The impact of adaptive mosquito behavior and insecticide-treated nets on malaria prevalence.

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Abstract

Malaria prevalence in sub-Saharan Africa remains high. Kenya for example, records about 3.5 million new cases and 11 thousand deaths each year [1]. Most of these cases and deaths are among children under five. The main control method in malaria endemic regions has been through the use of pyrethroid-treated bed nets. Although this approach has been fairly successful, the gains are threatened by mosquito-resistance to pyrethroids, physical and chemical degradation of ITNs that reduce their efficacy, inconsistent and improper use by humans, etc. We present a model to investigate the effects of insecticide-treated bed-net use and mosquito-resistance and adaptation to pyrethroids used to treat bed nets on malaria prevalence and control in malaria endemic regions. The model captures the development and loss of resistance to insecticides, the effects of bed-net use on malaria control in a setting where proper and consistent use is not guaranteed, as well as differentiated biting of human hosts by resistant and sensitive mosquitoes. Important thresholds, including the basic reproduction number and two parameter groupings that are important for disease control and for establishing the existence of endemic equilibria to the model are calculated. Furthermore, a global sensitivity analysis is carried out to identify important parameters such as insecticide treated bed-net coverage, insecticide treated bed-net efficacy, the maximum biting rate of resistant mosquitoes, etc., that drive the system and that can be targeted for disease control. Threshold levels of bed-net coverage and bed-net efficacy required for containing the disease are identified and shown to depend on the type of insecticide-resistance. For example, when mosquito-resistance to insecticides is not permanent and is acquired only through recruitment and the efficacy of insecticide-treated nets is 90%, about 70% net coverage is required to contain malaria. However, for the same insecticide-treated net efficacy, i.e., 90%, approximately 93% net coverage is required to contain the disease when resistance to insecticides is permanent and is acquired through recruitment and mutation in adult mosquitoes. We conclude that appropriate measures to reduce or eliminate mosquito-resistance to insecticides, ensure that more people in endemic areas own and use insecticide-treated nets properly, and that the efficacy of these nets remain high most of the times, as well as educating populations in malaria endemic areas on how to keep mosquito densities low and minimize mosquito bites are important for containing malaria.

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1. Introduction

Malaria is a vector-borne disease caused by *Plasmodium* parasites and spread by infected female mosquitoes as they seek blood required for development of their eggs. There are four major types of human malaria parasites: *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae*, and *Plasmodium ovale*. *Plasmodium falciparum* and *Plasmodium vivax* are the most common forms with *Plasmodium falciparum* the most deadly type, especially in sub-Saharan Africa, where it causes more than 400,000 deaths each year [2]. More than 90% of malaria-imposed deaths occur in Africa and mostly amongst children under the age of five. The disease costs economies in endemic areas thousands of dollars in treatment, control, management and elimination efforts each year. For example, it is estimated that US $12 billion is spent annually to fight malaria [3]. In Sub-Saharan Africa, there are two main malaria transmitting vector species–*Anopheles gambiae* and it Anopheles arebiansis. *Anopheles gambiae* is the world's most effective vector of human malaria because of its susceptibility to *Plasmodium* parasites, short development time, preference for human-blood, and preference for indoor-feeding and resting [4].

The fight against endemic malaria in Sub-Saharan Africa has been stepped up within the past 15 years. Most efforts have been directed towards vector control measures, which include provision and use of Insecticide Treated Nets (ITNs) (i.e., Long Lasting Insecticide Nets (LLINs) and treated regular nets) and Indoor Residual Spraying (IRS) with insecticides, which target *Anopheles* malaria vectors. Insecticide treated nets and indoor residual spraying use synthetic chemicals called pyrethroid insecticides that kill and repel mosquitoes. These two vector intervention strategies account for 25% of the total world pyrethroids market [5]. They are widely used in Kenya, especially in regions with increased malaria prevalence and vector resistance, e.g., the Western and Coastal regions of Kenya, where malaria is endemic and is transmitted year-round with increased transmission. Malaria prevalence in these areas remains high despite the control efforts made over the years [6]. The fight against the disease in Kenya spans several decades with enhanced strategies and concerted donor country efforts yielding successful results, although only to a limited extent. Different regions report success of different control strategies ranging from awareness campaigns on the role of mosquitoes in malaria transmission, reduction of mosquito breeding sites near homes, personal and family protection through proper use of ITNs and mosquito repellents, through indoor residual spraying [4, 7]. One common observation has been that sustained vector control is a key intervention measure for any control progress to translate into the ambitious goal of malaria elimination [8–10].

Since malaria affects mostly the rural poor populations, ITNs have been very useful in reducing morbidity and mortality in these populations due to their low cost and ease in implementation [11]. Distribution of free ITNs to the most vulnerable group of humans, i.e., pregnant women and children below five has seen malaria incidence decline in Africa [1, 12–15]. In particular, ITNs have been responsible for averting approximately 68% of malaria-related

deaths in Africa [16]. Insecticide-treated nets are about 90% effective when new, however, due to several factors including natural wear and misuse, the efficacy can drop to less than 70% over the lifespan (three years). Untreated bed-nets that are in good condition or ITNs that have lost their efficacy provide about 50% protection to humans [17]. Insecticide-treated net coverage in Kenya, for example, has increased drastically from 7% in 2004 through 67% in 2006 [18], to over 80% in 2015 [19]. To realize the expected reduction in malaria transmission through the use of ITNs, ITN efficacy and coverage for at risk populations must be high enough [11]. Unfortunately, low coverage and low efficacy coupled with differentiated adherence to the use of ITNs has a negative impact on malaria control [15]. The aim of universal ITN coverage is to attain a 1:1.6 ratio in order to reduce malaria prevalence to an acceptable level. But, achieving this goal is hampered by several challenges including ITN ownership, regular wear, misuse, inconvenience (e.g., people tend to sleep out of ITNs when it is hot), human behavior, perception, and literacy level, etc. [19–23]. These confounding factors make ITN coverage and efficacy variable in endemic areas. Understanding the impact of these limitations can help us assess the effectiveness of ITNs, devise optimal control strategies using these ITNs, and guide public health policy.

Another challenge to the gains from vector control measures against malaria such as ITNs is resistance exhibited by mosquitoes to pyrethroid insecticides used in ITNs [24–26]. Insecticide-resistance is defined as the increased ability of insects to withstand or overcome the toxic, killing, or repellent effects of insecticides through natural selection and mutation. Thus, resistance is measured by the effectiveness of insecticides in killing mosquitoes, as well as the ability of some vectors to tolerate the toxic effects. For example, when mosquitoes are exposed to insecticides, the resistance is low if the mosquitoes have a 0-40% survival probability, medium if they have a 40-60% survival probability, and high if the mosquito survival probability is at least 80% [27, 28]. Mosquitoes respond to insecticide exposure behaviorally, numerically, or evolutionarily [29]. Behavioral response involves mosquitoes backing off from toxic sprays or ITNs without biting to return for a blood meal only after active ingredients in the insecticides have subsided [30–32]. Numeric response has resulted in a decline in the population of mosquitoes, as well as a shortened lifespan of mosquitoes [33–35]. Evolutionary changes occur when there is reduced sensitivity to insecticides in ITNs. In this case, there is target site blocking and increased frequency of metabolism [36–38].

Many types of mosquito resistance to insecticides have been identified. These include behavioral, metabolic, and cuticular resistance. Behavioral resistance occurs when mosquitoes adapt to human protective behavior. For example, mosquitoes might bite earlier before humans sleep under ITNs and rest outside sprayed human homes to avoid the toxicity of pyrethroids. Metabolic resistance occurs when mosquitoes undergo several mutations (causing changes to the chemical target site), which enable them to able to detoxify the chemical or withstand prolonged exposure to insecticides without being killed [39–42]. Cuticular resistance is a physical characteristic of mosquitoes, where their cuticles are thickened and the composition of the cuticle is altered in order to absorb less insecticide [43, 44]. This can result in increased resistance to insecticides [45]. Although behavioral resistance can

be acquired and lost depending on survival from exposure, metabolic and cuticular resistance are permanent, i.e. a metabolic or cuticle resistant mosquito maintains its resistance until it dies. Mosquito-resistance to insecticides is widely distributed [46] and its intensity is increasing, thus reducing the effectiveness of ITNs and other pyrethroid-related malaria control measures [29, 46]. To make matters worst, multiple resistance to insecticides have been detected in most of the countries in which malaria is endemic [47]. For example, when multiple pyrethroid-related interventions, e.g., ITN, IRS, and mosquito-repellents are used, about 3-5% of the infectious mosquitoes develop resistance [48]. The emerging increase in resistance levels coupled with normal wear, misuse of ITNs, and human behavior is a major threat to the efficacy of protection from ITNs [26]. This calls for extensive studies to understand and monitor the effects of long-term implementation of vector control measures, the emergence of insecticide-resistance and the effects of resistance on the efficacy of these control measures [29, 30, 49]. This information is important for identifying and implementing better and more effective control measures [49].

One approach that has been useful for gaining insights into the complex processes that surround the persistence of malaria is mathematical modeling (see, for example, [50–62]). Some mathematical models have focused on understanding the role of ITNs, e.g., [60, 63–68] on malaria control, while others have focused on investigating the effects of mosquito-resistance to insecticides on malaria dynamics [69–73]. Here, we investigate the impact of ITNs and the extent to which insecticide resistance affect malaria control efforts in endemic areas. We approach this through a mathematical model that incorporates ITN-use and two types of mosquitoes–sensitive and resistant mosquitoes. To our knowledge, this is the first mathematical model framework for malaria dynamics that combines ITN-use and the impact of mosquito resistance on the efficacy of ITNs to understand malaria prevalence and control.

