{h2}}, \lambda_{I_{h1}}, \lambda_{I_{h2}}, \lambda_{R_h}, \lambda_{S_v}, \lambda_{I_{v1}}$ and $\lambda_{I_{v2}}$ satisfying

$$\begin{aligned}
-\frac{d\lambda_{S_{h1}}}{dt} &= ((1 - u_2) m \eta \beta \epsilon \phi (I_{v1} + I_{v2}) + \mu_h - \psi I_{h2}) \lambda_{S_{h1}} \\
&\quad - (1 - u_2) m \eta \beta \epsilon \phi (I_{v1} \lambda_{I_{h1}} + I_{v2} \lambda_{I_{h2}}), \\
-\frac{d\lambda_{S_{h2}}}{dt} &= -A_2 + u_1 v (\lambda_{S_{h2}} - \lambda_{S_{h1}}) - (1 - u_2) m \beta \epsilon \phi (I_{v1} \lambda_{I_{h1}} \\
&\quad + I_{v2} \lambda_{I_{h2}}) + ((1 - u_2) m \eta \beta \epsilon \phi (I_{v1} + I_{v2}) + \mu_h - \psi I_{h2}) \lambda_{S_{h2}}, \\
-\frac{d\lambda_{I_{h1}}}{dt} &= -A_1 - \omega \gamma \lambda_{S_{h1}} - (1 - \omega) \gamma \lambda_{S_{h2}} - u_3 b \alpha \lambda_{I_{h2}} \\
&\quad + (1 - u_2) \lambda \epsilon \phi S_v (\lambda_{S_v} - \lambda_{I_{v1}}) + (u_3 \alpha + \mu_h + \gamma) \\
&\quad - \psi I_{h2} - u_3 (1 - b) \alpha \lambda_{I_{h1}}, \\
-\frac{d\lambda_{I_{h2}}}{dt} &= -A_0 - \psi (S_{h1} \lambda_{S_{h1}} + S_{h2} \lambda_{S_{h2}} + R_h \lambda_{I_{h2}} + I_{h1} \lambda_{I_{h1}}) \\
&\quad + (\psi + \mu_h - 2 \psi I_{h2} \lambda_{I_{h2}}) + (1 - u_2) \epsilon \phi \lambda_{S_v} (\lambda_{S_v} - \lambda_{I_{v2}}), \\
-\frac{d\lambda_{R_h}}{dt} &= -\pi \kappa \lambda_{S_{h1}} - (1 - \pi) \kappa \lambda_{S_{h2}} + ((\kappa + \mu) - \psi I_{h2}) \lambda_{R_h} \\
&\quad + (1 - u_2) q \epsilon \phi \lambda_{S_v} (\lambda_{S_v} - \lambda_{I_{v1}}), \\
-\frac{d\lambda_{S_v}}{dt} &= ((1 - u_2) \lambda \epsilon \phi (I_{h1} + I_{h2} + q R_h) + \mu_v) \lambda_{S_v} - (1 - u_2) \lambda \epsilon \phi (I_{h1} + q R_h) \lambda_{I_{v1}} \\
&\quad - (1 - u_2) \lambda \epsilon \phi I_{h2} \lambda_{I_{v2}}, \\
-\frac{d\lambda_{I_{v1}}}{dt} &= (1 - u_2) m \beta \epsilon \phi (\eta S_{h1} \lambda_{S_{h1}} + S_{h2} \lambda_{S_{h2}}) - (1 - u_2) m \beta \epsilon \phi (\eta S_{h1} + S_{h2}) \lambda_{I_{h1}} \\
&\quad + \mu_v \lambda_{I_{v1}}, \\
-\frac{d\lambda_{I_{v2}}}{dt} &= (1 - u_2) m \beta \epsilon \phi (\eta S_{h1} \lambda_{S_{h1}} + S_{h2} \lambda_{S_{h2}}) - (1 - u_2) m \beta \epsilon \phi (\eta S_{h1} + S_{h2}) \lambda_{I_{h2}} \\
&\quad + \mu_v \lambda_{I_{v2}},
\end{aligned} \tag{24}$$

