Mathematics of an epidemiology-genetics model for assessing the role of insecticides resistance on malaria transmission dynamics

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Highlights

- A new epidemiology-genetics model for assessing the role of insecticides resistance (due to widespread use of insecticides treated bednets (ITNs) and indoors residual spraying (IRS)) on malaria is presented.
- Model incorporates several fitness costs of insecticide resistance.
- Effective size of ITNs and IRS coverage required for effective disease control and management of resstance depenends on level of resistance allele dominance and several fitness costs of resistance.

Abstract

Although the widespread use of indoors residual spraying (IRS) and insecticides treated bednets (ITNs; later replaced by long-lasting insecticidal nets (LLINs)) has led to a dramatic reduction of malaria burden in endemic areas, such usage has also resulted in the major challenge of the evolution of insecticide resistance in the mosquito population in those areas. Thus, efforts to combat malaria also include the urgent problem of effectively managing insecticide resistance. This study is based on the design and analysis of a new mathematical model for assessing the impact of insecticides resistance in the mosquito population (due to widespread use of IRS and ITNs) on the transmission dynamics and control of malaria in a community. The model, which couples disease epidemiology with vector population genetics, incorporates several fitness costs associated with insecticide resistance. Detailed rigorous analysis of the model is presented. Using data and parameter values relevant to malaria dynamics in moderate and high malaria transmission settings in some parts of Ethiopia, simulations of the model show that, while the ITNs-IRS strategy can lead to the effective control of the disease in both the moderate and high malaria transmission setting if the ITNs coverage level in the community is high enough (regardless of the level of IRS coverage), it fails to manage insecticide resistance (as measured in terms of the frequency of resistant allele at equilibrium in the community). It is further shown that the effective size of the coverage level of the ITNs and IRS required to effectively control the disease, while effectively managing insecticide resistance in the mosquito population, depends on the magnitude of the level of resistant allele dominance (in mosquitoes with heterozygous genotype) and several fitness costs associated with the insecticide resistance in the vector population. For instance, in a moderate transmission setting, malaria burden can be reduced to low levels of endemicity (even with low coverage of ITNs and IRS), and insecticide resistance effectively managed, if the fitness costs of resistance are at their assumed baseline values. Such reduction is not achievable if the fitness costs of resistance are lower than the baseline values.

Keywords

Malaria; Insecticide resistance; Population genetics; Equilibria; Stability

1. Introduction

Malaria, one of the biggest killers of humans worldwide [51], [52], is endemic in 91 countries and territories [51], [52]. In the year 2016 alone, the disease accounted for 216 million cases and 445,000 deaths (with most of the deaths occurring in Africa (91%), and South-East Asia (6%) [52]). A wide range of anti-malaria prevention (control) and treatment interventions, such as insecticide-treated nets (ITNs) or long-lasting insecticide-treated nets (LLINs), indoor residual spraying (IRS), intermittent preventive treatment (IPT), diagnostic testing and treatment (typically using *artemisinin*-based therapies) are being used to reduce (or prevent) malaria transmission in endemic areas [8], [37], [51]. Furthermore, concerted efforts are underway to develop a malaria vaccine (with a number of candidate vaccines at various stages of clinical trials [33], [51]). Unfortunately, however, despite all the existing prevention and treatment efforts, malaria remains a major global public health problem [51], and improving the effectiveness of the currently-available control strategies (such as the development of novel and more effective anti-malaria drugs and chemical insecticides) becomes even more pressingly-important.

ITNs and IRS are the commonly-used anti-malaria prevention strategies [8], [37], [51], and the use of the two intervention methods either singly, or in combination, has led to a significant decline in malaria-related morbidity and mortality in endemic areas [10], [37]. The World Health Organization (WHO) recommends the use of a combination of ITNs and IRS in many malaria transmission scenarios (particularly, for holoendemic and endemic situations) [37], [51]. Of the few insecticides approved for anti-malaria control, *pyrethroids* are the only chemical compounds/agents currently used on ITNs [3], [49]. A major concern associated with the widespread use of insecticides is the development of resistance to the chemical agents contained in the insecticides by the malaria vectors [6], [8], [10], [37], [42], [51], [52], [54]. Recent reports from some endemic regions showed that some principal malaria mosquito species (*Anopheles*) have developed resistance to most families of the insecticides recommended for public health use [6], [16], and the situation is worsening [42]. It is now generally believed that, if left unchecked, *Anopheles* insecticides resistance could lead to substantial increases in malaria incidence and mortality, with devastating public health consequences [42], [51].

The widespread use of ITNs and IRS in malaria-endemic areas pose important population genetics challenges associated with the selection of insecticide-resistant mosquito strains [31]. The study of population genetics (loosely defined as the study of the genetic variation within, and among, populations and the evolutionary factors that explain this variation [31], [32]) allows for the determination of the frequencies of alleles and genotypes in populations [8], [10], [13], [31]. Mosquitoes (or disease vectors in general) are said to be resistant to insecticides when the insecticides are no longer able to kill them on contact, or when they resist and survive the effect of the insecticides resistance and become able to reproduce in an insecticide-treated environment (or after being in contact with the chemical insecticides) [13], [31].

Mechanisms that decrease the insecticide toxicity originate from modifications in one or several genes of the mosquito (or the vector) [3], [31]. Mosquitoes that express the distinct genetic makeup pass along the genes for resistance to the next generation. That is, resistance is a heritable trait [3], [31], [49]. Gradually, the frequency of the allele that determines resistance, as well as the proportion of resistant mosquitoes in the community, increases over time (because they confer a strong survival advantage [3], [31], [49]). Through this process of selection, the mosquito population in the community gradually develops resistance to the insecticides [6], [13], [31].

The impact of insecticide resistance on the efficacy of mosquito control strategies (such as ITNs and IRS), and on the disease transmission process, may be measured by the survival rate of mosquito strains exposed to the insecticides [3], [49]. It should be mentioned that there are other factors that can reduce the ability of resistant mosquitoes to spread the disease (such as delayed insecticide effects in resistant mosquitoes, fitness costs associated with insecticide resistance, and increased parasite-induced mortality in insecticide resistant mosquitoes [3], [49]). Therefore, it is imperative for malaria modeling studies to incorporate the impact of these factors, as well as study the impact of insecticide resistance in mosquitoes on the efficacy of malaria control strategies (such as ITNs and IRS) and on the overall disease transmission dynamics [3], [8], [10], [13], [31], [49]. This forms the main motivation of the current study.

Mathematical models have, over the last century, been developed and used to investigate the effectiveness of the existing anti-malaria prevention and treatment interventions, and to understand the overall malaria transmission dynamics in human populations. Since the first mathematical model for malaria transmission introduced by Sir Ronald Ross [43], numerous mathematical models have been formulated and widely used to study transmission dynamics of malaria in a community, and to assess the impact and effectiveness of various anti-malaria control strategies (see, for instance, [1], [5], [15], [33], [34], [35], [36], [40], [53]). Furthermore, population genetic models have been formulated to study the evolution of insecticide resistance in the mosquito population, and its influence on malaria transmission dynamics (see, for instance, [8], [10], [13], [31] and some of the references therein).

As stated above, the incorporation of population genetics into population-level mathematical models for malaria transmission dynamics can be useful in the study of the impact of the evolution of insecticide resistance in mosquitoes on malaria dynamics, and in assessing the effectiveness of control strategies, such as ITNs and IRS. However, only few malaria modeling studies have formulated models that couple population genetics and population-level (i.e., epidemiology) dynamics of malaria disease. Kuniyoshi et al. [31] proposed a model that connects an SIR (susceptible-infected-recovered) formulation and population genetics (of vector insecticide resistance) for a vector-borne disease epidemic. Their study shows, *via* numerical simulations, that the presence of insecticide resistance gene is related to a larger number of infected humans and vectors. Luz et al. [32] developed a mathematical model of seasonal population dynamics of dengue mosquitoes (i.e., *Aedes* mosquitoes), that incorporates a population genetics framework describing insecticide resistance evolution when insecticide-based vector control (that target larvae, adult mosquitoes, or both) is used. Their results demonstrated that year-long continuous larval control and adult control imposed the greatest selection for resistance and combined targeting of larvae and adults at the start of the dengue season is optimal.

The main objective of the current study is to develop a novel mathematical model, that couples an SEIR (susceptible-exposed-infectious-recovered) deterministic formulation for the human dynamics; and an SEI formulation for the mosquitoes and population genetics, to study the population-level impact of mosquito insecticide resistance on the efficacy of ITNs and IRS interventions (and on the overall disease transmission dynamics). The primary goal of this study is to determine whether or not the combined use of ITNs and IRs in moderate and high malaria-endemic settings can lead to the effective control of the disease in these transmission settings, while effectively managing insecticide resistance. This will provide insight into the highly important global public health goal of understanding the link between insecticide resistance and malaria epidemiology. The model, which is formulated in Section 2, is rigorously analyzed in Section 3. Sensitivity analyses (based on computing elasticity indices of the associated reproduction number of the model) are carried out in Section 4. Numerical simulation results are presented in Section 5.

2. Model Derivation

The total human population at time t, denoted by $N_H(t)$, is split into various mutually-exclusive compartments of humans, where humans are classified into two groups based on how they use ITNs (that protects them from mosquito bites). Studies have shown that some individuals do not sleep under an ITNs, even-though they live within an area with high ITNs coverage [41] (due to several reasons, such as discomfort, heat, perceived low mosquito density, lack of awareness, etc). Individuals who exhibit this kind of behavior, or those who do not use ITNs properly (i.e., do not use ITNs correctly and consistently), are classified as belonging to a *high-risk* group, while individuals who use ITNs properly and consistently are classified as belonging to a *low-risk* group. The low-risk group is further classified as susceptible ($S_H^L(t)$), exposed ($E_H^L(t)$), infectious ($I_H^L(t)$), and recovered ($R_H^L(t)$) humans. Similarly, the high-risk group is classified into susceptible ($S_H^H(t)$), exposed ($E_H^H(t)$), infectious ($I_H^H(t)$), and recovered ($R_H^H(t)$) humans. Thus, the total human population at time t is given by:

$$N_H(t) = S_H^L(t) + E_H^L(t) + I_H^L(t) + R_H^L(t) + S_H^H(t) + E_H^H(t) + I_H^H(t) + R_H^H(t).$$

Mosquito insecticide resistance is determined by a single gene of two alleles (resistant (*R*) and susceptible (*S*) alleles), yielding three different mosquito genotypes namely: homozygous resistant (*RR*), homozygous sensitive (*SS*), and heterozygous (*RS*). The three genotypes have different levels of sensitivity to anti-malaria chemical insecticides [12]. Consequently, the total adult female *Anopheles* mosquito population at time *t*, denoted by $N_V(t)$, is split into sub-populations of homozygous resistant ($N^V_{RR}(t)$), homozygous sensitive ($N^V_{SS}(t)$) and heterozygous ($N^V_{RS}(t)$) mosquitoes. The population of homozygous resistant mosquitoes is stratified in terms of susceptible ($S^V_{RR}(t)$), exposed ($E^V_{RR}(t)$), and infectious ($I^V_{RR}(t)$) mosquitoes, while the population of homozygous sensitive mosquitoes is classified into susceptible ($S^V_{SS}(t)$), exposed ($E^V_{SS}(t)$), and infectious ($I^V_{SS}(t)$) mosquitoes. Finally, the heterozygous mosquito population is divided into susceptible ($S^V_{RS}(t)$), exposed ($E^V_{RS}(t)$), and infectious ($I^V_{RS}(t)$) mosquitoes. Thus,

$$N^V_{SS}(t) = S^V_{SS}(t) + E^V_{SS}(t) + I^V_{SS}(t), \quad N^V_{RS}(t) = S^V_{RS}(t) + E^V_{RS}(t) + I^V_{RS}(t),$$

$$N^V_{RR}(t) = S^V_{RR}(t) + E^V_{RR}(t) + I^V_{RR}(t) \quad \text{and} \quad N_V(t) = N^V_{RR}(t) + N^V_{RS}(t) + N^V_{SS}(t).$$