2. Model formulation

We develop the mathematical model in this section. Key features of the model include explicit incorporation of resistance to insecticides by mosquitoes and personal protection through the use of insecticide-treated bed nets. Schematics for the model system are presented in Fig. 1. We consider a Susceptible-Infectious-Partially immune-Susceptible (SIRS) framework for the human population. That is the total human population denoted by N_h is divided into three compartmental classes–susceptible humans S_h, infected/infectious humans I_h, and partially immune humans R_h. The susceptible human population is increased by natural births that occur at rate Λ_h (we are assuming that malaria is not vertically transmissible), and when partially immune humans lose immunity at rate ρ_h. The population of this class is decreased through natural deaths that occur at per capita μ_h and through new infections from infectious mosquitoes modeled through the force of infection λ_{vh}. The infected/infectious human population increases through new infections and decreases when humans die naturally at per capita rate μ_h, acquire partial-immunity at per capita rate γ_h, or are killed by the disease at per capita rate δ_h. The partially immune human population is increased by newly immune humans from the infectious class and reduced by natural mortalities and

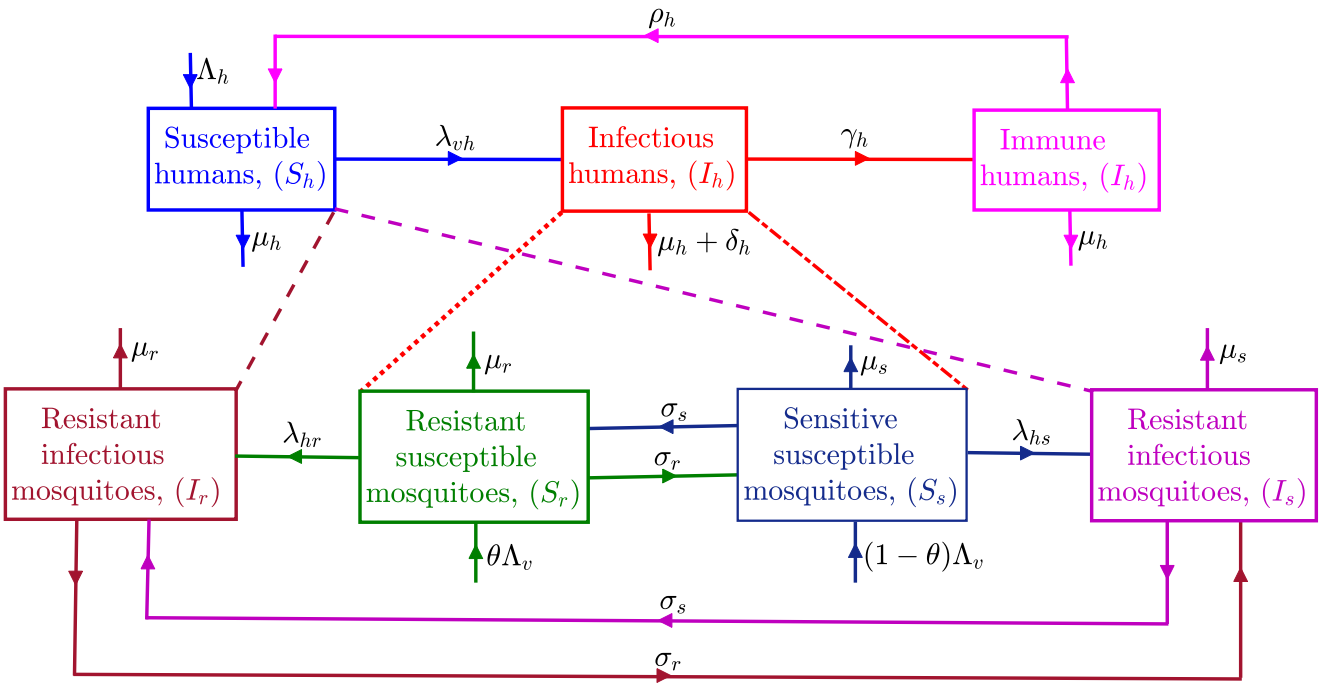

Figure 1: Model flow-chart showing the flow of humans and mosquitoes between different classes that represent the status of the disease (solid lines) and interactions between humans and mosquitoes (non solid lines). Interactions resulting in sensitive and resistant susceptible mosquito infections by infectious humans are denoted by dash-doted and dotted lines, respectively, and interactions resulting in susceptible human infections by sensitive and resistant infectious mosquitoes are denoted by dark red and light magenta dashed lines, respectively. The human population is broken down into susceptible S_h, infectious I_h, and partially immune R_h, while the mosquito population comprises susceptible sensitive and resistant (S_s and S_r, respectively,) and infectious sensitive and resistant classes (I_s and I_r, respectively). Descriptions of the transition rates (parameters) are presented in the text and in Table 1, while the forces of infection λ_{vh} and λ_{hr} are described in the text and presented in Eq (2.4).

through loss of immunity at per capita rate ρ_h. Based on this description and the schematics presented in Fig. 1, the human population and disease dynamics within the human population are described by the system of equations:

$$\begin{aligned} \dot{S}_h &= \Lambda_h + \rho_h R_h - (\lambda_{vh} + \mu_h) S_h, \\ \dot{I}_h &= \lambda_{vh} S_h - A_1 I_h, \\ \dot{R}_h &= \gamma_h I_h - A_2 R_h, \end{aligned} \tag{2.1}$$

where $A_1 = \delta_h + \mu_h + \gamma_h$, $A_2 = \mu_h + \rho_h$, and the total human population is described by: $\dot{N}_h = \Lambda_h - \mu_h N_h - \delta_h I_h$.

A Susceptible-infected/Infectious (SI) framework is used for the mosquito population. That is, the total mosquito population is broken down into susceptible and infected/infectious mosquitoes. Furthermore, each of these two groups of mosquitoes is broken down into sensitive and resistant mosquitoes leading to the following compartmental classes: sensitive susceptible mosquitoes S_s, which are susceptible mosquitoes that are not resistant to insecticides, resistant susceptible mosquitoes S_r, which are mosquitoes that have developed resistance to insecticides, sensitive infected/infectious mosquitoes I_s, and resistant infected/infectious mosquitoes, I_r. It is assumed that mosquitoes can develop, as well as lose resistance to insecticides over time depending on the efficacy

and coverage level of the treated bed nets. The development of resistance for sensitive mosquitoes occurs at per capita rate σ_s, while the loss of resistance by resistant mosquitoes occurs at per capita rate σ_r. Mortalities in the sensitive mosquito compartment occur at rate μ_s, while those within resistant mosquito compartments occur at rate μ_r. The sensitive susceptible mosquito class is increased by births occurring at rate $(1-\theta)\Lambda_v$, where $0 < \theta < 1$ is the proportion of mosquito births that are resistant and when resistant mosquitoes lose their resistance. The population of this class reduces when sensitive susceptible mosquitoes become infected by infectious humans with force of infection λ_{hs}, become resistant, die naturally, or die as a result of insecticides on nets. The sensitive infected/infectious mosquito population is increased by incoming newly infected/infectious sensitive mosquitoes and is reduced by natural deaths, insecticide-induced deaths, and when sensitive infected/infectious mosquitoes become resistant. The populations of the resistant susceptible and infectious mosquitoes are increased or reduced through similar processes, with the subscript s in the parameters replaced by the subscript r. Using this description and the schematics 1, the population and disease dynamics for the mosquitoes are described by the system of equations:

$$\begin{aligned}
\dot{S}_s &= (1-\theta)\Lambda_v + \sigma_r S_r - (\lambda_{hs} + B_1)S_s, \\
\dot{I}_s &= \lambda_{hs} S_s + \sigma_r I_r - B_1 I_s, \\
\dot{S}_r &= \theta\Lambda_v + \sigma_s S_s - (\lambda_{hr} + B_2)S_r, \\
\dot{I}_r &= \lambda_{hr} S_r + \sigma_s I_s - B_2 I_r,
\end{aligned} \tag{2.2}$$

where $B_1 = \sigma_s + \mu_s$, $B_2 = \sigma_r + \mu_r$, and the dynamics of the total mosquito population is described by the equation $\dot{N}_v = \Lambda_v - \mu_s(S_s + I_s) - \mu_r(S_r + I_r)$.

Since ITNs are designed to prevent mosquitoes from biting humans who sleep under them and also to kill mosquitoes that land on them, we follow the approach in Ngonghala et al. [60, 68] and model the mosquito mortality rate $\mu_j, j \in \{r, s\}$ by the functional form $\mu_j = \mu_j^0 + \mu_j^1 b_0 \epsilon$, where μ_i^0 is the per capita natural mortality rate of mosquitoes, μ_i^1 is the death rate of mosquitoes that land on ITNs, $0 \leq b_0 \leq 1$ is ITN coverage, and $0 \leq \epsilon \leq 1$ is the efficacy of ITNs. This implies that when ITN coverage and efficacy are high, mosquito mortalities resulting from ITN-use are also high and vice versa. We differentiate the biting rate of mosquitoes such that sensitive and resistant mosquitoes bite humans at respective rates β_{hs} and β_{hr} [74, 75]. As in Ngonghala et al. [60, 68], we model these biting rates with the functional forms: $\beta_{hs} = \beta_{hs}^{max} - (\beta_{hs}^{max} - \beta_{hs}^{min})b_0\epsilon$ and $\beta_{hr} = \beta_{hr}^{max} - (\beta_{hr}^{max} - \beta_{hr}^{min})b_0\epsilon$. Observe that for each type of mosquito, the biting rate is maximum when $b_0 = 0$ or $\epsilon = 0$, i.e., when there is no ITN coverage or there is coverage with non-effective ITNs and minimum when $b_0 = 1$ and $\epsilon = 1$, i.e., when the entire population uses highly effective ITNs. The force of infection $\lambda_{vh} = p_{vh}\left(\frac{\beta_{hs} I_s}{N_h} + \frac{\beta_{hr} I_r}{N_h}\right)$, where p_{vh} is the probability that a bite from a sensitive or resistant infectious mosquito will infect a susceptible human. On the other hand, the forces of infection λ_{hs} and λ_{hr} are given by $\lambda_{hs} = \frac{p_{hs}\beta_{hs} I_h}{N_h}$ and $\lambda_{hs} = \frac{p_{hr}\beta_{hr} I_h}{N_h}$, respectively. The full model that incorporates ITN-use, mosquito-resistance to insecticides, and differentiated infectivity captured

through different biting rates by sensitive and resistant mosquitoes is described by the nonlinear system:

$$\begin{aligned}
\dot{S}_h &= \Lambda_h + \rho_h R_h - (\lambda_{vh} + \mu_h) S_h, \\
\dot{I}_h &= \lambda_{vh} S_h - A_1 I_h, \\
\dot{R}_h &= \gamma_h I_h - A_2 R_h, \\
\dot{S}_s &= (1-\theta)\Lambda_v + \sigma_r S_r - (\lambda_{hs} + B_1) S_s \\
\dot{I}_s &= \lambda_{hs} S_s + \sigma_r I_r - B_1 I_s, \\
\dot{S}_r &= \theta \Lambda_v + \sigma_s S_s - (\lambda_{hr} + B_2) S_r, \\
\dot{I}_r &= \lambda_{hr} S_r + \sigma_s I_s - B_2 I_r,
\end{aligned} \tag{2.3}$$

where the forces of infection $\lambda_{vh}, \lambda_{hs}$, and λ_{hr} are defined as:

$$\lambda_{vh} = p_{vh}\left(\beta_{hs}\frac{I_s}{N_h} + \beta_{hr}\frac{I_r}{N_h}\right), \quad \lambda_{hs} = \beta_{hs} p_{hv}\frac{I_h}{N_h}, \quad \text{and} \quad \lambda_{hr} = \beta_{hr} p_{hv}\frac{I_h}{N_h}. \tag{2.4}$$

A summary of the description of model parameters together with baseline and ranges of numerical values for the parameters and their sources are presented in Table 1.