and with transversality conditions

$$\lambda_{S_{h1}}(t_f) = \lambda_{S_{h1}}(t_f) = \lambda_{I_{h1}}(t_f) = \lambda_{I_{h2}} = \lambda_{R_h}(t_f) = \lambda_{S_v}(t_f) = \lambda_{I_{v1}}(t_f) = \lambda_{I_{v2}}(t_f). \tag{25}$$

$$\begin{aligned} u_1^* &= \max \left\{ 0, \min \left(1, \frac{\rho(\lambda_{S_{h1}} - \lambda_{S_{h2}}) + \nu S_{h2}(\lambda_{S_{h2}} - \lambda_{S_{h1}})}{2A_3} \right) \right\}, \\ u_2^* &= \max \left\{ 0, \min \left(1, \frac{\Omega_4 + \lambda \epsilon \phi(I_{h2} \lambda_{I_{v2}} + (I_{h1} + qR_h) \lambda_{I_{v1}}) - \Omega_5}{2A_4} \right) \right\}, \\ u_3^* &= \max \left\{ 0, \min \left(1, \frac{\alpha I_{h1}(\lambda_{I_{h1}} - \rho_1 \lambda_{I_{h2}}) - (1-b)\alpha I_{h1} \lambda_{R_h}}{2A_5} \right) \right\}. \end{aligned} \quad (26)$$

where,

$$\Omega_4 = m\beta \epsilon \phi(\eta S_{h1} + S_{h2})(I_{v1} \lambda_{I_{h1}} + I_{v2} \lambda_{I_{h2}}),$$

$$\Omega_5 = \lambda \epsilon \phi(I_{h1} + I_{h2} + qR_h) S_v \lambda_{S_v} - m\beta \epsilon \phi(I_{v1} + I_{v2})(\eta S_{h1} \lambda_{S_{h1}} + S_{h2} \lambda_{S_{h2}}).$$

Proof Corollary 4.1 of [21] gives the existence of an optimal control due to 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 differentiation of the Hamiltonian function, evaluated at the optimal control. $\square$

Due to the *a priori* boundedness of the state system, adjoint system and the resulting *Lipschitz* structure of the ODEs, we obtain the uniqueness of the optimal control for small t_f . The uniqueness of the optimal control follows from the uniqueness of the optimality system, which consists of (24) and (25) with characterization (26). There is a restriction on the length of time interval in order to guarantee the uniqueness of the optimality system. This smallness restriction of the length on the time is due to the opposite time orientations of (24 and (25)); the state problem has initial values and the adjoint problem has final values. This restriction is very common in control problems [16–19].

4 Numerical results and discussion

In this section, we study numerically an optimal transmission parameter control for the drug-resistant strain malaria model. The optimal control is obtained by solving the optimality system, consisting of state system and adjoint system. An iterative scheme is used for solving the optimality system. We start to solve the state equations with a guess for the controls over the simulated time using fourth order Runge-Kutta scheme. Because of the transversality conditions (25), using the current iterations solutions of the state equation,

Table 2 The cost of the objective function under different control strategies and different weights

Para. ($A_0, A_1, A_2, A_3, A_4, A_5$)	$J(0, 0, 0)$	$J(0.25, 0.3, 0.15)$	$J(0.3, 0.4, 0.5)$	$J(0.6, 0.7, 0.8)$	$J(u_1^*, u_2^*, u_3^*)$
(700,600,200,250,100,400)	4282.3	7678.5	18271	44177	73956
(600,200,250,100,400,700)	4511.3	10369	29559	73191	1.1352e + 005
(200,250,100,400,700,600)	1910.7	12162	320098	89882	1.629e + 005
(250,100,400,700,600,200)	6142.3	16470	27251	74216	1.5241e + 005
(100,400,700,600,200,250)	10539	16712	25537	58413	1.12e + 005
(400,700,600,200,250,100)	9747	13509	181301	35856	63105

the adjoint equations are solved by a backward fourth order Runge-Kutta scheme. Then the controls are updated by using a convex combination of the previous controls and the value from the characterizations (26). This process is repeated and iterations stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iterations [22]. We examine a deterministic model with susceptible without access to basic amenities and we study its effects and treatments on the spread of malaria.