The use of ITNs and IRS is incorporated into the model to be developed as follows. When ITNs are used, the average number of bites *per* mosquito *per* unit time (i.e., mosquito-human contact rate), denoted by b_{Hi}, is defined as [1], [34]:

$$b_{Hi} = \beta_{max} - (\beta_{max} - \beta_{min})\, b, \tag{2.1}$$

where $\beta_{\max}$ is maximum mosquito-biting rate, $\beta_{\min}$ is minimum mosquito-biting rate, and b is the proportion of individuals in the population who use ITNs (i.e., ITNs coverage or proportion of ITNs usage/coverage in the community). The *forces of infections* for malaria transmission (i.e., the infection rates) are defined by (where λ_{HV} represents human-to-vector transmission rate and λ_{VH} represents vector-to-human transmission rate):

$$\lambda_{HV} = \frac{\beta_V b_{Hi}(I^L_H + I^H_H)}{N_H} \quad \text{and} \quad \lambda_{VH} = \frac{\beta_H b_{Hi}(I^V_{SS} + I^V_{RS} + I^V_{RR})}{N_H}, \tag{2.2}$$

where β_H is transmission probability from infectious mosquitoes to susceptible humans, and β_V is the transmission probability from infectious humans to susceptible mosquitoes. It is assumed that mating in the adult mosquito population (between opposite sexes) is random [31]. That is, all adult mosquitoes have the same chance of reproducing, and they mate with any other adult mosquito (of opposite sex) in the population with the same probability. A pair of alleles in the mosquito population is taken into account. These alleles determine the presence, or absence, of insecticide resistance, and, consequently, the value of the parameter for mosquito mortality and growth rate. The insecticide sensitive allele is represented by the letter *S*, and the insecticide resistant allele by the letter *R*. The frequency of each allele is calculated using the formulas [27], [31]:

$$q(t) = \frac{N_{SS}^{V}(t) + \frac{1}{2}N_{RS}^{V}(t)}{N_V(t)} \quad \text{and} \quad p(t) = \frac{N_{RR}^{V}(t) + \frac{1}{2}N_{RS}^{V}(t)}{N_V(t)}, \tag{2.3}$$

where $q(t)$ and $p(t)$ represent the frequencies of *S* and *R* alleles at time *t*, respectively. Thus, the probability of the formation of an *SS*-genotype is $q(t) \times q(t) = q^2(t)$. Similarly, the probability of the formation of an *RS*-genotype is $2p(t) \times q(t) = 2p(t)q(t)$ (that is, $p(t) \times q(t)$ for *RS* plus $q(t) \times p(t)$ for *SR*), and the probability of the formation of an *RR*-genotype is $p(t) \times p(t) = p^2(t)$. Consequently, the proportion of the *SS*, *RS* and *RR* genotypes in the next generation can be calculated by $q^2(t)$, $2p(t)q(t)$ and $p^2(t)$, in this order [31]. It should be observed that $q(t) + p(t) = 1$, and $q(t)^2 + 2p(t)q(t) + p(t)^2 = 1$ for all time $t \geq 0$ (which is the Hardy-Weinberg condition in population genetics [27], [31]). The following Verhulst–Pearl logistic birth functions, for the *SS*, *RS*, and *RR* genotypes (denoted, respectively, by B_{SS}^{V}, B_{RS}^{V} and B_{RR}^{V}), are chosen [31]:

$$\begin{aligned} B_{SS}^{V}(t) &= q^2(t)\, r_{SS} N_V(t) \left(1 - \frac{N_V(t)}{K_V}\right), \quad B_{RS}^{V}(t) = 2p(t)\, q(t)\, r_{RS} N_V(t) \left(1 - \frac{N_V(t)}{K_V}\right), \\ B_{RR}^{V}(t) &= p^2(t)\, r_{RR} N_V(t) \left(1 - \frac{N_V(t)}{K_V}\right), \end{aligned} \tag{2.4}$$

where $r_{SS} > 0$, $r_{RS} > 0$, and $r_{RR} > 0$ are the oviposition rates of adult female mosquitoes of *SS*-genotype, *RS*-genotype and *RR*-genotype, respectively. Furthermore, $K_V > 0$ is the environmental carrying capacity of adult female mosquitoes (it is assumed that $N_V(t) \leq K_V$ for all $t \geq 0$). It should be mentioned that, in this study, exposed humans or vectors mean infected humans or vectors who are not yet infectious.

The genetic-epidemiology model for the transmission dynamics of malaria, in the presence of ITNs and IRS interventions, is given by the following deterministic system of non-linear differential equations:

(2.5)

$$
\begin{aligned}
\frac{dS_H^L}{dt} &= \xi\Pi_H + \rho_H R_H^L - \theta\lambda_{VH} S_H^L - \mu_H S_H^L,\\
\frac{dE_H^L}{dt} &= \theta\lambda_{VH} S_H^L - (\nu_H + \mu_H) E_H^L,\\
\frac{dI_H^L}{dt} &= \nu_H E_H^L - (\gamma_H + \delta_H + \mu_H) I_H^L,\\
\frac{dR_H^L}{dt} &= \gamma_H I_H^L - (\rho_H + \mu_H) R_H^L,\\
\frac{dS_H^H}{dt} &= (1-\xi)\Pi_H + \rho_H R_H^H - \lambda_{VH} S_H^H - \mu_H S_H^H,\\
\frac{dE_H^H}{dt} &= \lambda_{VH} S_H^H - (\nu_H + \mu_H) E_H^H,\\
\frac{dI_H^H}{dt} &= \nu_H E_H^H - (\gamma_H + \delta_H + \mu_H) I_H^H,\\
\frac{dR_H^H}{dt} &= \gamma_H I_H^H - (\rho_H + \mu_H) R_H^H,\\
\frac{dS_{SS}^V}{dt} &= q^2 r_{SS} N_V \left(1 - \frac{N_V}{K_V}\right) - \lambda_{HV} S_{SS}^V - [\mu_V + (b+u_i)\delta_{Vi}] S_{SS}^V,\\
\frac{dE_{SS}^V}{dt} &= \lambda_{HV} S_{SS}^V - [\sigma_V + \mu_V + (b+u_i)\delta_{Vi}] E_{SS}^V,\\
\frac{dI_{SS}^V}{dt} &= \sigma_V E_{SS}^V - [\mu_V + \delta_V + (b+u_i)\delta_{Vi}] I_{SS}^V,\\
\frac{dS_{RS}^V}{dt} &= 2pqr_{RS} N_V \left(1 - \frac{N_V}{K_V}\right) - \lambda_{HV} S_{RS}^V\\
&\quad - [\alpha_{RS}\mu_V + (b+u_i)(1-h\rho_i)\delta_{Vi}] S_{RS}^V,\\
\frac{dE_{RS}^V}{dt} &= \lambda_{HV} S_{RS}^V - [\theta_{RS}\sigma_V + \alpha_{RS}\mu_V + (b+u_i)(1-h\rho_i)\delta_{Vi}] E_{RS}^V,\\
\frac{dI_{RS}^V}{dt} &= \theta_{RS}\sigma_V E_{RS}^V - [\alpha_{RS}\mu_V + \eta_{RS}\delta_V + (b+u_i)(1-h\rho_i)\delta_{Vi}] I_{RS}^V,\\
\frac{dS_{RR}^V}{dt} &= p^2 r_{RR} N_V \left(1 - \frac{N_V}{K_V}\right) - \lambda_{HV} S_{RR}^V\\
&\quad - [\alpha_{RR}\mu_V + (b+u_i)(1-\rho_i)\delta_{Vi}] S_{RR}^V,\\
\frac{dE_{RR}^V}{dt} &= \lambda_{HV} S_{RR}^V - [\theta_{RR}\sigma_V + \alpha_{RR}\mu_V + (b+u_i)(1-\rho_i)\delta_{Vi}] E_{RR}^V,\\
\frac{dI_{RR}^V}{dt} &= \theta_{RR}\sigma_V E_{RR}^V - [\alpha_{RR}\mu_V + \eta_{RR}\delta_V + (b+u_i)(1-\rho_i)\delta_{Vi}] I_{RR}^V.
\end{aligned}
$$

A schematic diagram of the model is depicted in Fig. 1 (the state variables are described in Table 1, and the parameters are described in Table 2). In (2.5), Π_H is the human recruitment rate (due immigration or birth). A proportion, ξ, of the recruited individuals is assumed to be low–risk, while the remaining proportion, $1-\xi$, is high–risk. The parameter ρ_H represents the rate of loss of temporary immunity acquired from prior malaria infection (i.e., the rate at which recovered humans become fully susceptible again). Susceptible humans acquire malaria infection, following effective contact with an infected female *Anopheles* mosquito, at a rate λ_{VH} ($\theta\lambda_{VH}$) for the high-risk (low-risk) human group (the parameter $0 < \theta < 1$ accounts for the assumed decrease in risk of infection for low-risk individuals, in comparison to high-risk individuals). Humans in all epidemiological compartments are assumed to suffer natural death at a rate μ_H. Exposed humans develop clinical symptoms of malaria, and become infectious, at a rate of ν_H. Infectious humans suffer additional death due to malaria infection at a rate of δ_H, and recover (naturally) at a rate of γ_H.

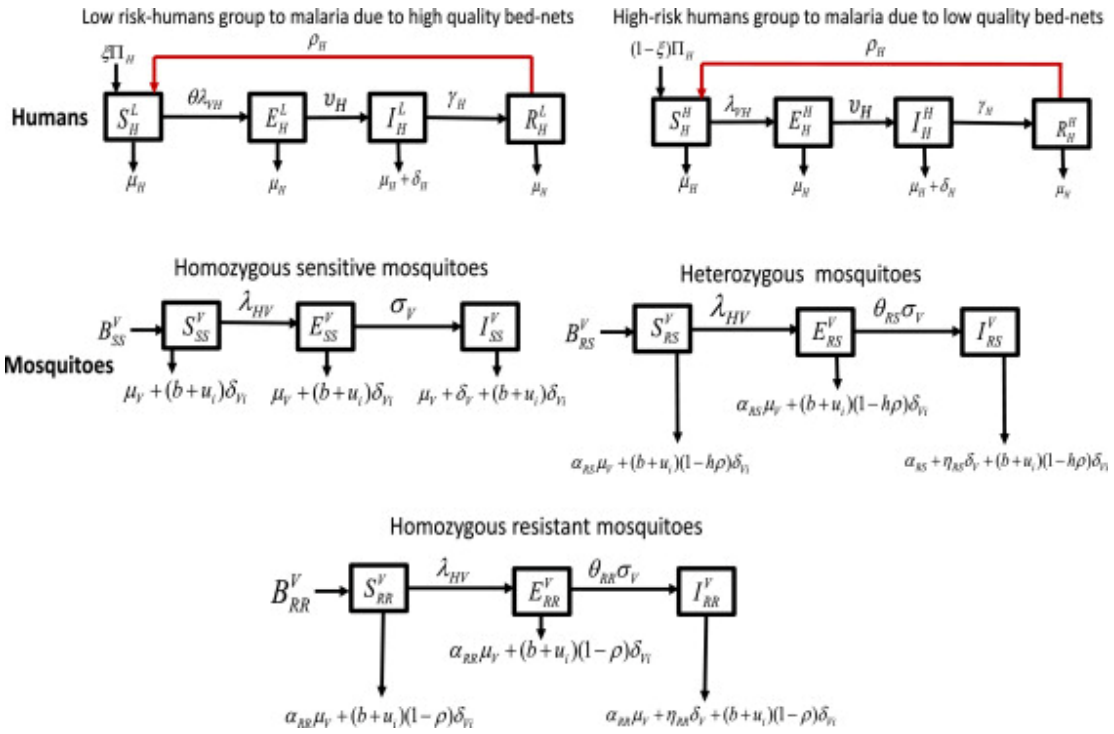

Fig. 1. Schematic Diagram of the Model (2.5).

Table 1
Descriptions of the state variables of the model.

Parameter	Description
S_H^l	Population of low-risk susceptible humans
E_H^l	Population of low-risk exposed humans
I_H^l	Population of low-risk infectious humans
R_H^l	Population of low-risk recovered humans
S_H^{ll}	Population of high-risk susceptible humans
E_H^{ll}	Population of high-risk exposed humans
I_H^{ll}	Population of high-risk infectious humans
R_H^{ll}	Population of high-risk recovered humans
S_{SS}^V	Population of adult female mosquitoes that are homozygous-sensitive to insecticides and susceptible to malaria
E_{SS}^V	Population of adult female mosquitoes that are homozygous-sensitive to insecticides and exposed to malaria
I_{SS}^V	Population of adult female mosquitoes that are homozygous-sensitive to insecticides and infectious to malaria
S_{RS}^V	Population of adult female mosquitoes that are heterozygous to insecticides and susceptible to malaria
E_{RS}^V	Population of adult female mosquitoes that are heterozygous to insecticides and exposed to malaria
I_{RS}^V	Population of adult female mosquitoes that are heterozygous to insecticides and infectious with malaria
S_{RR}^V	Population of adult female mosquitoes that are homozygous-resistant to insecticides and susceptible to malaria
E_{RR}^V	Population of adult female mosquitoes that are homozygous-resistant to insecticides and exposed to malaria
I_{RR}^V	Population of adult female mosquitoes that are homozygous-resistant to insecticides and infectious with malaria

It is assumed that mosquito insecticide resistance is inherited (vertically) [31], [32]. That is, an insecticide resistant adult female *Anopheles* mosquito produces insecticide resistant offsprings. Susceptible mosquitoes of all genotypes (S_{SS}^V, S_{RS}^V and S_{RR}^V) acquire malaria infection at the rate λ_{HV}, and mosquitoes of *SS*-genotype (S_{SS}^V, E_{SS}^V, and I_{SS}^V) suffer natural mortality at a rate of μ_V, and additional mortality due to the use of insecticides, at a rate of $(b + u_i)\,\delta_{Vi}$. Infected *SS*-genotype mosquitoes (I_{SS}^V) suffer additional disease-induced death at a rate δ_V, and exposed *SS*-genotype mosquitoes (E_{SS}^V) become infectious at a rate of σ_V.

It is further assumed that there is mortality fitness cost of homozygous resistant and heterozygous mosquitoes [2], [4], [8], and that mosquitoes of the *RR*-genotype suffer natural mortality at a rate $\alpha_{RR}\mu_V$ (with $\alpha_{RR} \geq 1$ accounting for the assumed increase in mortality rate of *RR*-genotype mosquitoes due to fitness cost in comparison to the natural mortality rate of *SS*-genotype mosquitoes) and mosquitoes of *RS*-genotype suffer natural mortality at a rate $\alpha_{RS}\mu_V$ (where $1 \leq \alpha_{RS} \leq \alpha_{RR}$ accounts for the assumed increase in mortality rate of *RS*-genotype mosquitoes due to fitness cost, in comparison to that of *SS*-genotype mosquitoes, it should be mentioned that $\alpha_{RS} = \alpha_{RR}$ if the resistant allele (*R*) is dominant, and $\alpha_{RS} = 1$ if the *R* allele is recessive).

Infected mosquitoes suffer disease-induced mortality at a rate δ_V (in particular, vectors with *RR*-genotype die at a rate of $\eta_{RR}\delta_V$, with $\eta_{RR} \geq 1$ accounting for the assumed increase in the disease-induced mortality of *RR*-genotype mosquitoes due to fitness cost, in comparison to the disease-induced mortality of vectors with *SS*-genotype; vectors of *RS*-genotype die at a rate $\eta_{RS}\delta_V$, where $1 \leq \eta_{RS} \leq \eta_{RR}$ accounts for the assumed increase in the disease-induced mortality of *RS*-genotype mosquitoes due to fitness cost, in comparison to the disease-induced mortality of vectors with *SS*-genotype. It should be noted that $\eta_{RS} = \eta_{RR}$ if the *R* allele is dominant, and $\eta_{RS} = 1$ if it is recessive). Similarly, exposed mosquitoes of *RR*-genotype become infectious at a rate $\theta_{RR}\sigma_V$ (with $\theta_{RR} \geq 1$ accounting for the assumed increase in disease progression rate of *RR*-genotype mosquitoes due to fitness cost, in comparison to exposed homozygous-sensitive mosquitoes) and mosquitoes of *RS*-genotype become infectious at rate $\theta_{RS}\sigma_V$ (where $1 \leq \theta_{RS} \leq \theta_{RR}$ accounts for the assumed increase in disease progression rate of *RS*-genotype mosquitoes due to fitness cost, in comparison to exposed homozygous-sensitive mosquitoes. Here, $\theta_{RS} = \theta_{RR}$ if the *R* allele is dominant, and $\theta_{RS} = 1$ if it is recessive).