As human and mosquito populations, each of the variables $S_h, I_h, R_h, S_s, I_s, S_r$, and I_r, and the parameters of the system (see Table 1) are non-negative. As in [60, 68], it is straight forward to verify that the system is well-posed within the epidemiologically feasible region $\Omega = \Omega_h \times \Omega_s \times \Omega_r \subset \mathbb{R}^3_+ \times \mathbb{R}^2_+ \times \mathbb{R}^2_+$, where $\Omega_h = \{(S_h, I_h, R_h) : 0 \leq S_h + I_h + R_h \leq \Lambda_h/\mu_h\} \subset \mathbb{R}^3_+$, $\Omega_s = \left\{(S_s, I_s) : 0 \leq S_s + I_s \leq \frac{\Lambda_v(B_2(1-\theta)+\sigma_r\theta)}{\mu_r\sigma_s+\mu_s B_2}\right\} \subset \mathbb{R}^2_+$, $\Omega_r = \left\{(S_r, I_r) : 0 \leq S_r + I_r \leq \frac{\Lambda_v(B_1\theta+\sigma_s(1-\theta))}{\mu_r\sigma_s+\mu_s B_2}\right\} \subset \mathbb{R}^2_+$, and that this region is positively invariant. That is, any solution of the model with initial data within Ω is trapped within Ω for $t > 0$.

Table 1: Table of parameter values and ranges used for the simulations of System (2.3). The dimension H, D, and M represent human, day, and mosquito, respectively. Dimensions are enclosed in parentheses at the end of parameter descriptions and excluded for dimensionless parameters.

Parameter	Description and dimension	Value	Range	Reference
Λ_h	Recruitment rate of humans (HD^{-1})	6.85×10^{-2}	$[3.65, 9.13] \times 10^{-2}$	[76, 77]
ρ_h	Rate of loss of immunity (D^{-1})	8.3×10^{-3}	$[5.5, 1100] \times 10^{-5}$	[68, 78]
μ_h	Human natural mortality rate (D^{-1})	4.09×10^{-5}	$[3.3, 5.5] \times 10^{-5}$	[76, 77]
γ_h	Rate at which humans recover from malaria (D^{-1})	1.25×10^{-2}	$[1.4, 17] \times 10^{-3}$	[78, 79]
δ_h	Malaria-induced death rate (D^{-1})	9.01×10^{-5}	$[0, 4.1] \times 10^{-4}]$	[55]
θ	Proportion reduction in sensitive mosquitoes recruitment due to resistance.	0.1	$[0, 1]$	
Λ_v	Mosquito recruitment rate (MD^{-1})	$10^4/14$	$[10^4/21, 10^4/7]$	[80]
σ_s	Mutation rate of sensitive mosquitoes (D^{-1})	0.600	$[0.1, 1]$	[81]
σ_r	Mutation rate of resistant mosquitoes (D^{-1})	0.5	$[0.1, 1]$	[27, 54]
μ_r^0	Natural death rate of resistant mosquitoes (D^{-1})	$1/21$	$[1/30, 1/7]$	[82, 83]
μ_s^0	Natural death rate of sensitive mosquitoes (D^{-1})	$1/14$	$[1/21, 1/7]$	[82, 83]

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Table 1 – *Continued*

Parameter	Description and dimension	Value	Range	Reference
μ_r^1	ITN death rate of resistant mosquitoes (D^{-1})	$1/21$	$[1/30, 1/7]$	[84]
μ_s^1	ITN death rate of sensitive mosquitoes (D^{-1})	$1/14$	$[1/21, 1/7]$	[84]
p_{hv}	Human to mosquito transmission probability	0.48	$[0.072, 0.64]$	[55, 85–87]
p_{vh}	Mosquito to human transmission probability	0.022	$[0.01, 0.27]$	[55, 82, 88, 89]
β_{sh}^{max}	Maximum sensitive mosquito biting rate (D^{-1})	0.5	$[0.1, 1]$	[55, 90, 91]
β_{sh}^{max}	Maximum resistant mosquito biting rate (D^{-1})	0.8	$[0.1, 1]$	[55, 90, 91]
β_{sh}^{min}	Minimum sensitive mosquito biting rate (D^{-1})	0.5	$[0.001, 0.1]$	[92]
β_{sh}^{min}	Minimum resistant mosquito biting rate (D^{-1})	0.03	$[0.001, 0.1]$	[92]
b_0	Initial ITN coverage	varies	$[0.01, 1]$	[3]
ϵ	ITN efficacy	varies	$[0.01, 1]$	

3. Model analysis

In this section, we determine the basic reproduction number and explore the existence and stability properties of equilibria to System (2.3). The basic reproduction number of the model system calculated using the next generation matrix approach [93] (see the online supplementary information for details) is

$$R_0 = \sqrt{\frac{p_{hv}p_{vh}\Lambda_v\mu_h(B_6+B_7)}{\Lambda_h A_1 B_3^2}} \tag{3.1}$$

where
$$\begin{aligned} B_3 &= \mu_r\mu_s + \mu_r\sigma_s + \mu_s\sigma_r, \quad B_4 = B_2(1-\theta) + \theta\sigma_r, \quad B_5 = B_1\theta + \sigma_s(1-\theta), \\ B_6 &= B_1B_5\beta_{hr}^2 + B_2B_4\beta_{hs}^2, \quad B_7 = \beta_{hr}\beta_{hs}(B_4\sigma_s + \sigma_r B_5). \end{aligned} \tag{3.2}$$

Equilibria are obtained by setting the left-hand side to zero and solving for the variables $S_h, I_h, R_h, S_s, I_s, S_r, I_r$:

$$\begin{aligned} S_h^* &= \frac{\Lambda_h A_1 A_2}{A_1A_2\mu_h + A_3\lambda_{vh}^*}, I_h^* = \frac{\Lambda_h A_2\lambda_{vh}^*}{A_1A_2\mu_h + A_3\lambda_{vh}^*}, R_h^* = \frac{\gamma_h\Lambda_h\lambda_{vh}^*}{A_1A_2\mu_h + A_3\lambda_{vh}^*}, N_h^* = \frac{\Lambda_h(A_1A_2 + A_4\lambda_{vh}^*)}{A_1A_2\mu_h + A_3\lambda_{vh}^*}, \\ S_s^* &= \frac{\Lambda_v(B_4 + (1-\theta)\lambda_{hr}^*)}{B_3 + B_1\lambda_{hr}^* + (B_2+\lambda_{hr}^*)\lambda_{hs}^*}, \quad I_s^* = \frac{\Lambda_v((B_2+\lambda_{hr}^*)B_4\lambda_{hs}^* + \sigma_r B_5\lambda_{hr}^*)}{B_3(B_3 + B_1\lambda_{hr}^* + (B_2+\lambda_{hr}^*)\lambda_{hs}^*)}, \\ S_r^* &= \frac{\Lambda_v(B_5 + \theta\lambda_{hs}^*)}{B_3 + B_1\lambda_{hr}^* + (B_2+\lambda_{hr}^*)\lambda_{hs}^*}, \quad I_r^* = \frac{\Lambda_v((B_1+\lambda_{hs}^*)B_5\lambda_{hr}^* + \sigma_s B_4\lambda_{hs}^*)}{B_3(B_3 + B_1\lambda_{hr}^* + (B_2+\lambda_{hr}^*)\lambda_{hs}^*)}, \end{aligned} \tag{3.3}$$

where $A_3 = \mu_h A_1 + \rho_h(\delta_h + \mu_h)$ and $A_4 = A_2 + \gamma_h$. Substituting I_h^*, I_s^*, I_r^*, and N_h^* into the forces of infection $\lambda_{hs}, \lambda_{hr}$, and λ_{vh} from Eqs. (2.4) yields

$$\lambda_{hs}^* = \frac{\beta_{hs}p_{hv}A_2\lambda_{vh}^*}{A_2A_1 + A_4\lambda_{vh}^*}, \quad \lambda_{hr}^* = \frac{\beta_{hr}p_{hv}A_2\lambda_{vh}^*}{A_2A_1 + A_4\lambda_{vh}^*}, \quad \text{and} \tag{3.4}$$

$$\begin{aligned} \lambda_{vh}^* &= \left(\frac{\beta_{hs}p_{vh}\Lambda_v(B_4(B_2+\lambda_{hr}^*)\lambda_{hs}^* + B_5\sigma_r\lambda_{hr}^*)(\mu_hA_1A_2 + A_3\lambda_{vh}^*)}{B_3((B_2+\lambda_{hr}^*)\lambda_{hs}^* + B_1\lambda_{hr}^* + B_3)(A_1A_2 + A_4\lambda_{vh}^*)\Lambda_h}\right) \\ &\quad + \left(\frac{\beta_{hr}p_{vh}\Lambda_v(B_5(B_1+\lambda_{hs}^*)\lambda_{hr}^* + \sigma_s B_4\lambda_{hs}^*)(\mu_hA_1A_2 + A_3\lambda_{vh}^*)}{B_3((B_2+\lambda_{hr}^*)\lambda_{hs}^* + B_1\lambda_{hr}^* + B_3)(A_1A_2 + A_4\lambda_{vh}^*)\Lambda_h}\right). \end{aligned} \tag{3.5}$$