Next, we investigate numerically the effect of the following optimal control strategies on the spread of malaria in a population.

- Strategy A: Combination of provision of basic amenities and use of treated bednets
- Strategy B: Combination of provision of basic amenities and treatment of infective
- Strategy C: Combination of use of treated bednets and treatment of infective individuals
- Strategy D: Combination of provision of basic amenities, use of treated bednets and treatment of infective individuals.

Fig. 2 Simulations of the malaria model showing the effect of the optimal strategies: Provision of basic amenities and treated bednets

4.1 Numerical experiments of optimal control

We now examine the cost of the objective function under different control strategies and weights.

From Table 2, it is clear that as efforts on control strategies increases under different weight values the cost of the objective function also increases. With the highest weight value on control u_3 , the optimal cost of the objective function is much (1.1352×10^5), when the highest weight value is on minimizing the number of infected humans with the drug-resistant strain (I_{h2}), the cost of the objective function is smaller (73956). Also, allocating the highest weight value to minimizing the numbers of susceptible without access to basic amenities (S_{h2}) gives a smaller cost of the objective function (1.12×10^5). With the highest weight value on control u_2 , the optimal cost of the objective function is much (1.629×10^5), but with the highest weight value on control u_1 , the optimal cost of the objective function is higher (1.5241×10^5), if the highest weight is assigned to minimizing the numbers of infected humans sensitive to drugs I_{h1} , the optimal cost of the objective function is the smallest 63105.

Fig. 3 Simulations of the malaria model showing the effect of the optimal strategies: Provision of basic amenities and treatment of infectives

Strategy A: Optimal provision of basic amenities and use of treated bednets The provision of basic amenities control u_1 and the treated bednets control u_2 are used to optimize the objective function J while we set the treatment of infective control u_3 to zero. We observed in Fig. 2b and d that due to the control strategies, the number of infected mosquito sensitive to drugs (I_{v1}) and infected mosquito with the drug-resistant strain (I_{v2}) decreases in the community. This shows that eliminating the spread of the disease in the mosquito population would lead to an indirect reduction among the human population.

Strategy B: Optimal provision of basic amenities and treatment of infectives The provision of basic amenities control u_1 and the treatment of infective control u_3 are used to optimize the objective function J while we set treated bednets control u_2 to zero. We observed in Fig. 3a and c that this control strategy has little effect on the number of infected human sensitive to drugs (I_{h1}), while there is no significant impact on infected human with the drug-resistant strain (I_{h2}). This may be as a result of the treatment administered on infective not having an effective impact on drug-resistant strains.

Fig. 4 Simulations of the malaria model showing the effect of the optimal strategies: Treated bednets and treatment of infectives

Strategy C: Optimal use of treated bednets and treatment of infectives We optimize the objective function J using the treated bednets control u_2 and treatment of infective control u_3 while the treated bednet control u_1 is set to zero. We observed in Fig. 4b and d that due to the control strategies, the number of infected mosquitoes sensitive to drugs (I_{v1}) and infected mosquitoes with the drug-resistant strain (I_{v2}) decreases in the community, while at the same time showing little effect on the number of infected human with malaria parasites sensitive to drugs (I_{h1}), Fig. 4a and c.