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RR-genotype become infectious at a rate $\theta_{RR}\sigma_V$ (with $\theta_{RR} \geq 1$ accounting for the assumed increase in disease progression rate of *RR*-genotype mosquitoes due to fitness cost, in comparison to exposed homozygous-sensitive mosquitoes) and mosquitoes of *RS*-genotype become infectious at rate $\theta_{RS}\sigma_V$ (where $1 \leq \theta_{RS} \leq \theta_{RR}$ accounts for the assumed increase in disease progression rate of *RS*-genotype mosquitoes due to fitness cost, in comparison to exposed homozygous-sensitive mosquitoes. Here, $\theta_{RS} = \theta_{RR}$ if the *R* allele is dominant, and $\theta_{RS} = 1$ if it is recessive).

Mosquitoes of *SS*-genotype die (when they encounter an ITN or when they become exposed to IRS) at a rate $(b + u_i)\,\delta_{Vi}$, where δ_{Vi} is death rate due to the (encounter with) insecticides, $0 \leq u_i \leq 1$ is the proportion of houses in the community that are sprayed with IRS, and $0 \leq b \leq 1$ is the proportion of humans in the community who use ITNs. The mosquito population of *SS*-genotype is decreased due to the use of insecticides, at a rate $(u_i + b)\,\delta_{Vi}$. Similarly, the population of mosquitoes of *RR*-genotype is decreased due to the use of insecticides at a rate of $(u_i + b)\,(1 - \rho_i)\,\delta_{Vi}$, where $0 \leq \rho_i \leq 1$ is a modification parameter accounting for the assumed decrease in the mortality rate of the *RR*-genotype vectors due to the insecticides, in comparison to vectors of the *SS*-genotype (due to mortality fitness cost). Finally, vectors of *RS*-genotype suffer mortality due to the use of insecticides at a rate $(u_i + b)\,(1 - h\rho_i)\,\delta_{Vi}$, where $0 \leq h \leq 1$ is a modification parameter accounting for the measure of the dominance of the resistant allele (i.e., $h = 1$ models the case where the resistant allele is dominant, and $h = 0$ represents the case when it is recessive). The parameter *h* is termed the *level of dominance of the resistant allele*. It measures the relative position of the *RS* heterozygote relative to the genotypes of the two corresponding homozygotes *SS* and *RR* [12].

In addition to being one of the very few malaria transmission models to couple epidemiology with adult mosquito population genetics associated with the use of chemical insecticides (such as the model in [31]), the model (2.5) is an extension of numerous malaria transmission models that study the impact of insecticide resistance and dynamics of insecticide-resistant vectors when chemical insecticides (such as ITNs, IRS, or larvacide) are used in vector control (such as those in [8], [10], [11], [13], [25], [31], [50]) by, *inter alia*:

i. Including ITNs and IRS controls in a population-level mathematical model with SEIR human and SEI (sensitive homozygous, hetrozygous, and resistant homozygous) mosquito classes coupled with population genetics (these are not included in the population genetic models in [8], [10], [13], or in the population-level mathematical models in [8], [10], [11], [13], [25], [50], or in the coupled model in [31]);

ii. Including the cost of resistance through reducing fecundity (growth rate) and increasing natural mortality in heterozygous and homozygous resistant mosquitoes (these are not included in the models in [11], [13], [25], [50]);

iii. Incorporating the level of dominance (h) that measures of the relative position of the *RS*-genotype relative to *SS* and *RR*-genotypes in terms of their sensitivity to insecticide (this is not included in the models in [11], [13], [25], [31], [50]).

The basic qualitative properties of the model (2.5) will now be explored.

2.1. Basic properties

All the state variables of the model (2.5) are non-negative (since they represent human and female mosquito populations).

Theorem 2.1

If $N_H(0) > 0$, *the biologically-feasible region*

$$\begin{aligned}\Omega \;=\; & \{(S_H^L, E_H^L, I_H^L, R_H^L, S_H^H, E_H^H, I_H^H, R_H^H, S_{SS}^V, E_{SS}^V, I_{SS}^V, S_{RS}^V, E_{RS}^V, I_{RS}^V, S_{RR}^V, E_{RR}^V, \\ & 0 < (N_H)_{min} \leq N_H(t) \leq \frac{\Pi_H}{\mu_H}, \text{ and } 0 \leq N_V \leq K_V(\mathscr{R}_V - 1)/\mathscr{R}_V\},\end{aligned} \tag{2.6}$$

where,

$$(N_H)_{min} = min\left(N_H(0), \tfrac{\Pi_H}{\mu_H+\delta_H}\right),$$

$$\omega_V = \min\{\mu_V + (b+u_i)\delta_{Vi}, \alpha_{RS}\mu_V + (b+u_i)(1-h\rho_i)\delta_{Vi}, \alpha_{RR}\mu_V + (b+u_i)(1-$$

$$\mathscr{R}_V = \tfrac{r_{SS}+r_{RS}+r_{RR}}{\omega_V},$$

is positively-invariant and attracts all solutions of the model (2.5) in $\mathbb{R}_+^{17}$.

Proof

Adding the equations related to the human population in the model system (2.5) gives:

$$\frac{dN_H}{dt} = \Pi_H - \delta_H \left(I_H^L + I_H^H\right) - \mu_H N_H \leq \mu_H \left(\frac{\Pi_H}{\mu_H} - N_H\right),$$

so that,

$$N_H(t) \leq \frac{\Pi_H}{\mu_H} + e^{-\mu_H t}\left(N_H(0) - \frac{\Pi_H}{\mu_H}\right).$$

Therefore, if $N_H(0) \leq \frac{\Pi_H}{\mu_H}$, then $N_H(t) \leq \frac{\Pi_H}{\mu_H}$ for all $t \geq 0$. On the other hand, if $N_H(0) \geq \frac{\Pi_H}{\mu_H}$, then $N_H(t) \to \frac{\Pi_H}{\mu_H}$, as $t \to \infty$. Similarly,

$$\frac{dN_H}{dt} \geq \Pi_H - (\delta_H + \mu_H) N_H = (\delta_H + \mu_H)\left(\frac{\Pi_H}{(\delta_H + \mu_H)} - N_H\right).$$

Hence,

$$N_H(t) \geq e^{-(\delta_H+\mu_H)t} N_H(0) + \frac{\Pi_H}{\delta_H + \mu_H}\left(1 - e^{-(\delta_H+\mu_H)t}\right). \tag{2.7}$$

The right-hand side of Inequality (2.7) is monotone (or constant if $N_H(0) = \Pi_H/(\delta_H + \mu_H)$), since its derivative with respect to t is

$(\delta_H + \mu_H) e^{-(\delta_H+\mu_H)t}\left(\frac{\mu_H}{\mu_H+\delta_H} - N_H(0)\right)$, and its absolute minimum ($(N_H)_{\min}$) is $(N_H)_{\min} = \min\left\{N_H(0), \frac{\Pi_H}{\delta_H+\mu_H}\right\}$. Therefore, $0 < (N_H)_{\min} \leq N_H(t)$ for all $t > 0$.
Finally, adding all the equations of the model related to the mosquito population gives:

$$\begin{aligned}
\frac{dN_V}{dt} &\leq q^2 r_{SS} N_V\left(1 - \frac{N_V}{K_V}\right) + 2pq r_{RS} N_V\left(1 - \frac{N_V}{K_V}\right) + p^2 r_{RR} N_V\left(1 - \frac{N_V}{K_V}\right) - \omega_V N_V, \\
&\leq (r_{SS} + r_{RS} + r_{RR})\left(1 - \frac{N_V}{K_V}\right) N_V - \omega_V N_V, \\
&= (r_{SS} + r_{RS} + r_{RR} - \omega_V)\left[1 - \frac{N_V}{K_V(r_{SS} + r_{RS} + r_{RR} - \omega_V)/(r_{SS} + r_{RS} + r_{RR})}\right] N_V, \\
&= (r_{SS} + r_{RS} + r_{RR} - \omega_V)\left[1 - \frac{N_V}{K_V(\mathscr{R}_V - 1)/\mathscr{R}_V}\right] N_V.
\end{aligned}$$

Thus,

$$\frac{dN_V}{dt} \leq (r_{SS} + r_{RS} + r_{RR} - \omega_V)\left[1 - \frac{N_V}{K_V(\mathscr{R}_V - 1)/\mathscr{R}_V}\right] N_V.$$

Hence, by Gronwall's inequality [14], the solution $N_V(t)$, of the above inequality, satisfies

$$N_V(t) \leq \frac{K_V(\mathscr{R}_V - 1)/\mathscr{R}_V}{1 + Ae^{-(r_{SS}+r_{RS}+r_{RR}-\omega_V)t}}, \quad \text{where} \quad A = \frac{K_V(\mathscr{R}_V - 1)/\mathscr{R}_V - N_V(0)}{N_V(0)},$$

which implies that $N_V(t) \leq K_V(\mathscr{R}_V - 1)/\mathscr{R}_V$ if the initial condition, $N_V(0)$, is in the feasible region Ω. Furthermore, $N_V(t) \leq K_V(\mathscr{R}_V - 1)/\mathscr{R}_V$, as $t \to \infty$, for any non-negative initial condition. Hence, the biologically-feasible region, Ω, is positively-invariant and attracts all solutions of the model (2.5) in $\mathbb{R}^{17}_+$.□

It should be observed that the upper bound of $N_V(t)$, given by $K_V(\mathscr{R}_V - 1)/\mathscr{R}_V$, is positive if

$$\mathscr{R}_V = \frac{r_{SS}+r_{RS}+r_{RR}}{\omega_V} > 1.$$

That is, the quantity $\frac{K_V(\mathscr{R}_V-1)}{\mathscr{R}_V}$ is positive if the sum mosquito growth rates of the three genotypes is higher than the minimum of the sum of the death rates due to natural, disease-induced and insecticide-induced death rates of all mosquito classes. In a closed environment, without immigration and migration, if mosquito death rate is higher than the birth rate, then the mosquito population will eventually die out. That is, the mosquito population eventually dies out if $\mathscr{R}_V < 1$ (i.e., the disease will die out if $\mathscr{R}_V < 1$). For the rest of this study, it is assumed that $\mathscr{R}_V > 1$ (so that mosquitoes always exist in the study area).

3. Mathematical analysis

3.1. Existence and asymptotic stability of disease-free equilibria

It is convenient to, first of all, define the quantities:

$$\begin{aligned}
g_1 &= \nu_H + \mu_H, \; g_2 = \gamma_H + \delta_H + \mu_H, \; g_3 = \rho_H + \mu_H,\\
g_4 &= \mu_V + (b+u_i)\delta_{Vi}, \quad g_5 = \sigma_V + \mu_V + (b+u_i)\delta_{Vi},\\
g_6 &= \mu_V + \delta_V + (b+u_i)\delta_{Vi}, \quad g_7 = \alpha_{RS}\mu_V + (b+u_i)(1-h\rho_i)\delta_{Vi},\\
g_8 &= \theta_{RS}\sigma_V + \alpha_{RS}\mu_V + (b+u_i)(1-h\rho_i)\delta_{Vi},\\
g_9 &= \alpha_{RS}\mu_V + \eta_{RS}\delta_V + (b+u_i)(1-h\rho_i)\delta_{Vi},\\
g_{10} &= \alpha_{RR}\mu_V + (b+u_i)(1-\rho_i)\delta_{Vi},\\
g_{11} &= \theta_{RR}\sigma_V + \alpha_{RR}\mu_V + (b+u_i)(1-\rho_i)\delta_{Vi} \quad \text{and}\\
g_{12} &= \alpha_{RR}\mu_V + \eta_{RR}\delta_V + (b+u_i)(1-\rho_i)\delta_{Vi}.
\end{aligned}$$

The disease-free equilibrium (DFE) of the model (2.5) is obtained by setting all the infected components $(E^L_H, I^L_H, E^H_H, I^H_H, E^V_{SS}, I^V_{SS}, E^V_{RS}, I^V_{RS}, E^V_{RR}, I^V_{RR})$ of the model to zero, and the non-infected components at the DFE, denoted by

$((S_H^L)^*, (R_H^L)^*, (S_H^H)^*, (R_H^H)^*, (S_{SS}^V)^*, (S_{RS}^V)^*, (S_{RR}^V)^*)$, are given by:

$(S_H^L)^* = \frac{\xi\Pi_H}{\mu_H}, (R_H^L)^* = 0, (S_H^H)^* = \frac{(1-\xi)\Pi_H}{\mu_H}, (R_H^H)^* = 0, q^* = \frac{(S_{SS}^V)^* + \frac{1}{2}(S_{RS}^V)^*}{N_V^*}$, and $p^* = \frac{(S_{RR}^V)^* + \frac{1}{2}(S_{RS}^V)^*}{N_V^*}$, where $N_V^* = (S_{SS}^V)^* + (S_{RS}^V)^* + (S_{RR}^V)^*$. It can be shown, at the DFE, that q^* satisfies the following equation:

$$q^*(q^* - 1)\{[(\mathscr{R}_{SS} - \mathscr{R}_{RS}) + (\mathscr{R}_{RR} - \mathscr{R}_{RS})]q^* - (\mathscr{R}_{RR} - \mathscr{R}_{RS})\} = 0, \tag{3.1}$$

where,

$$\mathscr{R}_{SS} = \frac{r_{SS}}{g_4}, \quad \mathscr{R}_{RS} = \frac{r_{RS}}{g_7}, \quad \text{and} \quad \mathscr{R}_{RR} = \frac{r_{RR}}{g_{10}}. \tag{3.2}$$

Lemma 3.1

It follows from Equation (3.1), at DFE, that q^* and p^* can take values from any one of the following four cases (this follows from the solution of Equation (3.1)) assuming positive initial mosquito population (i.e., $N_V(0) > 0$):

i. $q^* = 0$ *and* $p^* = 1$, *or*

ii. $q^* = 1$ *and* $p^* = 0$, *or*

iii. $q^* = \frac{\mathscr{R}_{RR} - \mathscr{R}_{RS}}{(\mathscr{R}_{SS} - \mathscr{R}_{RS}) + (\mathscr{R}_{RR} - \mathscr{R}_{RS})}$ *and* $p^* = \frac{\mathscr{R}_{SS} - \mathscr{R}_{RS}}{(\mathscr{R}_{SS} - \mathscr{R}_{RS}) + (\mathscr{R}_{RR} - \mathscr{R}_{RS})}$,

provided that $(\mathscr{R}_{SS} - \mathscr{R}_{RS})(\mathscr{R}_{RR} - \mathscr{R}_{RS}) > 0$, *or*

iv. *any value* q^*, p^* *in [0,1] with* $p^* + q^* = 1$, *if* $\mathscr{R}_{SS} = \mathscr{R}_{RS} = \mathscr{R}_{RR}$.