Substituting λ_{hs}^* and λ_{hr}^* from Eqs. (3.4) into Eq. (3.5) and collecting terms in powers of λ_{vh}^* results in

$$(\lambda_{vh}^{*3} + C_2\lambda_{vh}^{*2} + C_1\lambda_{vh}^* + C_0)\lambda_{vh}^* = 0, \tag{3.6}$$

where

$$C_2 = \frac{\Lambda_h A_1 A_2 B_3 (p_{hv} A_2 (p_{hv}\beta_{hr}\beta_{hs} A_2 + 2A_4 B_9) + 3A_4^2 B_3)(1 - R_2)}{\Lambda_h A_4 B_3 (p_{hv} A_2 (p_{hv}\beta_{hr}\beta_{hs} A_2 + A_4 B_9) + A_4^2 B_3)},$$

$$C_1 = \frac{\Lambda_h (A_1 A_2)^2 B_3 (p_{hv} A_2 B_9 + 3A_4 B_3)(1 - R_1)}{\Lambda_h A_4 B_3 (p_{hv} A_2 (p_{hv}\beta_{hr}\beta_{hs} A_2 + A_4 B_9) + A_4^2 B_3)},$$

$$C_0 = \frac{\Lambda_h (A_1 A_2)^3 B_3^2 (1 - R_0^2)}{\Lambda_h A_4 B_3 (p_{hv} A_2 (p_{hv}\beta_{hr}\beta_{hs} A_2 + A_4 B_9) + A_4^2 B_3)},$$

$$R_2 = \frac{p_{hv} p_{vh} \Lambda_v A_3 (p_{hv} A_2 B_8 + A_4 (B_6 + B_7))}{\Lambda_h A_1 B_3 (p_{hv} A_2 (p_{hv}\beta_{hr}\beta_{hs} A_2 + 2A_4 B_9) + 3A_4^2 B_3)}, R_1 = \frac{p_{hv} p_{vh} \Lambda_v (p_{hv}\mu_h A_2 + (A_3 + A_4\mu_h)(B_6 + B_7))}{A_1 B_3 \Lambda_h (p_{hv} A_2 B_9 + 3A_4 B_3)}, \quad (3.7)$$

$B_8 = \beta_{hr}\beta_{hs}(B_4\beta_{hs} + B_5\beta_{hr})$, and $B_9 = \beta_{hr} B_1 + \beta_{hs} B_2$. Note that $C_0 \geq 0$ if $R_0 \leq 1$, $C_0 < 0$ if $R_0 > 1$, $C_1 \geq 0$ if $R_1 \leq 1$, $C_1 < 0$ if $R_1 > 1$, and that $C_2 \geq 0$ if $R_2 \leq 1$, $C_2 < 0$ if $R_2 > 1$. Using Descartes' rule of signs, we guess that Eqs. (2.3) can have zero, one, two, or three endemic equilibria, which leads to the Theorem:

Theorem 3.1. *The model system* (2.3) *can have*

(a) *no endemic equilibrium point when* $c_0 \geq 0, C_1 \geq 0$, *and* $C_2 \geq 0$;

(b) *one possible endemic equilibrium point if* $C_0 < 0, C_1 \geq 0$, *and* $C_2 \geq 0$, *or* $C_0 \leq 0, C_1 < 0$, *and* $C_2 \geq 0$, *or* $C_0 \leq 0, C_1 \geq 0$, *and* $C_2 < 0$;

(c) *zero or two possible endemic equilibrium points if* $C_0 \geq 0, C_1 > 0$ *and* $C_2 < 0$, *or* $C_0 > 0, C_1 < 0$ *and* $C_2 \geq 0$, *or* $C_0 > 0, C_1 \leq 0$ *and* $C_2 < 0$;

(d) *one or three possible endemic equilibrium points if* $C_0 < 0, C_1 > 0$, *and* $C_2 < 0$.

Remark 3.2. *The possibility of two endemic equilibrium points when* $C_0 \geq 0$, *which corresponds to* $R_0 \leq 1$ *postulated in Theorem 3.1 highlights the possibility of a backward (sub-critical bifurcation). To identify specific conditions under which the polynomial equation* (3.6), *has a unique endemic equilibrium, or exactly two endemic equilibrium points, we can apply a combination of Sturm's Theorem and Descartes rule of signs applied to a canonical form the equation obtained through the subsitution* $\tilde{\lambda}_{vh}^* = \lambda_{vh}^* + C_2/3$ *(see [71] for details).*

3.1. Special case for which $\delta_h = 0$

For the case in which the disease-induced mortalities are negligible, e.g., the case of *Plasmodium vivax, Plasmodium ovale*, and *Plasmodium falciparum* in some regions, the polynomial equation (3.6) reduces to

$$(\lambda_{vh}^{*2} + C_1\lambda_{vh}^* + C_0)\lambda_{vh}^* = 0, \quad (3.8)$$

where

$$C_1 = \frac{\Lambda_h \mu_h A_1 A_2 B_3 (p_{hv}\mu_h A_2 B_9 + 2A_3 B_3)(1 - R_1)}{\Lambda_h B_3 (\mu_h p_{hv} A_2 (\mu_h p_{hv}\beta_{hr}\beta_{hs} A_2 + A_3 B_9) + A_3^2 B_3)}, \quad R_1 = \frac{\mu_h p_{hv} p_{vh} \Lambda_v (\mu_h p_{hv} A_2 B_7 + A_3 (B_6 + B_7))}{\Lambda_h A_1 B_3 (\mu_h p_{hv} A_2 B_9 + 2A_3 B_3)},$$

$$C_0 = \frac{\Lambda_h (\mu_h A_1 A_2 B_3)^2 (1 - R_0^2)}{\Lambda_h B_3 (\mu_h p_{hv} A_2 (\mu_h p_{hv}\beta_{hr}\beta_{hs} A_2 + A_3 B_9) + A_3^2 B_3)}, \quad R_0^2 = \frac{p_{hv} p_{vh} \Lambda_v \mu_h (B_6 + B_7)}{\Lambda_h A_1 B_3^2}.$$

Note that in this special case, $A_1 = \mu_h + \gamma_h$ and $A_3 = \mu_h(\mu_h + \gamma_h + \rho_h) = \mu_h A_4$. Although this special case for which there are no disease-induced mortalities, i.e., $\delta_h = 0$ suggests the possibility of two endemic equilibria when $R_0 < 1$ ($C_0 > 0$) and $R_1 > 1$ ($C_1 < 0$), the system does not exhibit a backward bifurcation within a feasible parameter regime. This is consistent with results in [60, 68] indicating that this class of models exhibit a backward bifurcation when disease induced mortalities are high compared to natural human mortalities, i.e., when $\delta_h > \mu_h$.

3.2. *The disease-free equilibrium*

The case of Eq. (3.6) for which $\lambda_{vh}^* = 0$ corresponds to the disease-free equilibrium $(S_h^0, I_h^0, R_h^0, S_s^0, I_s^0, S_r^0, I_r^0) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_v B_4}{B_3}, 0, \frac{\Lambda_v B_5}{B_3}, 0\right)$. The Jacobian of System (2.3) evaluated at this disease-free equilibrium is:

$$J = \begin{pmatrix} -\mu_h & 0 & \rho_h & 0 & -p_{vh}\beta_{sh} & 0 & -p_{vh}\beta_{rh} \\ 0 & -A_1 & 0 & 0 & p_{vh}\beta_{sh} & 0 & p_{vh}\beta_{rh} \\ 0 & \gamma_h & -A_2 & 0 & 0 & 0 & 0 \\ 0 & -\frac{\beta_{sh}p_{hv}\Lambda_v\mu_h B_4}{\Lambda_h B_3} & 0 & -A_3 & 0 & \sigma_r & 0 \\ 0 & \frac{\beta_{sh}p_{hv}\Lambda_v\mu_h B_4}{\Lambda_h B_3} & 0 & 0 & -A_3 & 0 & \sigma_r \\ 0 & -\frac{\beta_{rh}p_{hv}\Lambda_v\mu_h B_5}{\Lambda_h B_3} & 0 & \sigma_s & 0 & -A_4 & 0 \\ 0 & \frac{\beta_{rh}p_{hv}\Lambda_v\mu_h B_5}{\Lambda_h B_3} & 0 & 0 & \sigma_s & 0 & -A_4 \end{pmatrix}.$$

If ξ is an eigenvalue of J, then $\xi_1 = -\mu_h$, $\xi_2 = -A_2$, and $\xi_{3,4} = \frac{-(B_1+B_2)\pm\sqrt{(B_1+B_2)^2-4B_3}}{2}$ are four eigenvalues of J. Observe that all four eigenvalues are negative. The other three eigenvalues are given by the cubic equation:

$$\xi^3 + d_2\xi^2 + d_1\xi + d_0 = 0, \tag{3.9}$$

where $d_2 = A_1+B_1+B_2$, $d_1 = (A_1(B_1+B_2)+B_3)(1-R)$, $d_0 = A_1B_3(1-R_0^2)$, and $R = \frac{p_{hv}p_{vh}\mu_h\Lambda_v(\beta_{hr}^2B_5+\beta_{hs}^2B_4)}{\Lambda_h B_3(A_1(B_1+B_2)+B_3)}$. It can be verified that $R \leq R_0^2$. Hence, when $R_0 < 1$, $d_0 > 0$ and $d_1 > 0$. Since $d_2 > 0$, the Routh-Hurwitz condition assures us that no solution of Eq. (3.9) is positive when $R_0 < 1$. Therefore, all eigenvalues of J are negative or have negative real parts (if they are complex) when $R_0 < 1$. This proves the following Theorem:

Theorem 3.3. *The disease-free equilibrium* $(S_h^*, I_h^*, R_h^*, S_s^*, I_s^*, S_r^*, I_r^*) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_v B_4}{B_3}, 0, \frac{\Lambda_v B_5}{B_3}, 0\right)$ *of system* (2.3) *is locally and asymptotically stable when* $R_0 < 1$.

4. Results

The long-term dynamics of system (2) illustrating the existence of a stable endemic equilibrium when the basic reproduction number is greater than one is presented in Fig. 2. Parameters used for the simulations are presented in Table 1. For this parameter regime, although the sensitive and resistant susceptible mosquito populations at equilibrium are almost the same when resistant mosquitoes are able to lose resistance, i.e., $\sigma_s \neq 0, \sigma_r \neq 0$, there are more resistant infectious mosquitoes than sensitive infectious mosquitoes at equilibrium (Fig. 2 (e)). The disease is concentrated mostly among the sensitive mosquitoes when resistance is permanent (Fig. 2 (f), and (g)). Overall, disease prevalence is higher within the human and mosquito populations when resistance to insecticides is permanent. Additionally, the highest (respectively, lowest) disease prevalence is observed among the sensitive (respectively,

resistant) mosquitoes when resistance acquired through mosquito-recruitment or transition from adult sensitive to resistant mosquito at per capita rate σ_s is permanent (Fig. 2 (g)). On the other hand if sensitive mosquitoes only become resistant through mosquito recruitment, i.e., $\sigma_s = 0$ and resistance is not permanent, i.e., $\sigma_r \neq 0$, then the resistant mosquito population only exists at very low levels, while disease prevalence is predominantly among the human and sensitive mosquito population. The long term dynamics of the system for a parameter regime for which the basic reproduction number is less than one, e.g., when the ITN coverage level is 90% (not shown here) can also be produced to illustrate the possibility of a disease-free equilibrium.