Strategy D: Optimal provision of basic amenities, use of treated bednets, and treatment of infectives We use all the three controls u_1 , u_2 and u_3 to optimize the objective function J . We observed in Fig. 5b and d that due to the control strategies, the number of infected mosquitoes sensitive to drugs (I_{v1}) and infected mosquitoes with the drug-resistant strain (I_{v2}) decreases in the community, while at the same time showing little effect on the number of infected humans with malaria sensitive to drugs (I_{h1}), Fig. 5a and c.

Fig. 5 Simulations of the malaria model showing the effect of the optimal strategies: Treated bednets and treatment of infectives

Fig. 6 Simulations of the malaria model showing the effect of the optimal strategies on susceptible humans without basic amenities S_{H2} . Note the different values of u_1 , u_2 and u_3 in panels **a**, **b**, **c** and **d**

Impact of the strategies on the susceptible without access to basic amenities From the numerical simulations in Figs. 2–6 we can see that one cannot conclude which of the control strategies gives the optimal results. Strategy C and D produce similar patterns and effects, and also with a very close pattern with strategy B. We therefore need to further ascertain which of these strategies is most cost-effective and efficient. In the next section, we carry out the cost-effectiveness analysis.

4.2 Cost-effectiveness analysis

To quantify the cost-effectiveness of the control measures, we examine the cost effectiveness ratio of the strategies, so that we can draw our conclusions. There are three types of cost-effectiveness ratios: 1) the average cost-effectiveness ratio (ACER), which deals with a single intervention and evaluates that intervention against its baseline option (e.g., no intervention or current practice). It is calculated by dividing the net cost of the intervention by the total number of health outcomes prevented by the intervention. 2) the

Table 3 Description of variables and parameters of the malaria model (2)

Parameter	Description	Estimated value	Ref
ϕ	Mosquito contact rate with human	0.502 day ⁻¹	[7]
ϵ	Mosquito biting rate	0.2	[7]
β	Probability of human getting infected	0.03	[14]
λ	Probability of a mosquito getting infected	0.09	[7]
μ_h	Natural death rate in humans	0.00004 day ⁻¹	[23]
μ_v	Natural death rate in mosquitoes	0.1429 day ⁻¹	[14]
κ	Recovered individuals' loss of immunity	1/(2*365) day ⁻¹	[7]
α	Humans' progression rate from susceptible to infected	1/17 day ⁻¹	[7]
ρ	Proportion of humans with basic amenities	0.65 day ⁻¹	Assumed
Λ_v	Mosquito birth rate	1000 day ⁻¹	[7]
γ	Proportion of effectively treated individuals	0.01 - 0.7	Assumed
b	Proportion of infected who develops resistance	0.02	Assumed
q	Modification parameter of recovered humans	0.002	Assumed
ψ	Drug resistance induced death	0.05 day ⁻¹	[24]

marginal cost-effectiveness ratio (MCER) for the assessment of the specific changes in cost and effect when a program is expanded or contracted, and 3) the incremental cost-effectiveness ratio (ICER), used to compare the differences between the costs and health outcomes of two alternative intervention strategies that compete for the same resources and is generally described as the additional cost per additional health outcome (see [9])

We assume that the cost of the controls is directly proportional to the number of controls deployed. This assumption is based on the understanding that the primary goal of providing basic amenities, using treated bednets and treatment of infective individuals, is to reduce infection.

The total number of infections averted is calculated by estimating the difference between the total infectious individuals without control and the total infectious individuals with control, using the parameter values as in Table 3.

For the purpose of our study, we consider the incremental cost-effectiveness ratio (ICER). It allows us to compare the cost-effectiveness of the combination of at least two of the control strategies, use of treated bednets, treatment of infective individuals, and spray of insecticides. In ICER, when comparing two competing intervention strategies incrementally, one intervention should be compared with the next-less-effective alternative. The ICER numerator includes the differences in intervention costs, averted disease costs, costs of prevented cases, and averted productivity losses if applicable, while ICER's denominator is the difference in health outcomes (e.g., total number of infection averted, number of susceptibility cases prevented).