It should be noted that q^* and p^* (with the assumption as in Lemma 3.1) must satisfy the equality $p^* + q^* = 1$ in all cases. Therefore, the model (2.5) has four disease-free equilibria, namely a trivial disease-free equilibrium (TDFE; denoted by $\mathscr{E}_{0T}$), a non-trivial sensitive-only disease-free boundary equilibrium (NTSDFE; denoted by $\mathscr{E}_{0S}$, when $q^* = 1$ and $p^* = 0$), a non-trivial resistant-only disease-free boundary equilibrium (NTRDFE; denoted by $\mathscr{E}_{0R}$, when $q^* = 0$ and $p^* = 1$) and a non-trivial co-existence disease-free equilibrium (NTCDFE; denoted by $\mathscr{E}_{0C}$, when $q^* > 0$ and $p^* > 0$), as given below:

(i) TDFE:

$$\begin{aligned}\mathscr{E}_{0T} &= \Big((S_H^L)^{*T}, (E_H^L)^{*T}, (I_H^L)^{*T}, (R_H^L)^{*T}, (S_H^H)^{*T}, (E_H^H)^{*T}, (I_H^H)^{*T}, (R_H^H)^{*T}, (S_{SS}^V)^{*T}, \\ &\quad (E_{SS}^V)^{*T}, (I_{SS}^V)^{*T}, (S_{RS}^V)^{*T}, (E_{RS}^V)^{*T}, (I_{RS}^V)^{*T}, (S_{RR}^V)^{*T}, (E_{RR}^V)^{*T}, (I_{RR}^V)^{*T}\Big), \\ &= \Big((S_H^L)^{*T}, 0, 0, 0, (S_H^H)^{*T}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0\Big),\end{aligned}$$

(ii) NTSDFE:

$$\begin{aligned}\mathscr{E}_{0S} &= \Big(\left(S_H^L\right)^{*S}, \left(E_H^L\right)^{*S}, \left(I_H^L\right)^{*S}, \left(R_H^L\right)^{*S}, \left(S_H^H\right)^{*S}, \left(E_H^H\right)^{*S}, \left(I_H^H\right)^{*S}, \left(R_H^H\right)^{*S}, \left(S_{SS}^V\right)^{*S}, \\ &\quad \left(E_{SS}^V\right)^{*S}, \left(I_{SS}^V\right)^{*S}, \left(S_{RS}^V\right)^{*S}, \left(E_{RS}^V\right)^{*S}, \left(I_{RS}^V\right)^{*S}, \left(S_{RR}^V\right)^{*S}, \left(E_{RR}^V\right)^{*S}, \left(I_{RR}^V\right)^{*S}\Big), \\ &= \Big(\left(S_H^L\right)^{*S}, 0, 0, 0, \left(S_H^H\right)^{*S}, 0, 0, 0, \left(S_{SS}^V\right)^{*S}, 0, 0, 0, 0, 0, 0, 0, 0\Big),\end{aligned}$$

(iii) NTRDFE:

$$\begin{aligned}\mathscr{E}_{0R} &= \Big(\left(S_H^L\right)^{*R}, \left(E_H^L\right)^{*R}, \left(I_H^L\right)^{*R}, \left(R_H^L\right)^{*R}, \left(S_H^H\right)^{*R}, \left(E_H^H\right)^{*R}, \left(I_H^H\right)^{*R}, \left(R_H^H\right)^{*R}, \left(S_{SS}^V\right)^{*R}, \\ &\quad \left(E_{SS}^V\right)^{*R}, \left(I_{SS}^V\right)^{*R}, \left(S_{RS}^V\right)^{*R}, \left(E_{RS}^V\right)^{*R}, \left(I_{RS}^V\right)^{*R}, \left(S_{RR}^V\right)^{*R}, \left(E_{RR}^V\right)^{*R}, \left(I_{RR}^V\right)^{*R}\Big), \\ &= \Big(\left(S_H^L\right)^{*R}, 0, 0, 0, \left(S_H^H\right)^{*R}, 0, 0, 0, 0, 0, 0, 0, 0, 0, \left(S_{RR}^V\right)^{*R}, 0, 0\Big),\end{aligned}$$

where,

$$\begin{aligned}\left(S_H^L\right)^{*T} &= \left(S_H^L\right)^{*S} = \left(S_H^L\right)^{*R} = \left(S_H^L\right)^{*C} = \frac{\xi\Pi_H}{\mu_H}, \\ \left(S_H^H\right)^{*T} &= \left(S_H^H\right)^{*S} = \left(S_H^H\right)^{*R} = \left(S_H^H\right)^{*C} = \frac{(1-\xi)\,\Pi_H}{\mu_H}, \\ \left(S_{SS}^V\right)^{*S} &= \frac{K_V\left(\mathscr{R}_{SS}-1\right)}{\mathscr{R}_{SS}}, \\ \left(S_{RR}^V\right)^{*R} &= \frac{K_V\left(\mathscr{R}_{RR}-1\right)}{\mathscr{R}_{RR}}, \\ \left(S_{SS}^V\right)^{*C} &= \frac{\left(q^*\right)^2\mathscr{R}_{SS}K_V\left(\mathscr{R}_C-1\right)}{\mathscr{R}_C^2}, \\ \left(S_{RS}^V\right)^{*C} &= \frac{2p^*q^*\mathscr{R}_{RS}K_V\left(\mathscr{R}_C-1\right)}{\mathscr{R}_C^2}, \quad \text{and} \\ \left(S_{RR}^V\right)^{*C} &= \frac{\left(p^*\right)^2\mathscr{R}_{RR}K_V\left(\mathscr{R}_C-1\right)}{\mathscr{R}_C^2},\end{aligned} \tag{3.3}$$

with, q^* and p^* given by options (iii) or (iv) of the possible solutions given in Lemma 3.1 (where $p^* > 0$ and $q^* > 0$) and

$$\mathscr{R}_C = \left(q^*\right)^2\mathscr{R}_{SS} + 2p^*q^*\mathscr{R}_{RS} + \left(p^*\right)^2\mathscr{R}_{RR}. \tag{3.4}$$

It follows from Eq. (3.3) that

(i.) The NTSDFE ($\mathscr{E}_{0S}$) exists if and only if $\mathscr{R}_{SS} > 1$,

(ii.) The NTRDFE ($\mathscr{E}_{0R}$) exists if and only if $\mathscr{R}_{RR} > 1$, and

(iii.) The NTCDFE ($\mathscr{E}_{0C}$) exists if and only if $\left(\mathscr{R}_{SS} - \mathscr{R}_{RS}\right)\left(\mathscr{R}_{RR} - \mathscr{R}_{RS}\right) > 0$ and $\mathscr{R}_C > 1$, or if and only if $\mathscr{R}_{SS} = \mathscr{R}_{RS} = \mathscr{R}_{RR}$ and $\mathscr{R}_C > 1$.

The trivial disease-free equilibrium (TDFE) is not ecologically realistic in a malaria-endemic setting(since it is associated with having no mosquitoes in the community. Consequently, the asymptotic stability of this ecologically-unrealistic equilibrium is not investigated in this study). The local asymptotic stability of the NTSDFE ($\mathscr{E}_{0S}$), NTRDFE ($\mathscr{E}_{0R}$) and NTCDFE ($\mathscr{E}_{0C}$) will be discussed in Section 3.2.

It is convenient to define, for $\mathscr{R}_V > 1$, the following general non-trivial disease-free equilibrium of the model (2.5), denoted by $\mathscr{E}_{df}$:

$$\begin{aligned}\mathscr{E}_{df} &= (S_H^L, E_H^L, I_H^L, R_H^L, S_H^H, E_H^H, I_H^H, R_H^H, S_{SS}^V, E_{SS}^V, I_{SS}^V, S_{RS}^V, E_{RS}^V, I_{RS}^V, S_{RR}^V, E_{RR}^V, \\ &\quad I_{RR}^V), \\ &= \left(\frac{\xi\Pi_H}{\mu_H}, 0, 0, 0, \frac{(1-\xi)\,\Pi_H}{\mu_H}, 0, 0, 0, \left(S_{SS}^V\right)^0, 0, 0, \left(S_{RS}^V\right)^0, 0, 0, \left(S_{RR}^V\right)^0, 0, 0\right).\end{aligned} \tag{3.5}$$

That is,

(i.) If $\mathscr{E}_{df} = \mathscr{E}_{0S}$, then $\left(S_{SS}^V\right)^0 = \left(S_{SS}^V\right)^{*S}$, $\left(S_{RS}^V\right)^0 = 0$, and $\left(S_{RR}^V\right)^0 = 0$.

(ii.) If $\mathscr{E}_{df} = \mathscr{E}_{0R}$, then $\left(S_{SS}^V\right)^0 = 0$, $\left(S_{RS}^V\right)^0 = 0$, and $\left(S_{RR}^V\right)^0 = \left(S_{RR}^V\right)^{*R}$.

(iii.) If $\mathscr{E}_{df} = \mathscr{E}_{0C}$, then $\left(S_{SS}^V\right)^0 = \left(S_{SS}^V\right)^{*C}$, $\left(S_{RS}^V\right)^0 = \left(S_{RS}^V\right)^{*C}$, and $\left(S_{RR}^V\right)^0 = \left(S_{RR}^V\right)^{*C}$.

3.2. local asymptotic stability of the generalized non-trivial disease-free equilibrium ($\mathscr{E}_{df}$)

The linear stability of the generalized non-trivial disease-free equilibrium ($\mathscr{E}_{df}$) of the model (2.5) can be established using the next generation operator method [21], [22] on the model (2.5). The following ordering is used for the infected compartments: $\left(E_H^L, I_H^L, E_H^H, I_H^H, E_{SS}^V, I_{SS}^V, E_{RS}^V, I_{RS}^V, E_{RR}^V, I_{RR}^V\right)$. It follows, using the notation in [22], that the next generation matrices F and V (for the new infection terms and the remaining transfer terms, respectively) associated with the model (2.5) are given, respectively, by:

(3.6)

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \theta\beta_H b_{Hi}\xi & 0 & \theta\beta_H b_{Hi}\xi & 0 & \theta\beta_H b_{Hi}\xi \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_H b_{Hi}\,(1-\xi) & 0 & \beta_H b_{Hi}\,(1-\xi) & 0 & \beta_H b_{Hi}\,(1-\xi) \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\beta_V b_{Hi}\mu_H \left(S_{SS}^V\right)^0}{\Pi_H} & 0 & \frac{\beta_V b_{Hi}\mu_H \left(S_{SS}^V\right)^0}{\Pi_H} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\beta_V b_{Hi}\mu_H \left(S_{RS}^V\right)^0}{\Pi_H} & 0 & \frac{\beta_V b_{Hi}\mu_H \left(S_{RS}^V\right)^0}{\Pi_H} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\beta_V b_{Hi}\mu_H \left(S_{RR}^V\right)^0}{\Pi_H} & 0 & \frac{\beta_V b_{Hi}\mu_H \left(S_{RR}^V\right)^0}{\Pi_H} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$V = \begin{pmatrix} g_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\nu_H & g_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & g_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\nu_H & g_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & g_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\sigma_V & g_6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & g_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\theta_{RS}\sigma_V & g_9 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & g_{11} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\theta_{RR}\sigma_V & g_{12} \end{pmatrix}, \tag{3.7}$$

so that the *basic reproduction number* of the model (2.5) is given by [21], [22]:

$$\mathscr{R}_0 = \rho\left(FV^{-1}\right) = \sqrt{\mathscr{R}_h\left(\mathscr{R}_{0_{SS}} + \mathscr{R}_{0_{RS}} + \mathscr{R}_{0_{RR}}\right)}, \tag{3.8}$$

where,

$$\begin{aligned} \mathscr{R}_h &= \frac{b_{Hi}\beta_H\mu_H\nu_H}{g_1 g_2 \Pi_H}, \quad \mathscr{R}_{0_{SS}} = \frac{b_{Hi}\beta_V\sigma_V\left[\theta\xi + (1-\xi)\right]\left(S_{SS}^V\right)^0}{g_5 g_6}, \\ \mathscr{R}_{0_{RS}} &= \frac{b_{Hi}\beta_V\sigma_V\left[\theta\xi + (1-\xi)\right]\theta_{RS}\left(S_{RS}^V\right)^0}{g_8 g_9} \quad \text{and} \quad \mathscr{R}_{0_{RR}} \\ &= \frac{b_{Hi}\beta_V\sigma_V\left[\theta\xi + (1-\xi)\right]\theta_{RR}\left(S_{RR}^V\right)^0}{g_{11} g_{12}}. \end{aligned} \tag{3.9}$$

It is convenient to define the following threshold quantities:

$$\mathscr{R}_0^{0S} = \mathscr{R}_0\Big|_{\mathscr{E}_{df}=\mathscr{E}_{0S}} = \sqrt{\frac{b_{Hi}\beta_H\mu_H\nu_H}{g_1 g_2 \Pi_H}\left(\frac{b_{Hi}\beta_V\sigma_V\left[\theta\xi+(1-\xi)\right]\left(S_{SS}^V\right)^{*S}}{g_5 g_6}\right)}, \tag{3.10}$$

$$\mathscr{R}_0^{0R} = \mathscr{R}_0\Big|_{\mathscr{E}_{df}=\mathscr{E}_{0R}} = \sqrt{\frac{b_{Hi}\beta_H\mu_H\nu_H}{g_1 g_2 \Pi_H}\left(\frac{b_{Hi}\beta_V\sigma_V\left[\theta\xi+(1-\xi)\right]\theta_{RR}\left(S_{RR}^V\right)^{*R}}{g_{11} g_{12}}\right)}, \tag{3.11}$$

$$\mathscr{R}_0^{0C} = \mathscr{R}_0\Big|_{\mathscr{E}_{df}=\mathscr{E}_{0C}} = \sqrt{\mathscr{R}_h\left(\mathscr{R}_{0_{SS}}^{0C}+\mathscr{R}_{0_{RS}}^{0C}+\mathscr{R}_{0_{RR}}^{0C}\right)}, \tag{3.12}$$

where,

$$\mathscr{R}_{0_{SS}}^{0C} = \frac{b_{Hi}\beta_V\sigma_V\left[\theta\xi+(1-\xi)\right]\left(S_{SS}^V\right)^{0C}}{g_5 g_6}, \quad \mathscr{R}_{0_{RS}}^{0C} = \frac{b_{Hi}\beta_V\sigma_V\left[\theta\xi+(1-\xi)\right]\theta_{RS}\left(S_{RS}^V\right)^{0C}}{g_8 g_9} \tag{3.13}$$

and

$$\mathscr{R}_{0_{RR}}^{0C} = \frac{b_{Hi}\beta_V\sigma_V\left[\theta\xi+(1-\xi)\right]\theta_{RR}\left(S_{RR}^V\right)^{0C}}{g_{11} g_{12}}.$$

Hence, using the above analyses and Theorem 2 in [22], the following result is established.