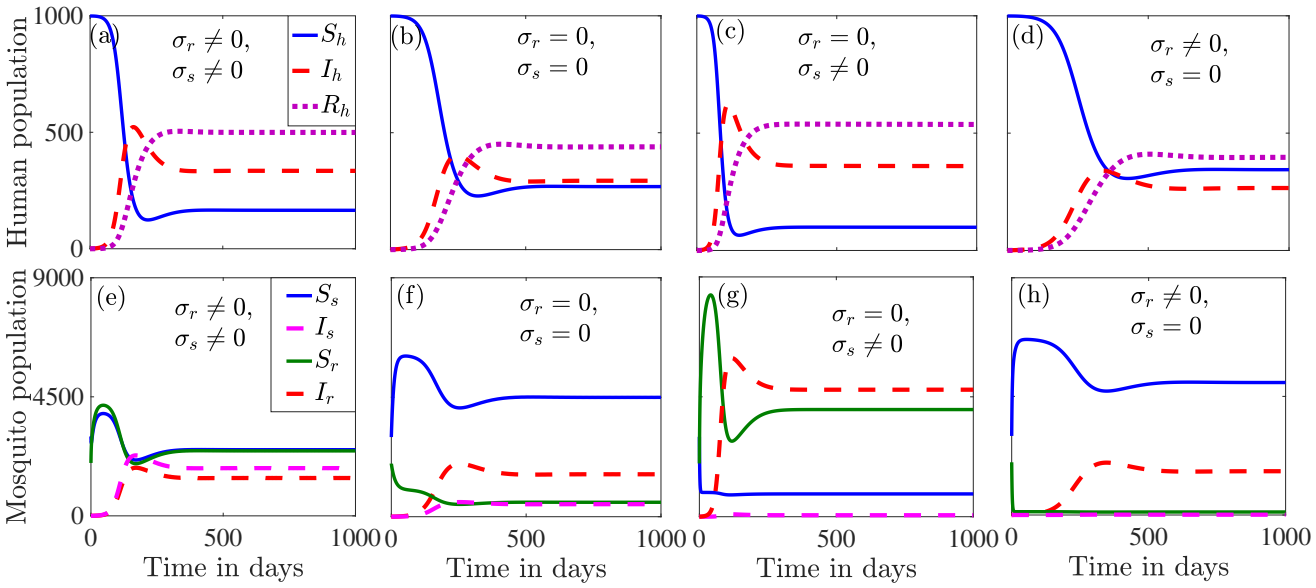

Figure 2: Numerical simulation results illustrating the existence of an endemic equilibrium to System (2) when $R_0 > 1$. Graphs (a) and (e) show the dynamics for the case in which resistance is acquired at rate $\sigma_s \neq 0$ and lost over time at rate $\sigma_r \neq 0$. Graphs (b) and (f) illustrate the dynamics when resistance is acquired only through mosquito recruitment and is permanent. Graphs (c) and (g) illustrate the dynamical behavior of the system when resistance is permanent and can be acquired through mosquito recruitment or transition of sensitive mosquitoes to resistant mosquitoes at rate $\sigma_s \neq 0$. Graphs (d) and (h) illustrate the dynamical behavior of the system when resistance is not permanent and can only be acquired through mosquito recruitment, i.e., $\sigma_r \neq 0$ and $\sigma_s = 0$. Parameter values used for the simulations are presented in Table 1.

Next, we identify important model parameters that drive the system and that can be targeted for control purposes through a global uncertainty and sensitivity analyses using the Latin-Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC) methods (see the online supplementary information for details on the methodology). We found out that uncertainty or variability in the efficacy of ITNs ϵ, and ITN coverage b_0, contribute most to uncertainty or variability in the basic reproduction number R_0, and the threshold parameter groupings R_1 and R_2 from Eq. (3.7) (Fig. 3). Each of these thresholds is useful for determining the existence of endemic equilibria and hence disease prevalence or disease elimination. There is a negative correlation between each of these thresholds and ITN efficacy and coverage, i.e., raising ITN efficacy or coverage results in a reduction in the basic reproduction number, R_1, and R_2. Thus, allowing these parameters to fall will trigger an increase in the basic reproduction num-

ber, R_1, and R_2, and hence an increase in disease prevalence. Other important parameters that can be targeted for control include the maximum biting rate of resistant mosquitoes β_{hr}^{max}, the transmission probability from infectious humans to sensitive and resistant susceptible mosquitoes p_{hv}, the transmission probability from sensitive and resistant mosquitoes to susceptible humans p_{vh}, and the mosquito recruitment rate Λ_v. Other important parameters that do not impose as much variability and uncertainty as the above are the maximum biting rate of sensitive mosquitoes βhs^{max} and the natural mortality rates of sensitive and resistant mosquitoes. Among the least influential parameters are the minimum biting rates of sensitive and resistant mosquitoes βhs^{min} and βhr^{min}, respectively, confirming the low malaria risk in areas with low mosquito densities, or where mosquitoes are not allowed to bite humans.

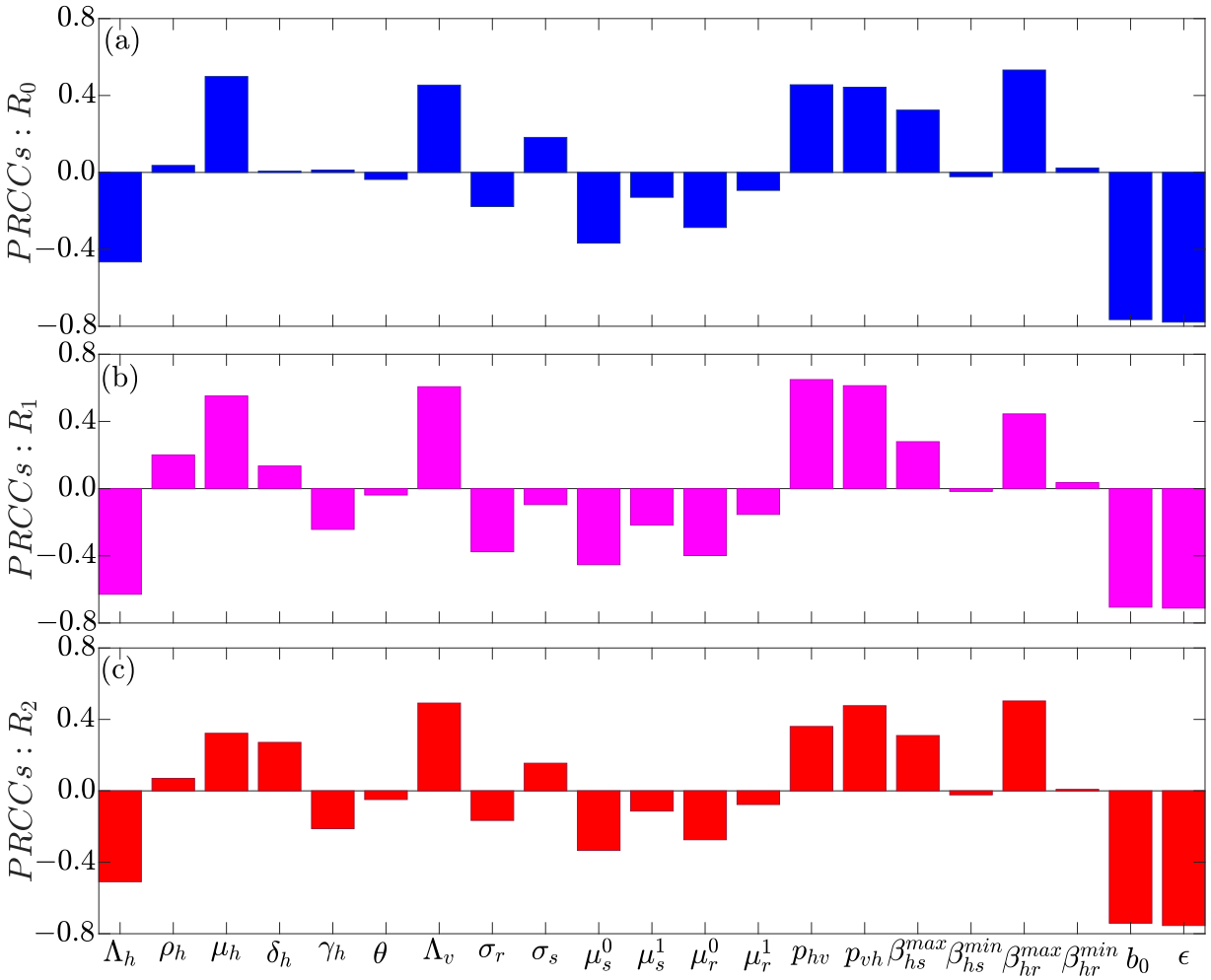

Figure 3: Global uncertainty and sensitivity analysis results showing the contributions of uncertainty or variability in model parameters to uncertainty or variability to the (a) basic reproduction number R_0, and (b)-(c) threshold quantities R_1 and R_2 (Eq. (3.7)). Positive PRCCs represent positive correlation, i.e., an increase in a parameter will trigger an increase in R_0, R_1, or R_2, while negative PRCCs represent negative correlations. The magnitude of the PRCC represents the level of significance. Parameters used for the simulations are presented in Table 1.

Also, our numerical results indicate that uncertainty or variability in the efficacy of ITNs, ITN coverage, the human recovery rate from infection, the maximum biting rate of resistant mosquitoes, and the transmission prob-

ability from infectious humans to infectious mosquitoes are more influential in imposing variability or uncertainty to the infectious human, resistant, and sensitive mosquito populations (Fig. 4).