Based on the model simulation results, we rank the strategies in order of increasing effectiveness

Strategies	Total infection averted	Total costs (\$)	ICER
No Strategy	0	0	—
Strategy A	0.008179	\$5986	732510.19
Strategy B	1.1827	\$3464.4	−2146.91

The ICER, is calculated as follows:

$$\text{ICER(A)} = \frac{5986}{0.0081719} = 732510.19$$

$$\text{ICER(B)} = \frac{3464.4 - 5986}{1.1827 - 0.0081719} = -2146.91$$

The comparison between strategies A and B shows a cost saving of \$2146.91 for strategy B over strategy A. The negative ICER for strategy B indicates that strategy A is “strongly dominated”, that is, strategy A is more costly and less effective than strategy B. Therefore, strategy A is excluded from the set of alternatives so it does not consume limited resources.

We recalculate ICER

Strategies	Total infection averted	Total costs (\$)	ICER
Strategy B	1.1827	\$3464.4	2929.23
Strategy C	1.188	\$37213	6367660.38

The comparison between strategies B and C shows a cost saving of \$2929.33 for strategy B over strategy C. Similarly, the high ICER for strategy C indicates that strategy C is “strongly dominated”, that is, strategy C is more costly and less effective than strategy B. Therefore, strategy C is excluded from the set of alternatives so it does not consume limited resources.

We recalculate ICER

Strategies	Total infection averted	Total costs (\$)	ICER
Strategy B	1.1827	\$3464.4	2929.23
Strategy D	1.188	\$3459.9	−849

With this result, we conclude that strategy D (combination of use of treated bednets, provision of basic amenities to susceptibles, and treatment of infectives) has the least ICER and therefore is more cost-effective than strategy B. It is clear that efforts on provision of basic amenities such as access to clean water, electricity, good roads, health care, and education is more desirable for effective control of malaria.

5 Conclusions

In this paper, we derived and analyzed a deterministic model for the transmission of malaria disease in the presence of a drug-resistant strain that includes provision of basic amenities, use of treated bednets, and treatment of infectives, and performed an optimal control analysis of the model.

We derived and analyzed the necessary conditions for the optimal control of the disease. The results show that using optimal control the disease can be brought to a stable DFE equilibrium point (Fig. 7). We also investigated the cost-effectiveness of the controls to determine the most effective strategy for eliminating malaria with minimum costs. Using ICER, we found that the total cost of the objective function for using treated bednets and treatment of infective individuals as a control strategy is \$37213; this is very costly. On

Fig. 7 Simulations of the malaria model showing the effect of varying parameters ϕ and γ . We observed that no matter the values of ϕ or γ , the optimal control is stable, unlike the cases without controls. However, varying γ has no fluctuating effects on the infected mosquito with the drug-resistance strain

the other hand, the total cost of the objective function for providing basic amenities and using treated bednets is \$5986; this strategy is not very effective in eliminating the disease. Also, the total cost of the objective function for combining the treatment of infective individuals and provision of basic amenities is \$3464.4. This strategy is very effective in eliminating the disease. The costs for using the three interventions together; provision of basic amenities, use of treated bednets and treatment of infective individuals costs \$3459.9, which is lower compared to the cost of implementing strategy B. This strategy is very effective for efficient control of the disease. Strategy B (combination of treatment of infective individuals and provision of basic amenities) has a very similar impact or results as strategy D (combination of use of treated bednets, treatment of infective individuals, and provision of basic amenities) on the disease control. Where there are limited resources, we suggest that policy-makers adopt strategy B over D, which includes the additional cost of treated bednets.

We conclude that according to our model, the most cost-effective of all combinations of these three strategies for malaria control is the combination of use of treated bednets, treatment of infective individuals, and provision of basic amenities.

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