Theorem 3.2

Consider the model (2.5).

(a). *If* $\mathscr{R}_{SS} > 1$, *then the NTSDFE* ($\mathscr{E}_{0S}$) *is locally-asymptotically stable (LAS) if* $\mathscr{R}_0^{0S} < 1$, *and unstable if* $\mathscr{R}_0^{0S} > 1$.

(b). *If* $\mathscr{R}_{RR} > 1$, *then the NTRDFE* ($\mathscr{E}_{0R}$) *is LAS if* $\mathscr{R}_0^{0R} < 1$, *and unstable if* $\mathscr{R}_0^{0R} > 1$.

(c). *If* $(\mathscr{R}_{SS} - \mathscr{R}_{RS})(\mathscr{R}_{RR} - \mathscr{R}_{RS}) > 0$ *or* $\mathscr{R}_{SS} = \mathscr{R}_{RS} = \mathscr{R}_{RR}$, *then the NTCDFE (* $\mathscr{E}_{0C}$*) is LAS if* $\mathscr{R}_0^{0C} < 1$, *and unstable if* $\mathscr{R}_0^{0C} > 1$ *provided that* $\mathscr{R}_C > 1$.

The epidemiological significance of Theorem 3.2 is that the disease can be effectively-controlled (when $\mathscr{R}_0^{0C} < 1$) if the initial sizes of the sub-populations of the model are in the basin of attraction of the non-trivial disease-free equilibrium ($\mathscr{E}_{0C}$). The quantity, $\mathscr{R}_h$, measures the average number of secondary infections in the mosquito population due to one infectious human. Similarly, $\mathscr{R}_{0_{SS}}^{0C}$ is the average number of secondary infections in the human population due to homozygous sensitive mosquitoes. The quantity $\mathscr{R}_{0_{RS}}^{0C}$ is the average number of

secondary infections in the human populations due to heterozygous mosquitoes, and the expressions $\mathscr{R}_{0_{RR}}^{0C}$ is the average number of secondary infections in the human populations due to homozygous resistant mosquitoes. For the effective disease control (or elimination) to be independent of initial sizes of the sub-populations of the model, a global asymptotic stability result must be established for the disease-free equilibrium. This is explored in Section 3.3 below.

3.3. Global asymptotic stability of non-trivial disease-free equilibrium ($\mathscr{E}_{df}$): Special case ($\delta_H = 0$)

In this section, the global asymptotic stability property of the non-trivial disease-free equilibrium ($\mathscr{E}_{df}$) will be explored for the special case of the model (2.5) with negligible disease-induced mortality in the human population (that is, it is assumed that $\delta_H = 0$). These assumptions are made for mathematical tractability. Furthermore, define the following regions:

$$\begin{aligned}\Omega_C = \{&(S_H^L, E_H^L, I_H^L, R_H^L, S_H^H, E_H^H, I_H^H, R_H^H, S_{SS}^V, E_{SS}^V, I_{SS}^V, S_{RS}^V, E_{RS}^V, I_{RS}^V, S_{RR}^V, E_{RR}^V, I_{RR}^V) \in \Omega : \\ &N_H^L(t) \leq \frac{\xi\Pi_H}{\mu_H}, N_H^H(t) \leq \frac{(1-\xi)\Pi_H}{\mu_H},\ S_{SS}^V(t) \leq \left(S_{SS}^V\right)^{*C},\ S_{RS}^V(t) \\ &\leq \left(S_{RS}^V\right)^{*C}, \\ &S_{RR}^V(t) \leq \left(S_{RR}^V\right)^{*C}\},\end{aligned} \tag{3.15}$$

$$\begin{aligned}\Omega_{SS} = \{&(S_H^L, E_H^L, I_H^L, R_H^L, S_H^H, E_H^H, I_H^H, R_H^H, S_{SS}^V, E_{SS}^V, I_{SS}^V, S_{RS}^V, E_{RS}^V, I_{RS}^V, S_{RR}^V, E_{RR}^V, I_{RR}^V) \in \Omega : \\ &N_H^L(t) \leq \frac{\xi\Pi_H}{\mu_H}, N_H^H(t) \leq \frac{(1-\xi)\Pi_H}{\mu_H},\ S_{SS}^V(t) \leq \left(S_{SS}^V\right)^{*S},\ S_{RS}^V(t) = 0, \\ &S_{RR}^V(t) = 0\},\end{aligned} \tag{3.16}$$

$$\begin{aligned}\Omega_{RR} = \{&(S_H^L, E_H^L, I_H^L, R_H^L, S_H^H, E_H^H, I_H^H, R_H^H, S_{SS}^V, E_{SS}^V, I_{SS}^V, S_{RS}^V, E_{RS}^V, I_{RS}^V, S_{RR}^V, E_{RR}^V, I_{RR}^V) \in \Omega : \\ &N_H^L(t) \leq \frac{\xi\Pi_H}{\mu_H}, N_H^H(t) \leq \frac{(1-\xi)\Pi_H}{\mu_H},\ S_{SS}^V(t) = 0,\ S_{RS}^V(t) = 0, S_{RR}^V(t) \\ &\leq \left(S_{RR}^V\right)^{*R}\},\end{aligned}$$

where, $N_H^L(t) = S_H^L(t) + E_H^L(t) + I_H^L(t)$ and $N_H^H(t) = S_H^H(t) + E_H^H(t) + I_H^H(t)$.

Lemma 3.3

Consider the special case of the model (2.5) with $\delta_H = 0$.
(a). *If $(\mathscr{R}_{SS} - \mathscr{R}_{RS})(\mathscr{R}_{RR} - \mathscr{R}_{RS}) > 0$ or $\mathscr{R}_{SS} = \mathscr{R}_{RS} = \mathscr{R}_{RR}$, then the region Ω_C is positively-invariant for the model (2.5) provided that $\mathscr{R}_C > 1$ and $\frac{(q^*)^2(\mathscr{R}_C - 1)}{\mathscr{R}_C^2} \geq \frac{1}{4}$.*

(b). *If* $\mathscr{R}_{SS} > 1$ *and* $\frac{\mathscr{R}_{SS}-1}{\mathscr{R}_{SS}} \geq \frac{1}{4}$, *then the region* Ω_{SS} *is positively-invariant for the model (2.5).*

(c). *If* $\mathscr{R}_{RR} > 1$ *and* $\frac{\mathscr{R}_{RR}-1}{\mathscr{R}_{RR}} \geq \frac{1}{4}$, *then the region* Ω_{RR} *is positively-invariant for the model (2.5).*

Proof

(a). Adding all the equations for the low-risk components of the model (2.5), and noting that $\delta_H = 0$, gives

$$\frac{dN_H^L}{dt} = \xi\Pi_H - \mu_H N_H^L = \mu_H \left(\frac{\xi\Pi_H}{\mu_H} - N_H^L\right).$$

Hence, $N_H^L(t) = N_H^L(0)\, e^{-\mu_H t} + \frac{\xi\Pi_H}{\mu_H}(1 - e^{-\mu_H t})$. Thus, if $N_H^L(0) \leq \frac{\xi\Pi_H}{\mu_H}$, then $N_H^L(t) \leq \frac{\xi\Pi_H}{\mu_H}$ for all $t \geq 0$. Furthermore, adding all the equations for the high-risk human group gives

$$\frac{dN_H^H}{dt} = (1-\xi)\Pi_H - \mu_H N_H^H = \mu_H \left(\frac{(1-\xi)\Pi_H}{\mu_H} - N_H^H\right).$$

Thus, $N_H^H(t) = N_H^H(0)\, e^{-\mu_H t} + \frac{(1-\xi)\Pi_H}{\mu_H}(1 - e^{-\mu_H t})$. Hence, if $N_H^H(0) \leq \frac{(1-\xi)\Pi_H}{\mu_H}$, then $N_H^H(t) \leq \frac{(1-\xi)\Pi_H}{\mu_H}$ for all $t \geq 0$. Similarly, it follows from the ninth equation of the model (2.5) that

$$\begin{aligned}\frac{dS_{SS}^V}{dt} &= q^2 r_{SS} N_V \left(1 - \frac{N_V}{K_V}\right) - \lambda_{HV} S_{SS}^V - g_4 S_{SS}^V, \\ &\leq r_{SS} N_V \left(1 - \frac{N_V}{K_V}\right) - g_4 S_{SS}^V.\end{aligned}$$

Observe that the quadratic polynomial (in N_V) in the inequality above has a global maximum value $\frac{K_V}{4}$ (attained when $N_V = \frac{K_V}{2}$). Thus, the above inequality can be simplified as follows:

$$\begin{aligned}
\frac{dS_{SS}^{V}}{dt} &\leq r_{SS}N_V\left(1-\frac{N_V}{K_V}\right)-g_4S_{SS}^{V},\\
&\leq r_{SS}\frac{K_V}{4}-g_4S_{SS}^{V},\\
&\leq r_{SS}K_V\frac{(q^*)^2(\mathscr{R}_C-1)}{\mathscr{R}_C^2}-g_4S_{SS}^{V},\\
&= g_4\left[\frac{r_{SS}}{g_4}K_V\frac{(q^*)^2(\mathscr{R}_C-1)}{\mathscr{R}_C^2}-S_{SS}^{V}\right],\\
&= g_4\left[\mathscr{R}_{SS}K_V\frac{(q^*)^2(\mathscr{R}_C-1)}{\mathscr{R}_C^2}-S_{SS}^{V}\right],\\
&= g_4\left[\left(S_{SS}^{V}\right)^{*C}-S_{SS}^{V}\right].
\end{aligned}$$

Hence, $S_{SS}^{V}(t)=S_{SS}^{V}(0)\,e^{-g_4t}+\left(S_{SS}^{V}\right)^{*C}(1-e^{-g_4t})$. Thus, if $S_{SS}^{V}(0)\leq\left(S_{SS}^{V}\right)^{*C}$, then $S_{SS}^{V}(t)\leq\left(S_{SS}^{V}\right)^{*C}$ for all $t\geq 0$. Using similar arguments, it can be shown that $S_{RS}^{V}(t)\leq\left(S_{RS}^{V}\right)^{*C}$ and $S_{RR}^{V}(t)\leq\left(S_{RR}^{V}\right)^{*C}$ for all $t\geq 0$ if the relevant initial conditions are in Ω_C. Thus, the region Ω_C is positively-invariant for the special case of the model (2.5) with $\mathscr{R}_C>1$, $\frac{(q^*)^2(\mathscr{R}_C-1)}{\mathscr{R}_C^2}\geq\frac{1}{4}$, $(\mathscr{R}_{SS}-\mathscr{R}_{RS})(\mathscr{R}_{RR}-\mathscr{R}_{RS})>0$ or $\mathscr{R}_{SS}=\mathscr{R}_{RS}=\mathscr{R}_{RR}$, and $\delta_H=0$. Items (b) and (c) can be proved similarly (hence not repeated here).□

It is convenient to define $\overline{\mathscr{R}}_0^{0S}=\mathscr{R}_0^{0S}\big|_{\delta_H=0}$, $\overline{\mathscr{R}}_0^{0R}=\mathscr{R}_0^{0R}\big|_{\delta_H=0}$ and $\overline{\mathscr{R}}_0^{0C}=\mathscr{R}_0^{0C}\big|_{\delta_H=0}$

Theorem 3.4

Consider the special case of the model (2.5) with $\delta_H=0$.