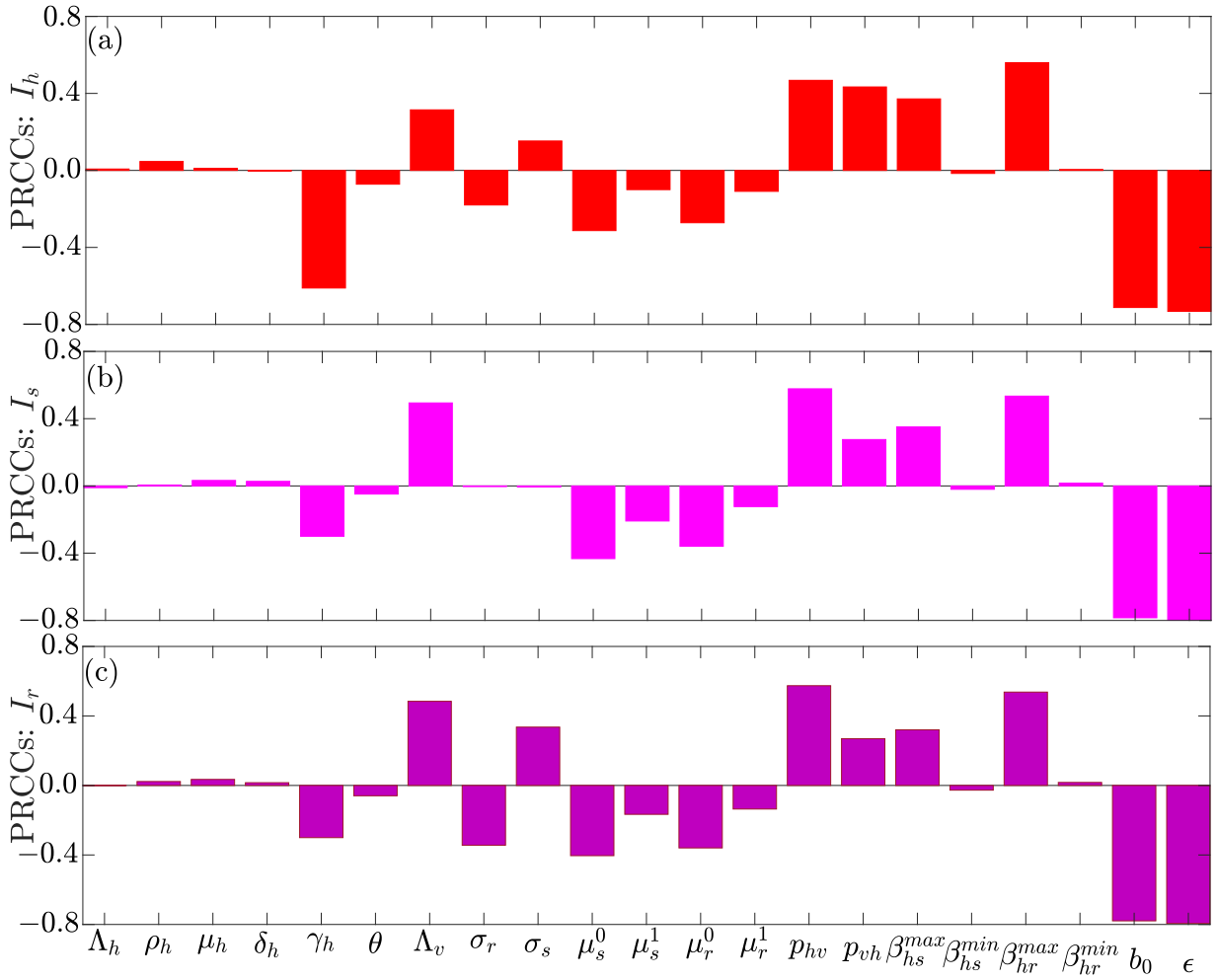

Figure 4: Global uncertainty and sensitivity analysis results showing the contributions of uncertainty or variability in model parameters to uncertainty or variability to the (a) infectious human population (I_h), (b) sensitive mosquito population (I_s), and (c) resistant mosquito population (I_r). Positive PRCCs represent positive correlations, i.e., an increase in a parameter will trigger an increase in I_h, I_s, or I_r, while negative PRCCs represent negative correlations. The magnitude of the PRCC represents the strength or level of significance. Parameters used for the simulations are presented in Table 1.

Next, we investigate the impact of ITN coverage (b_0), ITN efficacy (ϵ), and resistance to insecticide used in ITNs by mosquitoes through the resistance acquisition and loss rates σ_s and σ_r, respectively, on a key measure of disease intensity–the basic reproduction number. Figure 5 shows ITN coverage levels for different ITN efficacy and acquisition and loss rates of resistance appropriate for containing the malaria disease. For very high ITN efficacy, e.g., 100%, approximately 76% ITN coverage is necessary for containing the disease, while for ITN efficacy below 76%, even 100% ITN coverage is not enough for containing the disease (Fig. 5(a)).

Figures 5(a) and (d) correspond to behavioral resistance to insecticides, which is not permanent. Unlike be-

havioral resistance where resistant mosquitoes lose their resistance over time, resistance to insecticides can be permanent. That is once a mosquito becomes resistant, it maintains this status until death. This is the case with metabolic and cuticle resistance [42–44]. Hence, we consider three slightly simplified versions of the model: 1) The case in which there is no transition between the sensitive and resistant mosquito classes ($\sigma_r = \sigma_s = 0$). That is, we are assuming that resistance is acquired only through mosquito-recruitment and is permanent (Fig. 5(b)). 2) The case in which resistance is permanent and acquired both through mosquito recruitment and adult sensitive mosquitoes becoming resistant, i.e., $\sigma_r = 0, \sigma_s \neq 0$ (Fig. 5(c)). 3) The case in which resistance is not permanent and acquired only through mosquito recruitment, i.e., $\sigma_r \neq 0, \sigma_s = 0$ (Fig. 5(d)). For the case in which resistance is permanent and acquired only through mosquito recruitment (Fig. 5(b)), when ITN efficacy is $70\%, 80\%, 90\%$, or 100% approximately $98\%, 86\%, 76\%$ or 69% ITN coverage, respectively, is required to contain the disease. However, for ITN efficacy below 68% even full ITN coverage might not be enough for containment. For the case in which resistance is permanent and acquired both through mosquito recruitment and transition of adult mosquitoes from the sensitive to the resistant compartmental class (Fig. 5(c)), when ITN efficacy is 90%, or 100% approximately 93% or 84% ITN coverage, respectively, is required to contain the disease. However, for ITN efficacies below 84% even full ITN coverage might not be enough for containment. For the case in which resistance is not permanent and only through mosquito recruitment (Fig. 5(d)), when ITN efficacy is $70\%, 80\%, 90\%$, or 100% about $90\%, 79\%, 70\%$, or 63% ITN coverage, respectively, is required to contain the disease. But for ITN efficacies below 63% even full ITN coverage might not be enough for containment.

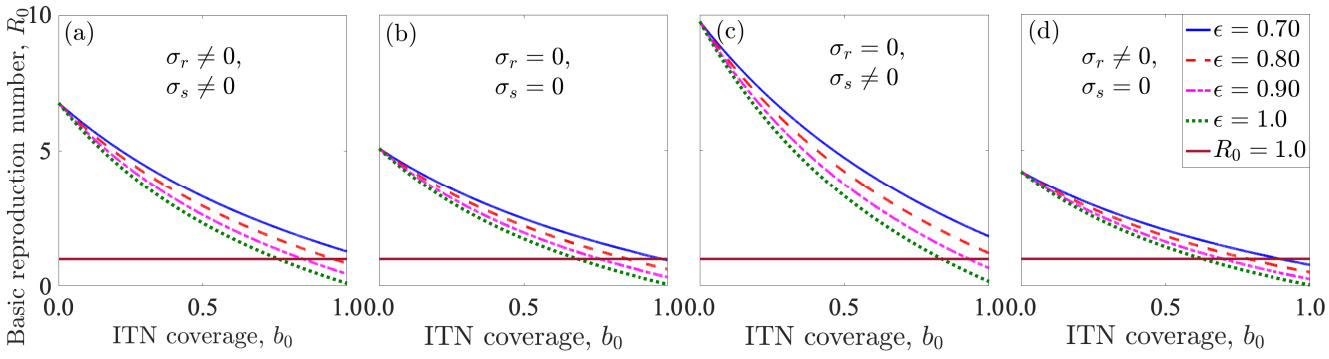

Figure 5: Numerical simulations illustrating insecticide-impregnated bed-net coverage levels required for bringing malaria under control for four values of insecticide-impregnated bed-net efficacy (ϵ) when mosquito resistant to insecticides is permanent or non-permanent. (a) Mosquito resistance to insecticides is not permanent and acquired through mosquito resistant and through transition of adult mosquitoes occurring at rate $\sigma_s \neq 0$. (b) Mosquito resistance is permanent and is only acquired through mosquito recruitment. (c) Resistance is permanent and acquired through mosquito recruitment and adult sensitive mosquito transition. (d) Resistance is not permanent and is acquired only through mosquito-recruitment. Other parameters used for the simulations are presented in Table 1.

Furthermore, we investigate the ITN coverage levels required for disease containment for different maximum mosquito biting rates, β_{hr}^{max} and β_{hs}^{max} (Fig. 6(a) and (b)), ITN-induced mosquito mortality rates, μ_r^1 and μ_s^1, (Fig. 6(c) and (d)) and resistance acquisition and loss rates, σ_s and σ_r, respectively, (Fig. 6(e) and (f)). When either

the sensitive or resistant mosquitoes bite a lot, even 100% ITN coverage might not be enough to contain malaria. However, when either sensitive or resistant mosquitoes do not bite a lot, there is a threshold level of ITN coverage that might be enough to contain the disease. For example, if sensitive mosquitoes do not bite, while the biting rate of resistant mosquitoes is 0.5 per day, about 75% ITN coverage with efficacy of 90% is required to contain the disease. Insecticide treated nets must be complemented with other control measures if their efficacy is below 70%.