(a). *If $(\mathscr{R}_{SS}-\mathscr{R}_{RS})(\mathscr{R}_{RR}-\mathscr{R}_{RS})>0$ or $\mathscr{R}_{SS}=\mathscr{R}_{RS}=\mathscr{R}_{RR}$, then the NTCDFE ($\mathscr{E}_{0C}$) is globally-asymptotically stable (GAS) in $\Omega_C\setminus\{\mathscr{E}_{0T}\}$ whenever $\overline{\mathscr{R}}_0^{0C}<1$ provided that $\mathscr{R}_C>1$ and $\frac{(q^*)^2(\mathscr{R}_C-1)}{\mathscr{R}_C^2}\geq\frac{1}{4}$.*

(b). *If $\mathscr{R}_{SS}>1$ and $\frac{(\mathscr{R}_{SS}-1)}{\mathscr{R}_{SS}}\geq\frac{1}{4}$, then the NTSDFE ($\mathscr{E}_{0S}$) is GAS in $\Omega_{SS}\setminus\{\mathscr{E}_{0T}\}$ whenever $\overline{\mathscr{R}}_0^{0S}<1$.*

(c). *If $\mathscr{R}_{RR}>1$ and $\frac{\mathscr{R}_{RR}-1}{\mathscr{R}_{RR}}\geq\frac{1}{4}$, then the NTRDFE (jmoh$\mathscr{E}_{0R}$) is GAS in $\Omega_{RR}\setminus\{\mathscr{E}_{0T}\}$ whenever $\overline{\mathscr{R}}_0^{0R}<1$.*

The proof of Theorem 3.4, based on using a comparison theorem [39], [47], is given in Appendix A. The epidemiological implication of Theorem 3.4 is that malaria can be effectively-controlled if $\overline{\mathscr{R}}_0^{0S}$ (or $\overline{\mathscr{R}}_0^{0R}$) can be reduced to (and

maintained at) a value less than unity. For example, for the special case of the model (2.5) with $\delta_H = 0$, if $\mathcal{R}_C > 1$, $(\mathcal{R}_{SS} - \mathcal{R}_{RS})(\mathcal{R}_{RR} - \mathcal{R}_{RS}) > 0$ or $\mathcal{R}_{SS} = \mathcal{R}_{RS} = \mathcal{R}_{RR}$ and $\frac{(q^*)^2(\mathcal{R}_C - 1)}{\mathcal{R}_C^2} \geq \frac{1}{4}$, then the classical epidemiological requirement of $\overline{\mathcal{R}}_0^{0C} < 1$ is necessary and sufficient for the effective control (or elimination) of malaria from the community.

4. Sensitivity analysis elasticity indices of the reproduction threshold $\mathcal{R}_0^{0C}$

Sensitivity analyses are carried out to determine the key parameters that influence the dynamics of the model (2.5). The reproduction threshold ($\mathcal{R}_0^{0C}$) will be used as the response function (and its sensitivity with respect to the two intervention parameters, b and u_i, will be assessed). It should be recalled, first of all, the normalized forward sensitivity index of a variable, y, that depends differentially on a parameter, p, is obtained by calculating $\frac{\partial y}{\partial p} \times \frac{p}{y}$ [35]. The sensitivity index quantifies the sensitivity of the variable y to the parameter p. The variable is highly sensitive to the parameter with the largest sensitivity index value (in magnitude) and least sensitive to the parameter with the smallest sensitivity index value (in magnitude) [35]. Table 3 shows the value of the sensitivity indices of the basic reproduction number ($\mathcal{R}_0^{0C}$) of the model (2.5), with respect to the control-related parameters (the baseline values of the parameters provided in Table 2, with the parameters Π_H, r_{SS}, r_{RS}, r_{RR}, K_V, and $\beta_{\max}$ taking their corresponding values for the high malaria transmission setting, are used to compute the sensitivity indices). In should be mentioned that the simulations in this study will be based on using data from study areas in Ethiopia (as discussed in Section 5) [18], [19], [29]. Consequently, for the purpose of the sensitivity analyses, the ITNs coverage parameter (b) is set at 0.35 (i.e., 35% ITNs coverage is assumed, based on the study by Deressa et al. in South-Central Ethiopia [19]), and the IRS coverage parameter (u_i) is set at 0.25 (i.e., 25% IRS coverage is assumed, based on the study in Ethiopia reported in Jima et al. [29]). Furthermore, the human recruitment rate (Π_H) is set at 2.19 *per* day (for the Jimma zone of Ethiopia [18]; an area of high malaria transmission). For these parameter values (and those in Table 2 for high malaria transmission setting), it can be shown that $(\mathcal{R}_{SS} - \mathcal{R}_{RS})(\mathcal{R}_{RR} - \mathcal{R}_{RS}) = 12.382 > 0$, $\mathcal{R}_C = 10.869 > 1$ and $\mathcal{R}_0^{0C} = 4.036 > 1$, and that the NTCDFE ($\mathcal{E}_{0C}$) exists and is unstable.

Table 2
Descriptions of the parameters of the model.

Parameter	Description	Baseline-value (*per* day)	Source
Π_H	Human recruitment rate (due to birth or immigration)	2.19 (3.18) for high (moderate) malaria transmission setting	[18], [26]
ξ	Proportion of new recruited humans that are low-risk	0.47 (dimensionless)	[23]
μ_H	Natural death rate for humans	4.405×10^{-5}	[17]
θ	Modification parameter for decreased risk of infection of low-risk humans, in comparison to high-risk humans	0.5 (dimensionless)	[35]
ν_H	Rate at which exposed humans become infectious	1/14	[35]
γ_H	Recovery rate of humans	6.58×10^{-3}	[7,28,38,44–46]
ρ_H	Rate of loss of natural immunity for humans	5.6×10^{-3}	[36]
δ_H	Disease-induced death rate for humans	9.0×10^{-5}	[36]
h	Level of dominance of *R*-allele in mosquitoes of *RS*-genotype ($0 \le h \le 1$)	0.25 (dimensionless)	Estimated from [10]
r_{SS}	Production (birth) rate of new adult female mosquitoes of *SS*-genotype	6.353 ($\frac{3}{4} \times 6.353$) for high (moderate) malaria transmission setting	Estimated from [31]
r_{RS}	Production (birth) rate of new adult female mosquitoes of *RS*-genotype	$\frac{3}{4} r_{SS}$ for moderate and high malaria transmission setting	Estimated
r_{RR}	Production (birth) rate of new adult female mosquitoes of *RR*-genotype	$\frac{1}{2} r_{SS}$ for moderate and high malaria transmission setting	Estimated from [2]
K_V	Environmental carrying capacity of mosquitoes	2×10^5 (1×10^5) (dimensionless) for high (moderate) malaria transmission setting	[31,33]
μ_V	Natural death rate of mosquitoes of SS-genotype	1/14	[36]
α_{RS}	Modification parameter for the increase in natural death rate of mosquitoes of *RS*-genotype due to fitness cost, in comparison to mosquitoes of *SS*-genotype ($\alpha_{RS} \ge 1$)	1.5 (dimensionless)	Estimated from [2,4]
α_{RR}	Modification parameter for the increase in natural death rate of mosquitoes of *RR*-genotype due to fitness cost, in comparison to mosquitoes of *SS*-genotype ($\alpha_{RR} \ge 1$)	2.0 (dimensionless)	Estimated from [2,4]
δ_{Vt}	Death rate of mosquitoes of *SS*-genotype due to IRS and ITNs	0.84	Estimated from [10]
ρ_t	Modification parameter for the decrease in mortality, due to insecticide, of vectors of *RR*-genotype, in comparison to vectors of *SS*-genotype ($0 \le \rho_t \le 1$)	0.95 (dimensionless)	Estimated from [10]
σ_V	Rate at which exposed mosquitoes of *SS*-genotype become infectious	0.1	[35]
θ_{RS}	Modification parameter for the increase in progression rate of exposed vectors of *RS*-genotype due to fitness cost, in comparison to exposed mosquitoes of *SS*-genotype ($\theta_{RS} \ge 1$)	1.5 (dimensionless)	Estimated from [2,4]
θ_{RR}	Modification parameter for the increase in progression rate of the exposed vectors of *RR*-genotype due to fitness cost, in comparison to exposed mosquitoes of *SS*-genotype ($\theta_{RR} \ge 1$)	2.0 (dimensionless)	Estimated from [2,4]
δ_V	Disease-induced death rate of infected mosquitoes of *SS*-genotype	3×10^{-2}	[4]
η_{RS}	Modification parameter for the increase in disease-induced mortality rate of the mosquitoes of *RS*-genotype due to fitness cost, in comparison to mosquitoes of *SS*-genotype ($\eta_{RS} \ge 1$)	1.5 (dimensionless)	Estimated from [2,4]
η_{RR}	Modification parameter for the increase in disease-induced mortality rate of the mosquitoes of *RR*-genotype due to fitness cost, in comparison to mosquitoes of *SS*-genotype ($\eta_{RR} \ge 1$)	2.0 (dimensionless)	Estimated from [2,4]
u_t	Proportion of houses (indoors) sprayed with IRS ($0 \le u_t \le 1$)	Varied (dimensionless)	Varied
$\beta_{\max}$	Maximum mosquito biting rate	2.0 (0.67) for high (moderate) malaria transmission setting	[20,38]
$\beta_{\min}$	Minimum mosquito biting rate	1.0×10^{-2}	[36]
β_H	Transmission probability from infectious mosquitoes to susceptible humans	0.14 (dimensionless)	[15]
β_V	Transmission probability from infectious humans to susceptible mosquitoes	0.48 (dimensionless)	[15]
b	Proportion of humans who use ITNs ($0 \le b \le 1$)	Varied (dimensionless)	Varied

Table 3
Elasticity indices of $\mathcal{R}_0^{\alpha C}$ for model (2.5). Top-five parameters highlighted in the bold font.

Parameter	Elasticity index	Parameter	Elasticity index	Parameter	Elasticity index	Parameter	Elasticity index
r_{SS}	+ 1.5288	β_V	+ 0.5000	α_{RS}	+ 0.2073	θ_{RR}	+ 0.0448
r_{RS}	− 1.1632	K_V	+ 0.5000	α_{RR}	+ 0.1681	η_{RR}	− 0.0258
b	− 1.1182	μ_H	+ 0.4964	ξ	− 0.1536	η_{RS}	− 0.0106
δ_{VI}	− 1.0009	γ_H	− 0.4900	θ	+ 0.1536	δ_H	− 0.0067
$\beta_{\max}$	+ 0.9973	u_t	− 0.4170	μ_V	+ 0.1239	$\beta_{\min}$	+ 0.0027
ρ_t	− 0.7949	σ_V	+ 0.3763	θ_{RS}	+ 0.0966	ν_H	+ 0.0003
Π_H	− 0.5000	r_{RR}	− 0.3149	δ_V	− 0.0500	ρ_H	+ 0.0000
β_H	+ 0.5000	h	− 0.2316				

It follows from Table 3 that the parameters related to the birth rate of adult vectors of *SS*-genotype (r_{SS}), birth rate of adult vectors of *RS*-genotype (r_{RS}), death rate of adult mosquitoes due to insecticides (δ_{Vi}), and ITNs coverage in the community (b) have the highest (in magnitude) elasticity indices. This implies, for example, that an increase in ITNs coverage (b) by r% will result in a decrease in the value of $\mathscr{R}_0^{0C}$ by $1.1182r$%. Similarly, a decrease in the production (birth) rates of new adult SS-genotype mosquitoes (r_{SS}) by r% will result in a decrease in $\mathscr{R}_0^{0C}$ by $1.5288r$%. Thus, it follows from the sensitivity indices values in Table 3 that the disease burden in a community can be significantly decreased using control strategies that:

i. Increase ITNs coverage (i.e., increase the value of the parameter b),

ii. Minimize the production rate of new adult SS-genotype mosquitoes (i.e., reduce the value of the parameter r_{SS}),

iii. Increase the production rate of new adult RS-genotype mosquitoes (i.e., increase the value of the parameter r_{RS}),

iv. Increase the death rate of mosquitoes due to the use of insecticides (i.e., increase the value of the parameter δ_{Vi}).

5. Numerical simulations

5.1. Study area

Numerical simulations of the model (2.5) will be carried out using data from areas of high and moderate malaria transmission in Ethiopia (a malaria-endemic nation, located in the Horn of Africa). In particular, the following study areas are chosen.

5.1.1. High malaria transmission setting:

The Asendabo Health Center, located in the Jimma zone of Southwest Ethiopia, is a high malaria transmission region [18]. It serves an estimated population of 49,817, with malaria prevalence of about 32.4% [18]. Based on the report in [18], the following initial values are chosen for the simulations (splitting the prevalence into 12% exposed and 20.4% symptomatic, for humans: 47% in low-risk group and 53% in high-risk group). Also, for the mosquito population, the following initial genotype distribution and initial infections are calculated (based on the ratio provided in [31]): $S_H^L(0) = 11,241$, $E_H^L(0) = 2,810$, $I_H^L(0) = 4,682$, $R_H^L(0) = 4,682$, $S_H^H(0) = 12,675$, $E_H^H(0) = 3,167$, $I_H^H(0) = 5,280$, $R_H^H(0) = 5,280$, $S_{SS}^V(0) = 25,000$, $E_{SS}^V(0) = 12,500$, $I_{SS}^V(0) = 12,500$, $S_{RS}^V(0) = 12,500$,

$E^V_{RS}(0) = 6,250$, $I^V_{RS}(0) = 6,250$, $S^V_{RR}(0) = 12,500$, $E^V_{RR}(0) = 6,250$, and $I^V_{RR}(0) = 6,250$. The human recruitment rate parameter (Π_H) is set at 2.19 *per* day (it is calculated based on the above mentioned total population size of the Jimma zone and the average human lifespan in Ethiopia [17]). The simulations are carried out for various values of the ITN and IRS coverage parameters (b and u_i). Other parameter values used for these simulations are as given in Table 2, with Π_H, r_{SS}, r_{RS}, r_{RR}, K_V, and $\beta_{\max}$ taking their corresponding values for the high malaria transmission setting. It should be mentioned that, for the worst-case scenario associated with this (high malaria transmission) setting (i.e., when $b = u_i = 0$), the reproduction thresholds, $\mathscr{R}_0^{0S}$ and $\mathscr{R}_0^{0R}$, take the values $\mathscr{R}_0^{0S} = 26.4611 > 1$ and $\mathscr{R}_0^{0R} = 13.0029 > 1$, respectively.