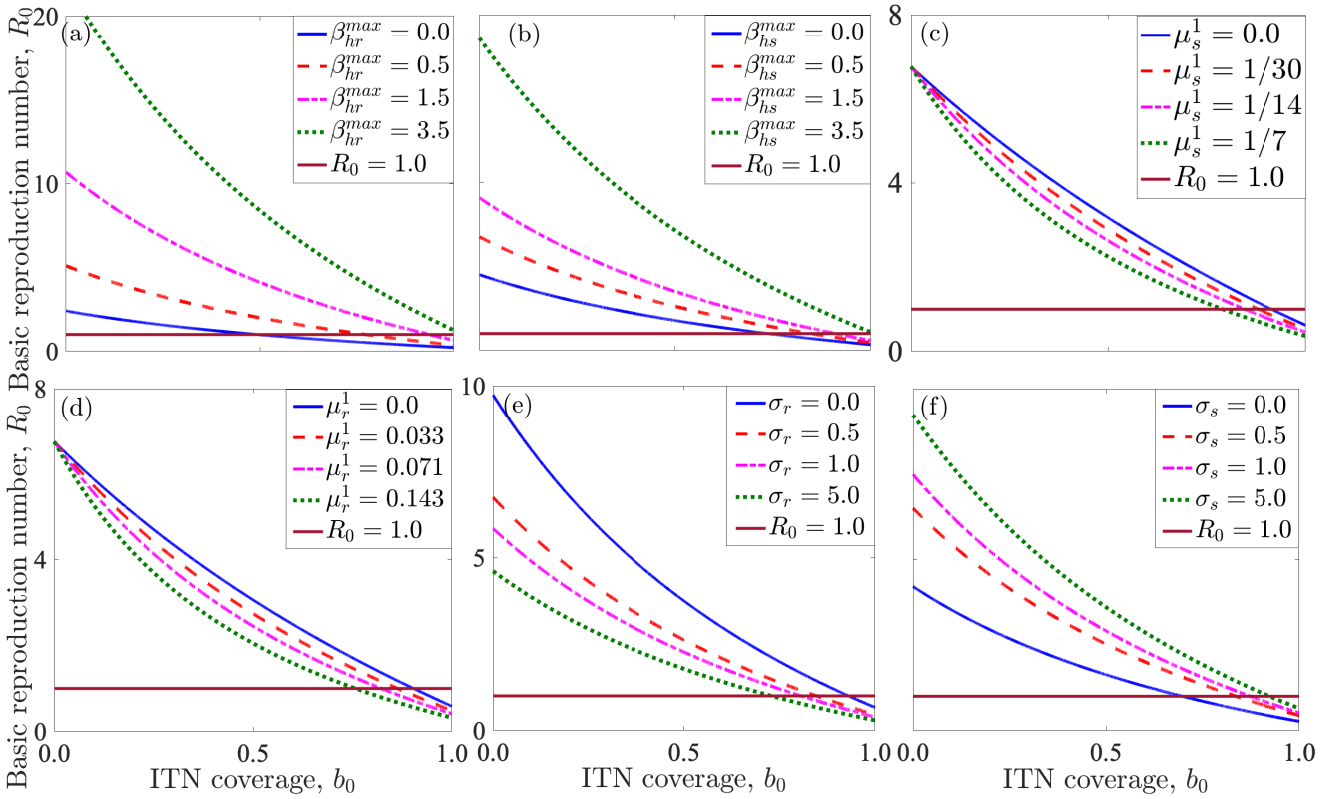

Figure 6: Numerical simulation results illustrating various insecticide-impregnated bed-net coverage levels required for bringing malaria under control for four values of (a)-(b) the maximaum biting rates of resistant and sensitive mosquitoes (β_{hr}^{max} and β_{hs}^{max}, respectively), (c)-(d) insecticide-induced mortality rates of resistant and sensitive mosquitoes (μ_r^1 and μ_r^s),and (e)-(f) the resistant development and loss rates for mosquitoes (σ_r and σ_s, respectively). Other parameters used for the simulations are presented in Table 1.

Our analysis also shows that if the sensitive mosquitoes do not bite humans or have a very low biting rate, a higher at the same efficacy level, higher ITN coverage is required than when the biting rate of resistant mosquitoes is low. For example, when ITN efficacy is 90% and the biting rate of sensitive mosquitoes is 0.0 or 0.5 per day, about 74% or 85% ITN coverage, respectively, is required to contain malaria, while if the biting rate of resistant mosquitoes is 0 or 0.5 per day, approximately 50% or 77% ITN coverage, respectively, is required to get rid of malaria. On the other hand, when ITNs do not kill sensitive or resistant mosquitoes that land on them, over 90% ITN coverage is required for containing malaria. However, when ITNs kill mosquitoes that land on them, over 82% ITN coverage is required for eradication if the respective ITN killing rates for sensitive and resistant mosquitoes are $\mu_r^1 = \mu_s^1 = 1/14$. If the killing ability of ITNs is stronger, e.g., $\mu_r^1 = \mu_s^1 = 1/7$, then less ITN coverage

(approximately 75%) is required for malaria containment. When resistance to insecticides is permanent, about 93% ITN coverage is required. However, when resistant mosquitoes lose their resistance over time at respective rates $0.5, 1.0$, or 5.0 per day, approximately $85\%, 81\%$, or 73% ITN coverage is required for eliminating malaria. When sensitive mosquitoes become resistant at respective rates $0.0, 0.5, 1.0$, or 5.0 per day, about $70\%, 84\%, 87\%$, or 92% ITN coverage is required for eliminating malaria.

In the next set of results (Figs. 7-9), we present heat maps to demonstrate the impact of ITN coverage and one other parameter, e.g., ITN efficacy, maximum biting rate of mosquitoes, development and loss rates of resistance, etc., on two measures of disease intensity–the basic reproduction number R_0 and the equilibrium infectious human populations, I_h^*. Similar results for the sensitive and resistant infectious mosquito populations and for the threshold parameters R_1 and R_2 are presented in the online supplementary information (SI).

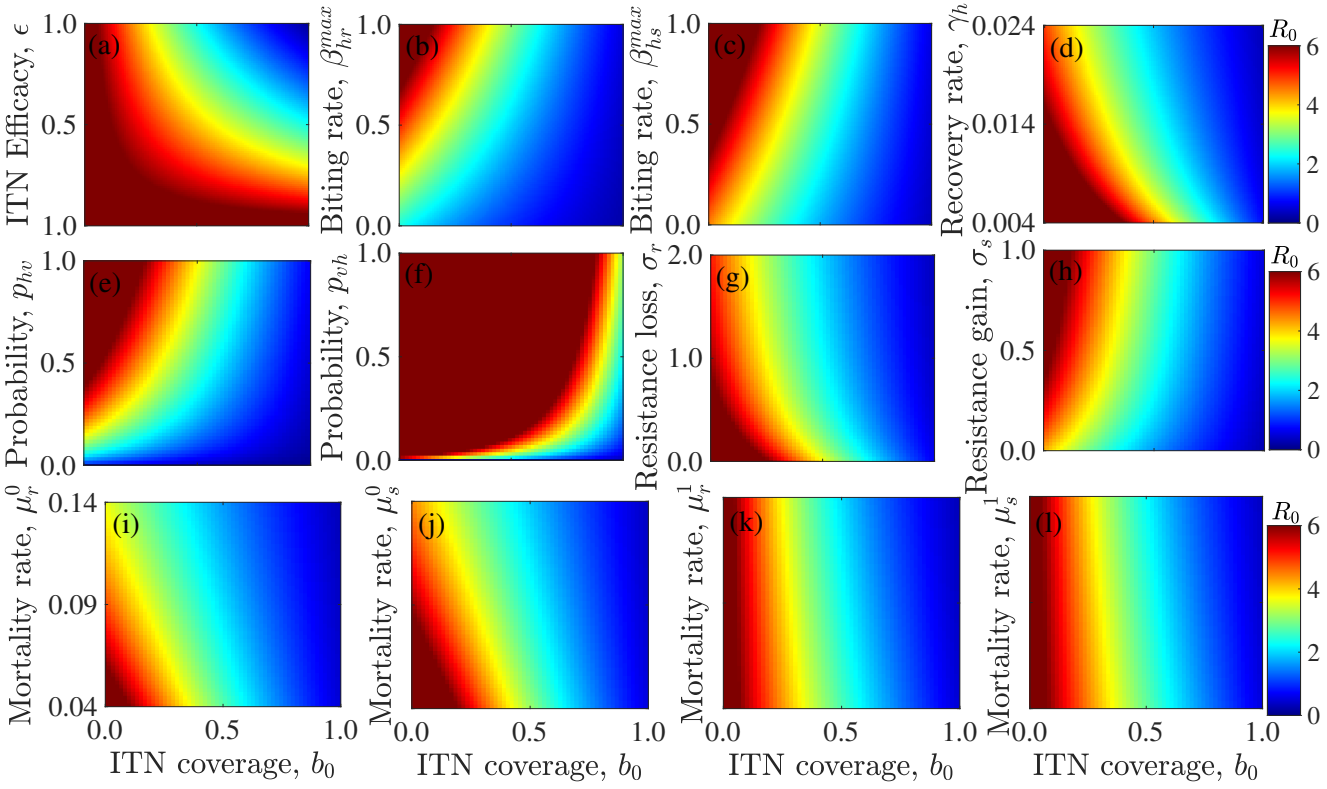

Figure 7: Heat maps from numerical simulations illustrating the impact on the basic reproduction number R_0, of ITN coverage b_0 and (a) ITN efficacy ϵ, (b) the maximum biting rate of resistant mosquitoes β_{hr}^{max}, (c) the maximum biting rate of sensitive mosquitoes β_{hs}^{max}, (d) the recovery rate from infection γ_h, (e) the probability of an infectious human infecting a susceptible mosquito p_{hv}, (f) the probability of infectious mosquito infecting a susceptible human p_{vh}, (g) the rate at which resistant mosquitoes lose resistance σ_r, (h) the rate at which sensitive mosquitoes develop resistance σ_s, (i) the natural mortality rate of resistant mosquitoes μ_r^0, (j) the natural mortality rate of sensitive mosquitoes μ_s^0, (k) the ITN-induced mortality rate of resistant mosquitoes μ_r^1, and (l) the ITN-induced mortality rate of sensitive mosquitoes μ_s^1. The values of the other parameters are presented in Table 1.

Disease prevalence is highest in areas in which fewer people are protected by ITNs when the efficacy of ITNs is very low (Fig. 7(a) and Fig. 8(a)). As observed earlier, when ITN efficacy is low, it becomes difficult to contain the

disease even if everybody uses ITNs for protection and vice versa. There will also be more infectious individuals in the population when fewer humans are protected by ITNs and the human recovery rate from infection, the rate at which resistant mosquitoes lose resistance, or the rate at which mosquitoes die (naturally or as a result of ITN-use) is low, (Fig. 7(d), (g), (i)-(l) and Fig. 8(d), (g), (i)-(l)). On the other hand, disease prevalence is highest for combinations of low ITN coverage and high mosquito biting rate, high probability of humans infecting mosquitoes, when more sensitive mosquitoes develop resistance (Fig. 7(b), (c), (e), (h) and Fig. 8(b), (c), (e), (h)).