5.1.2. Moderate malaria transmission setting:

The Arsi Negele Health Center in Southeast Ethiopia is considered to be a moderate malaria transmission region [26]. The Health Center serves an estimated population of 72,114, and has prevalence of about 11.45% [26]. Based on the report in [26], the following initial values are chosen for the simulations (splitting the prevalence into 3.45% exposed and 8% symptomatic for humans: 47% in low-risk group and 53% in high-risk group). Also, for mosquito population, initial genotype distribution and initial infections are calculated based on the ratio provided in [31]): $S^L_H(0) = 27,301$, $E^L_H(0) = 1,169$, $I^L_H(0) = 2,712$, $R^L_H(0) = 2,712$, $S^H_H(0) = 30,785$, $E^H_H(0) = 1,319$, $I^H_H(0) = 3,058$, $R^H_H(0) = 3,058$, $S^V_{SS}(0) = 44,275$, $E^V_{SS}(0) = 198$, $I^V_{SS}(0) = 5,527$, $S^V_{RS}(0) = 22,137$, $E^V_{RS}(0) = 99$, $I^V_{RS}(0) = 2,764$, $S^V_{RR}(0) = 22,137$, $E^V_{RR}(0) = 99$, and $I^V_{RR}(0) = 2,764$. For this malaria transmission setting, the human recruitment rate parameter (Π_h) is set at 3.18 *per* day (it is calculated based on the above mentioned total population size of the Jimma zone and the average human lifespan in Ethiopia [17]) (as indicated in Table 2). Furthermore, the values of the parameters K_V, β_{max} and r_{SS} are reduce to $K_V = 1 \times 10^5$, $\beta_{\max} = 0.67$ and $r_{SS} = \frac{3}{4} \times 6.353$, respectively (it should be noted that, owing to this reduction, the values of the parameters r_{RS} and r_{RR} are also reduced, based on their associated formulas with values given in Table 2 corresponding to this malaria transmission setting). The simulations are carried out for various values of the IRS (u_i) and ITNs (b) coverage (and, for this setting under the worst-case scenario (i.e., with $u_i = b = 0$). Other parameter values the same as in Table 2. The threshold quantities $\mathscr{R}_0^{0S}$ and $\mathscr{R}_0^{0R}$ take the values $\mathscr{R}_0^{0S} = 5.1918 > 1$ and $\mathscr{R}_0^{0R} = 2.5360 > 1$, respectively).

5.2. Level of dominance of resistant allele (h)

In this study, allele "dominance" is defined in terms of insecticide-induced mortality of the adult vector (i.e., it is defined in terms of the value of the parameter $0 \leq h \leq 1$, where $h = 0$ represents the case where the resistant (R) allele is fully recessive, while the case $h = 1$ represents the scenario where the R allele is dominant). It should be mentioned that dominance is not an intrinsic property of an allele, and a resistant allele may be dominant over the sensitive (S) allele for one insecticide and recessive for another [12]. Furthermore, the value of the dominance parameter (h) is obtained by taking various factors (such as genetic background and environmental conditions) into account [12]. To account for the uncertainty in the estimate of the level of resistant allele dominance (h), simulations will be carried out using various values of h. In particular, the first set of simulations (used to generate Fig. 2, Fig. 3, Fig. 4 and 6) are based on using the the baseline value of $h = 0.25$ [10]. Other simulations (used to generate Fig. 5) will be based on using three other values of h, namely $h = 0.5$ (Figs. 5(a)–(c)), $h = 0.75$ (Figs. 5(e)–(h)) and $h = 1.0$ (Figs. 5(i)–(l)). These simulations enable for the determination of the effect of such (resistant allele) dominance on the effectiveness of IRS and ITNs to control malaria disease while managing insecticide resistance.

5.3. Simulation results

The model (2.5) is simulated, using the parameter values and ranges tabulated in Table 2 (with the IRS and ITNs coverage levels varying from 0 to 1; that is $0 < b < 1$ and $0 < u_i < 1$, respectively), to assess the impact of the combined use of ITNs and IRS to combat malaria burden (as measured in terms of the proportion of infectious humans in the community) and on the dynamics of the R-allele/S-allele frequency in the mosquito population at equilibrium. Results are provided for the moderate and high malaria transmission settings discussed above.

5.3.1. Results for moderate malaria transmission setting

Simulating the model using parameters relevant to the moderate malaria transmission setting discussed above shows that the disease (as measured by the proportion of infectious humans in the community) can be effectively controlled if the ITNs coverage in the community is at least 72% (i.e., $b \geq 0.72$), regardless of the level of IRS coverage (u_i) (Fig. 2(a)–(b)). This (high) level of ITNs coverage fails to effectively manage insecticide resistance (since, as shown in Fig. 2(d), this

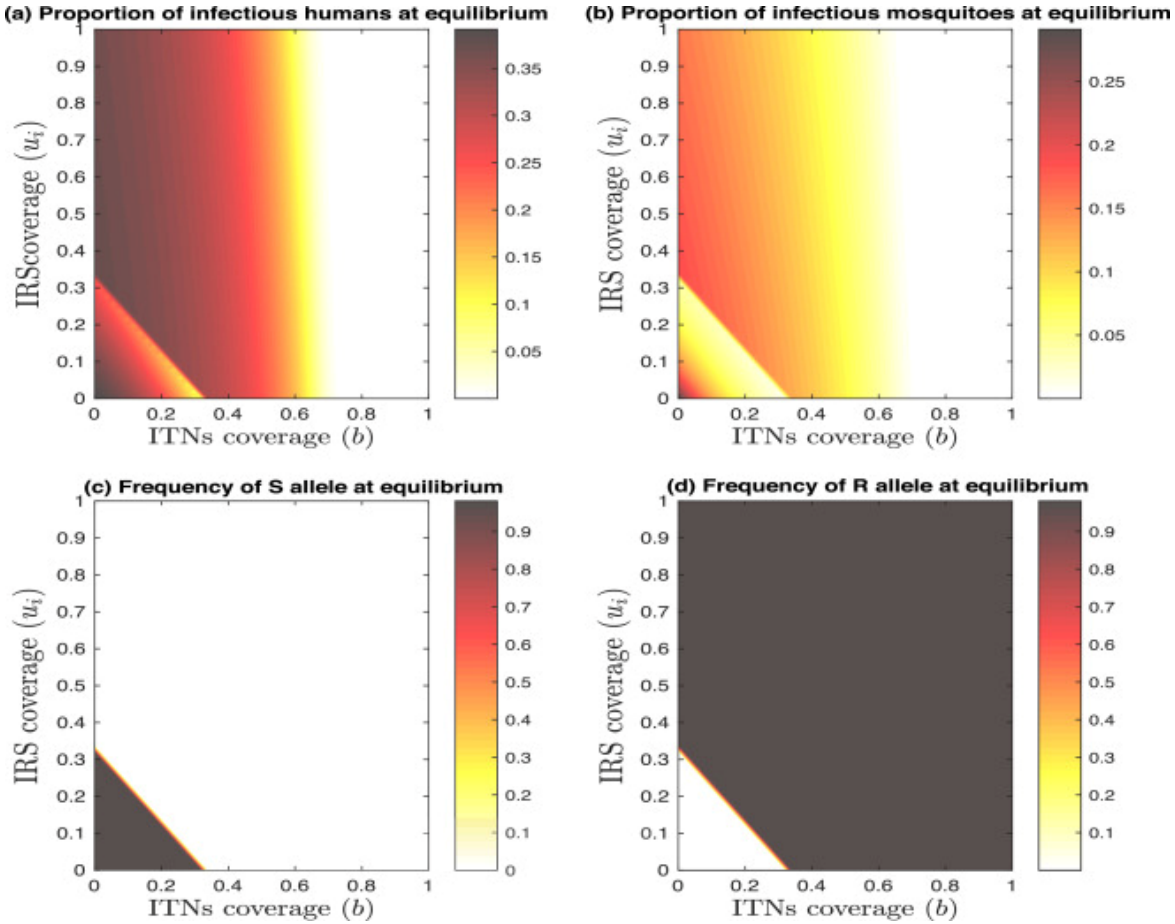

Fig. 2. Simulations of the model (2.5) for malaria dynamics in moderate transmission setting. (a) proportion of infectious humans at equilibrium, as a function of ITNs coverage. (b) proportion of infectious mosquitoes at equilibrium, as a function of ITNs (b) and IRS (u_i) coverage. (c) frequency of S allele at equilibrium, as a function of ITNs and IRS coverage. (d) frequency of R allele at equilibrium as a function of ITNs and IRS coverage. Parameter values used are as given in Table 2, with the parameters Π_H, r_{SS}, r_{RS}, r_{RR}, K_V, and $\beta_{\max}$ taking their corresponding values for the moderate malaria transmission setting, with $0 < b \leq 1$ and $0 < u_i \leq 1$.

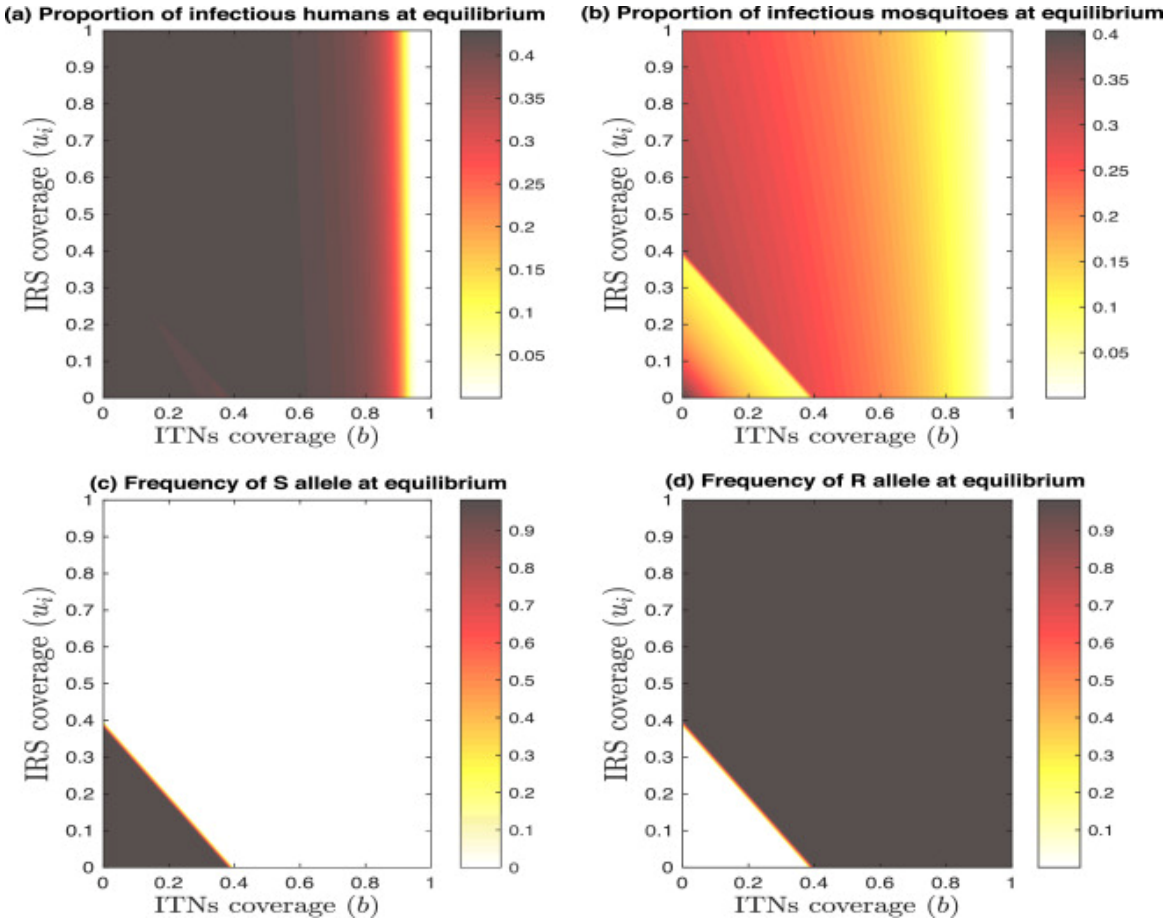

Fig. 3. Simulations of the model (2.5) for malaria dynamics in high malaria transmission setting. (a) proportion of infectious humans at equilibrium, as a function of ITNs coverage. (b) proportion of infectious mosquitoes at equilibrium, as a function of ITNs (b) and IRS (u_i) coverage. (c) frequency of S allele at equilibrium, as a function of ITNs and IRS coverage. (d) frequency of R allele at equilibrium as a function of ITNs and IRS coverage. Parameter values used are as given in Table 2, with the parameters Π_H, r_{SS}, r_{RS}, r_{RR}, K_V, and $\beta_{\max}$ taking their corresponding values for the high malaria transmission setting, with $0 < b \leq 1$ and $0 < u_i \leq 1$.