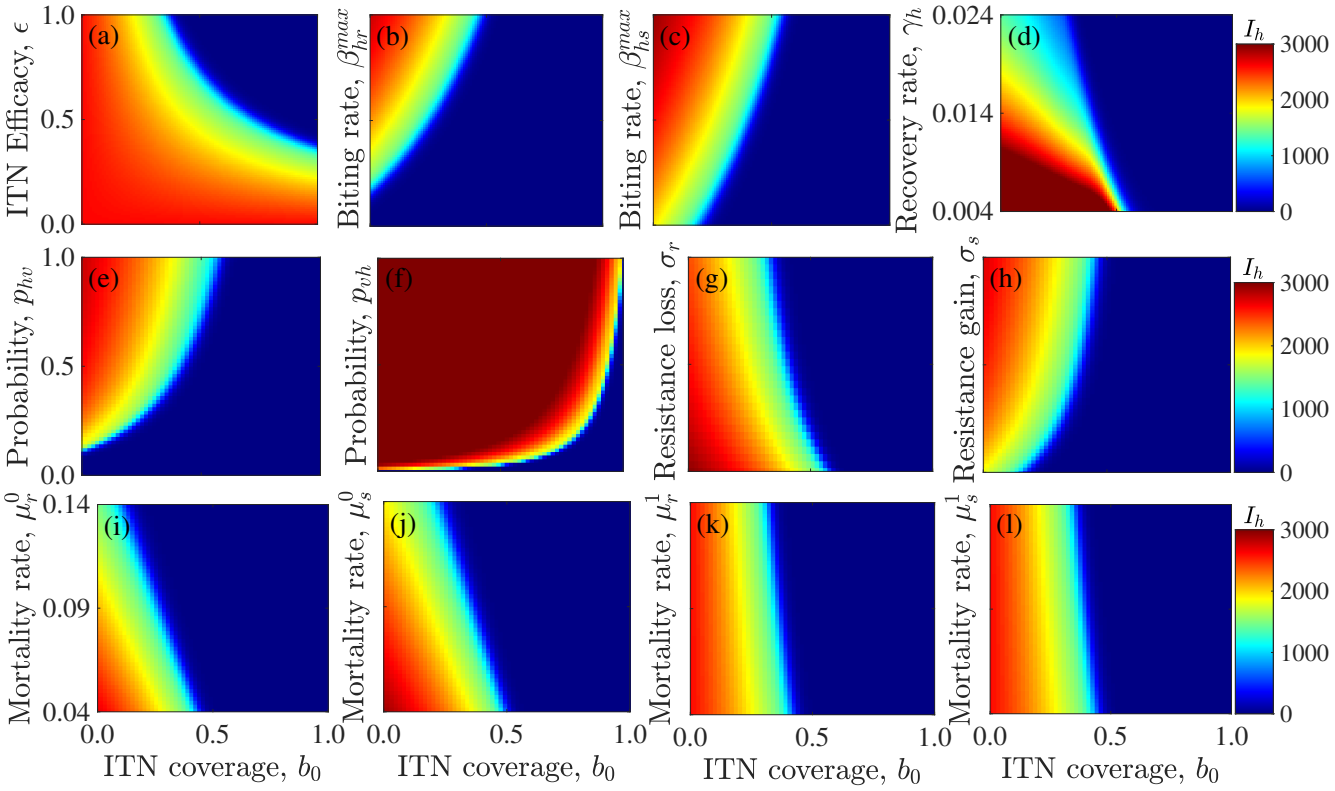

Figure 8: Numerical simulation results illustrating the impact on the Infectious human population I_h, of ITN coverage b_0 and (a) ITN efficacy ϵ, (b) the maximum biting rate of resistant mosquitoes β_{hr}^{max}, (c) the maximum biting rate of sensitive mosquitoes β_{hs}^{max}, (d) the recovery rate from infection γ_h, (e) the probability of an infectious human infecting a susceptible mosquito p_{hv}, (f) the probability of infectious mosquito infecting a susceptible human p_{vh}, (g) the rate at which resistant mosquitoes lose resistance σ_r, (h) the rate at which sensitive mosquitoes develop resistance σ_s, (i) the natural mortality rate of resistant mosquitoes μ_r^0, (j) the natural mortality rate of sensitive mosquitoes μ_s^0, (k) the ITN-induced mortality rate of resistant mosquitoes μ_r^1, and (l) the ITN-induced mortality rate of sensitive mosquitoes μ_s^1. Other parameters used for the simulations are presented in Table 1.

Heat maps showing the impact on the basic reproduction number (Fig. 9 (a)-(c)) of the infectious human population (Fig. 9 (d)-(f)), and the resistant infectious mosquito population (Fig. 9 (g)-(i)) for combinations of the maximum biting rate of resistant mosquitoes and the development rate of resistance, the loss rate of resistance, and the human recovery rate from infection. Disease prevalence is reduced, i.e., disease control is more feasible in areas of low resistant mosquito populations or when resistant mosquitoes do not bite a lot. Disease control is also feasible when more resistant mosquitoes lose their resistance or more humans are diagnosed and treated early

enough. On the other hand, disease prevalence is high in areas with high resistant mosquito densities (or when resistant mosquitoes bite more) and when more sensitive mosquitoes develop resistance.

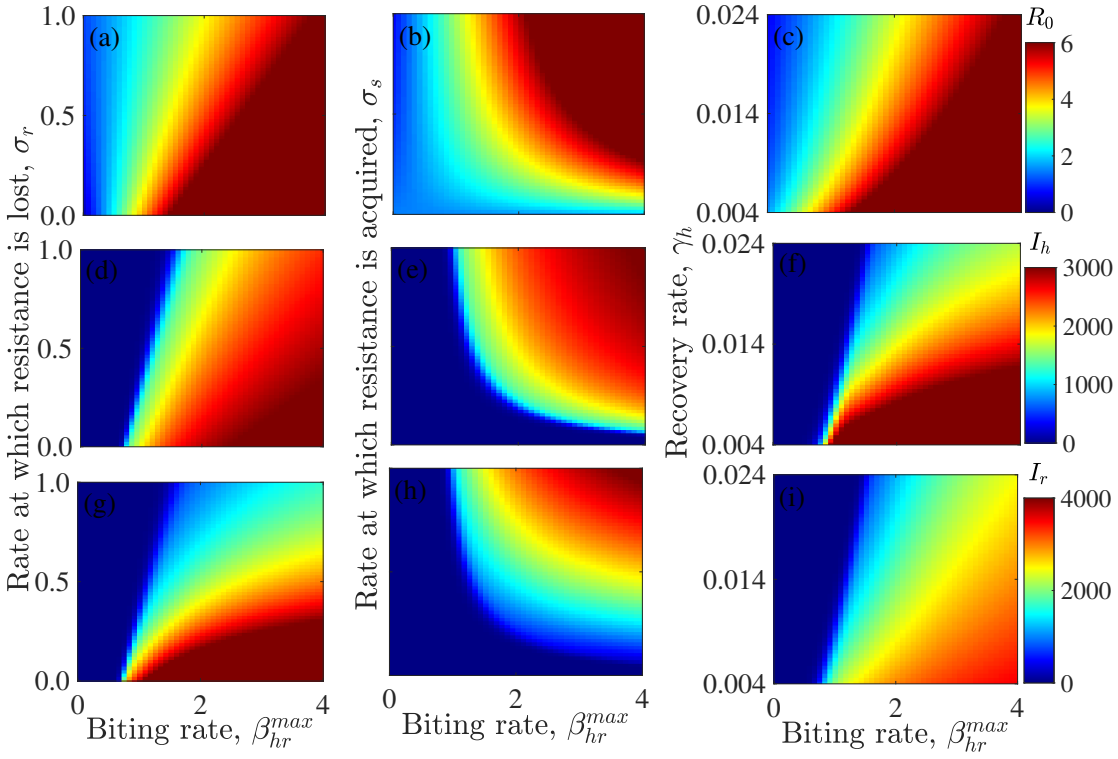

Figure 9: Numerical simulation results illustrating the effects on the basic reproduction number ((a)-(c)), the infectious human population ((d)-(f)), and the resistant infectious mosquito population ((g)-(i)) for combinations of the maximum biting rate of resistant mosquitoes and the development rate of resistance ((a), (d), (g)), the rate at which resistance is lost ((b), (e), (h)), and the human recoevery rate ((c), (f), (i)). The other parameter values used for the simulations are presented in Table 1.

5. Conclusion

Malaria prevalence in sub-Saharan Africa remains high, despite the tremendous success in control efforts recorded over the past decade. For example, although some counties in Kenya boost of up to 80% personal protection through ITNs [94], malaria is still a major problem to the country. The gains of malaria control programs, especially those related to vector control such as ITNs and IRS continue to be dampened by human behavior, natural deterioration in ITN efficacy, misuse, and resistance to insecticides developed by mosquitoes. In this study, we developed and used a compartmental model to explore the interplay between ITN coverage, ITN efficacy, and resistance exhibited by mosquitoes to insecticides in relation to malaria prevalence and control.

Our results indicate that ITN efficacy and coverage are very important parameters to pay attention to in the fight against malaria. We found out that low ITN efficacy, or differentiated adherence to the use of ITNs has a negative impact on the outcomes of malaria risk and control. We also found out that as long as mosquitoes are resistant to insecticides, a combination of low ITN efficacy and high coverage, or high ITN efficacy and low coverage is not

enough for reducing malaria to appreciable levels. The situation is worst when resistance to insecticides is permanent, i.e., for the case of metabolic or cuticle resistance. Hence, disease containment and possible elimination might be impossible when either ITN coverage or ITN efficacy is low and ITNs are not complemented with other control measures such as IRS, treatment, eliminating mosquito breeding sites near homes, etc. This is consistent with empirical studies in Ref. [15] indicating that both ITN efficacy and coverage for at risk populations must be high in order to achieve the target reduction in malaria prevalence. However, our results indicate that high ITN efficacy and moderately high ITN coverage and vice versa can be enough for appreciable reduction in malaria prevalence under certain circumstances, e.g., when resistance is only through mosquito recruitment (either permanent or not) or when more resistant mosquitoes are killed by ITNs. Consistent with common practice and public health recommendations, our results indicate that reducing mosquito populations, e.g., through killing, or eliminating their breeding sites near human homes and preventing mosquito bites, especially in areas of high mosquito density and high malaria prevalence are important for disease control.

Finally, our analysis and results indicate that reducing resistance to insecticides is an important step towards malaria elimination. In fact, the 1:1.6 optimal target for containing malaria, which in itself is a challenge to attain [20] underestimates the effort required to contain malaria, especially in the presence of resistance. With this coverage level, elimination is impossible even when ITN efficacy is very high, e.g., 90-100%, unless when resistant mosquitoes do not bite, which at the moment is an impossibility. Therefore, designing control measures that prevent the development of resistance, or that target and eliminate resistant mosquitoes will improve disease control. This might involve using chemicals that mosquitoes might not easily resist or switching to new chemicals that mosquitoes are not resistant to for treating both long lasting and regular bed-nets.

Limitations of the current study involve the assumptions that ITN efficacy over the useful life of ITNs as prescribed by the World Health Organization (three years) and mosquito resistance to insecticides are both constant. However, these quantities might change over time, with ITN efficacy waning and resistance to insecticides strengthening. In fact, the development of resistance occurs over time with the frequency of new resistant vectors increasing with each generation. These limitations and other aspects of the malaria disease are currently under investigation and will be reported in a separate paper.

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