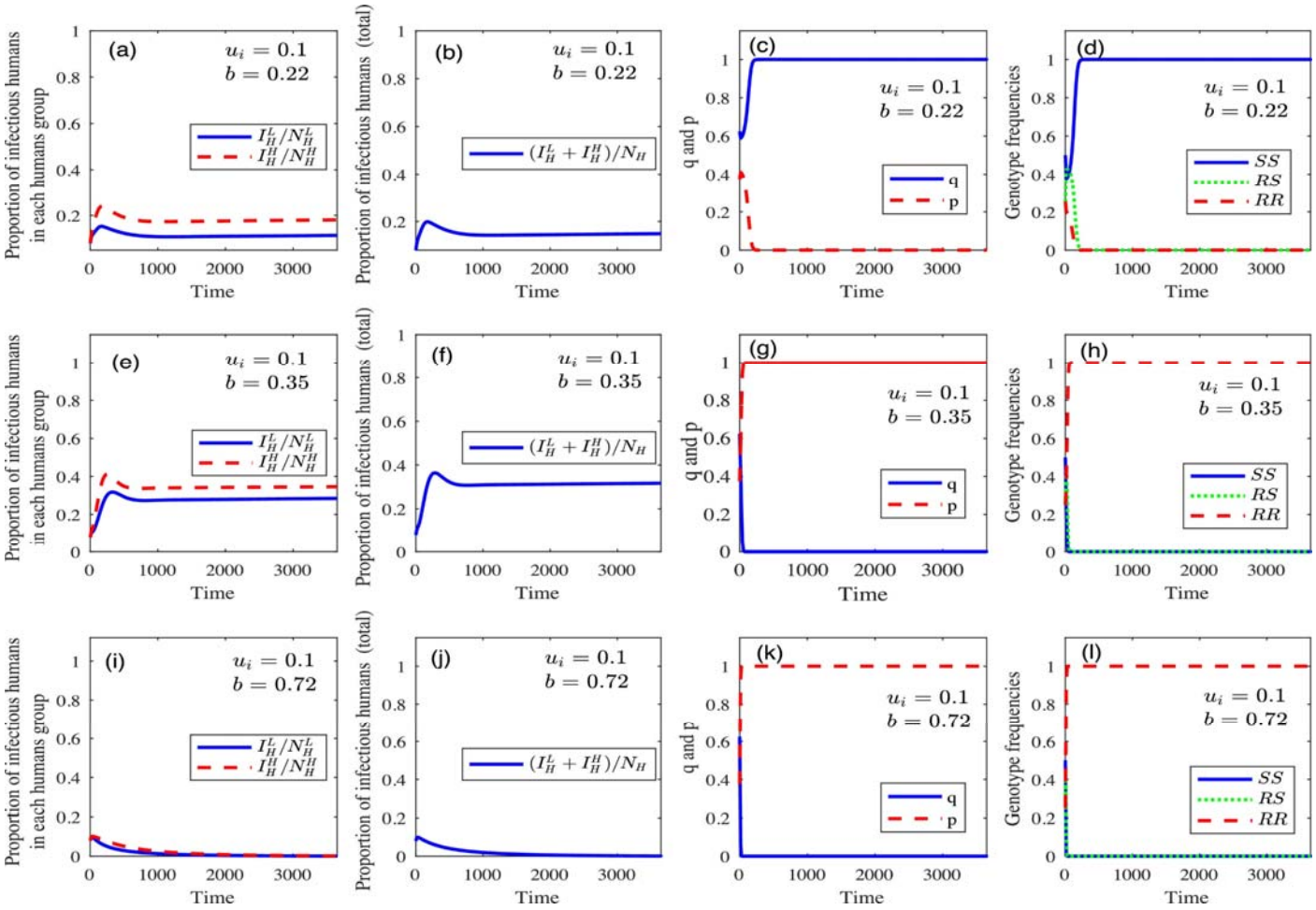

Fig. 4. Simulations of the model (2.5), showing the proportion of infectious humans and allele and genotype frequencies (in mosquitoes), as a function of time in moderate malaria transmission setting. (a)–(d): $(b, u_i) = (0.22, 0.1)$, (e)–(h): $(b, u_i) = (0.35, 0.1)$, (i)–(l): $(b, u_i) = (0.75, 0.1)$. All other parameter values are as given in Table 2, with the parameters Π_H, r_{SS}, r_{RS}, r_{RR}, K_V, and $\beta_{\max}$ taking their corresponding values for the moderate malaria transmission setting, with $0 < b \leq 1$ and $0 < u_i \leq 1$.

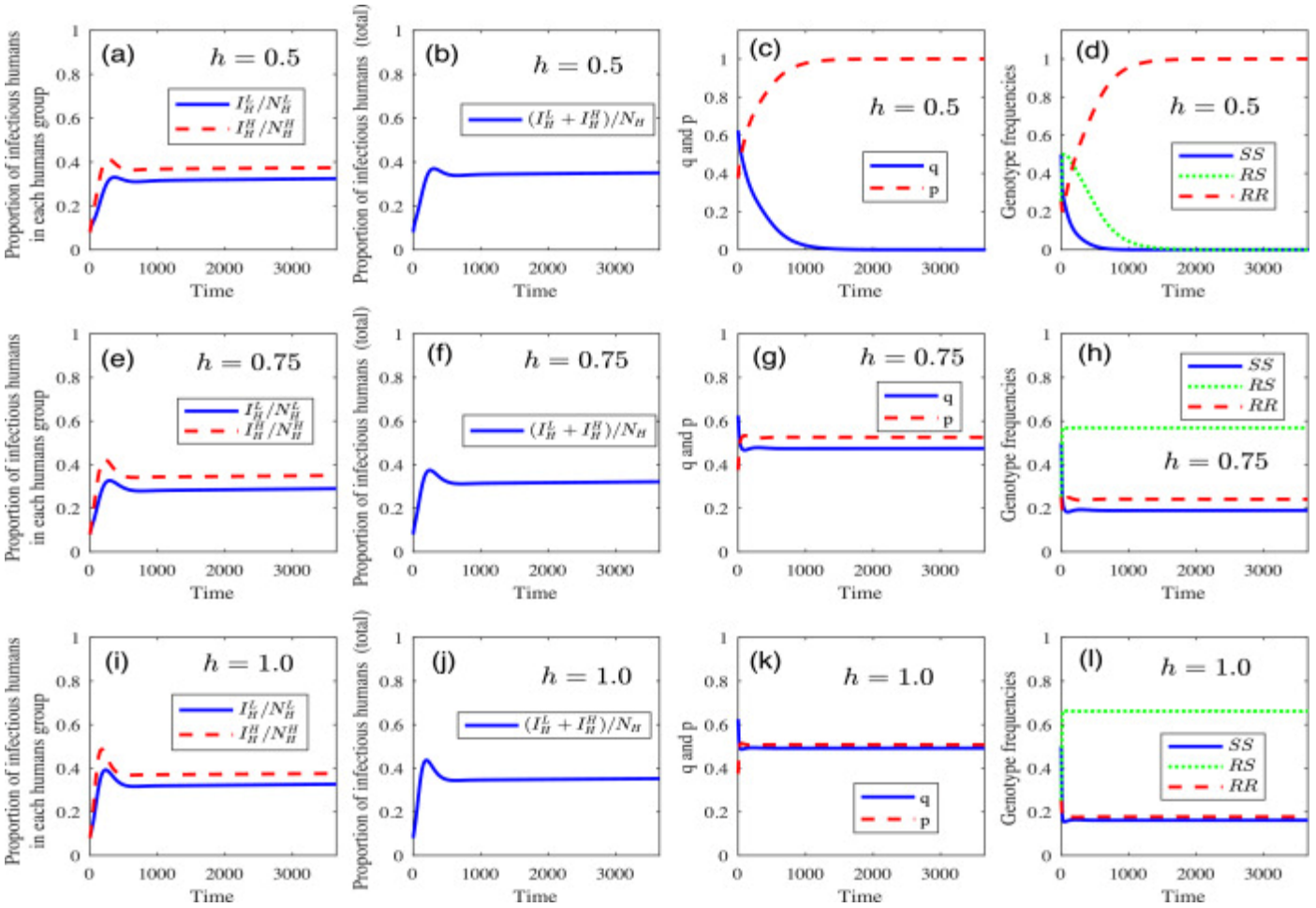

Fig. 5. Simulations of the model (2.5) for the effect of level of dominance of resistant allele (*h*), showing the proportion of infectious humans, as well as the allele and genotype frequencies (in mosquitoes), as a function of time in moderate malaria transmission setting. (a)–(d): *h=0.5* and *(b,u_1)=(0.22, 0.1),* (e)–(h): *h=0.75* and *(b,u_1)=(0.22, 0.1),* (i)–(l): *h=1.0* and *(b,u_1)=(0.22, 0.1),* . All other parameter values are as given in Table 2, with the parameters Π_H, r_{SS}, r_{RS}, r_{RR}, K_V, and β_{max} taking their corresponding values for the moderate malaria transmission setting), with $0 < b \leq 1$ and $0 < u_i \leq 1$.

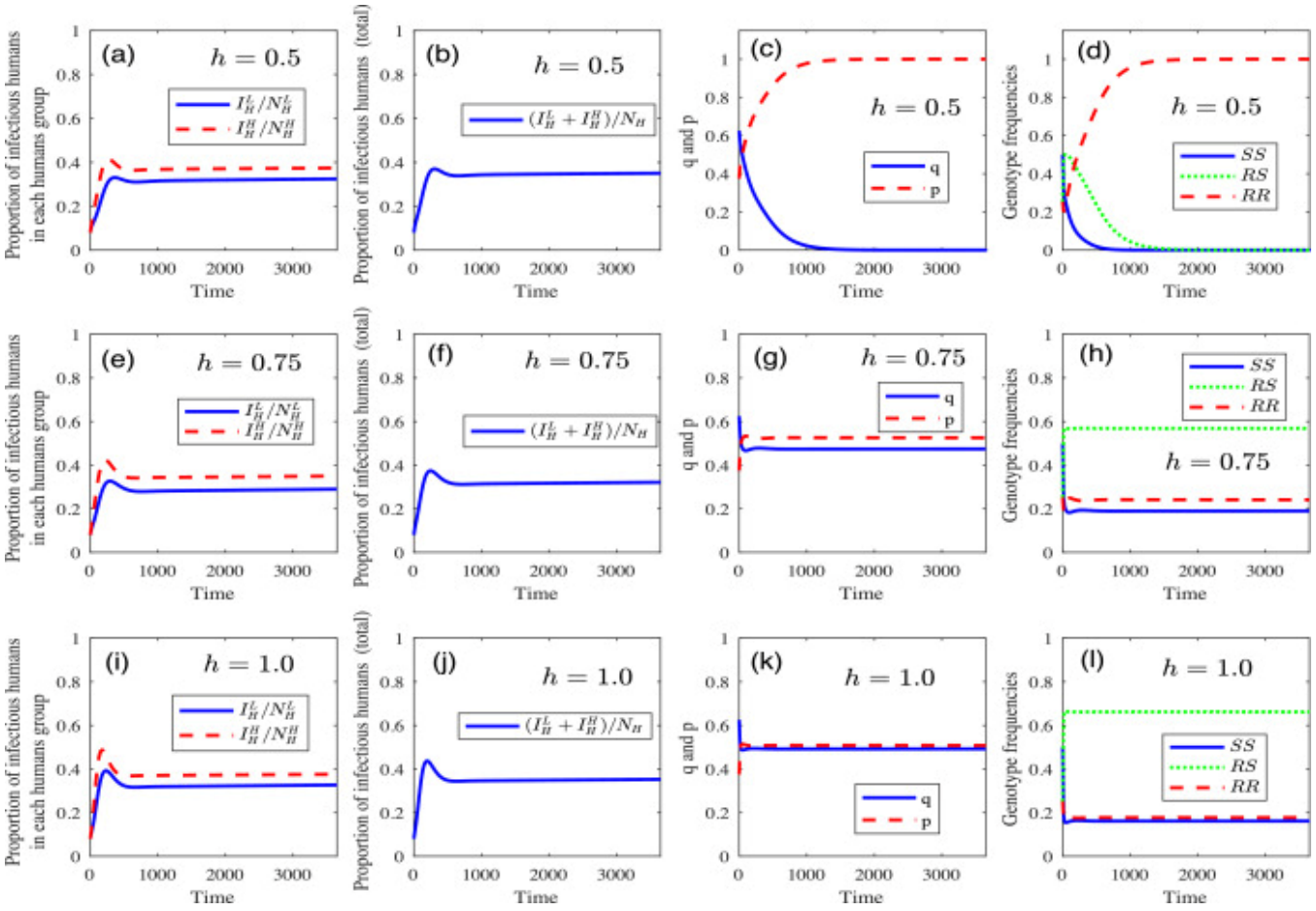

Fig. 6. Simulation of the model (2.5) to assess the impact of reducing fitness costs of resistance in moderate malaria transmission setting. (a)–(b): proportion of infectious (a) humans and (b) mosquitoes at equilibrium, as a function of ITNs (b) and IRS (u_i) coverage. (c)–(d): distribution malaria and allele frequencies (S and R) in the plane. The parameters associated to fitness costs to insecticide resistance are reduced from the baseline values in Table 2 to $\alpha_{RS} = 1.15, \alpha_{RS} = 1.25, \theta_{RS} = 1.2, \theta_{RR} = 1.4, \eta_{RS} = 1.15$ and $\eta_{RR} = 1.25$. All other parameter values are as given in Table 2, with the parameters Π_H, r_{SS}, r_{RS}, r_{RR}, K_V, and β_{max} taking their corresponding values for the moderate malaria transmission setting, with $0 < b \leq 1$ and $0 < u_i \leq 1$.

level of ITN coverage is associated with very high frequency of the resistant allele at equilibrium). For this moderate transmission setting, insecticide resistance is effectively managed provided the ITNs-IRS coverage pair lie in the region below the straight line joining the points $(b, u_i) = (0, 0.32)$ and $(b, u_i) = (0.32, 0)$ in the

$b - u_i$ plane. For all other ITNs-IRS coverage levels outside this region, insecticide resistance is not effectively managed (Fig. 2(c)–(d)). On the other hand, for ITNs coverage levels below 72%, simulations show that, although the disease is not effectively controlled, the proportion of infectious humans can be drastically reduced (for values of ITNs coverage close to the 72% cut-off, such as $b \, \varepsilon$ (0.6, 0.71)) regardless of the level of IRS coverage (and, for this scenario, insecticide resistance is also not effectively managed). On the other hand, insecticide resistance effectively managed (since the frequency of the resistant allele at equilibrium is greatly reduced), if the ITNs-IRS coverage pair lie below (but close to) the straight line joining the points $(b, u_i) = (0, 0.32)$ and $(b, u_i) = (0.32, 0)$. It is noteworthy from Fig. 2 that, while the prospect for effective disease control increases with increasing ITNs coverage (regardless of the IRS coverage), the prospect for effectively managing insecticide resistance dramatically decreases. For instance, for a fixed IRS coverage of $u_i = 0.1$, the three points, $(b, u_i) = (0.22, 0.1)$, $(b, u_i) = (0.35, 0.1)$ and $(b, u_i) = (0.72, 0.1)$, correspond, respectively, to a scenario where the following outcomes occur:

(i) The proportion of infectious humans is low (i.e., the disease prevalence is brought down to manageable level) and insecticide resistance is effectively managed;

(ii) The disease is not effectively controlled and insecticide resistance is not effectively managed;

(iii) The disease is effectively controlled, but insecticide resistance is not effectively managed.

5.3.2. High malaria transmission setting

The results for the numerical simulations of the model for high malaria transmission setting, depicted in Fig. 3, show that ITNs coverage level of at least 95% (regardless of the level of IRS coverage) will be needed to achieve the effective control of the (Fig. 3(a)–(b)). However, for this (high) transmission setting,

insecticide resistance can be effectively managed only if the ITNs-IRS coverage level lie in the region below the straight line joining the points $(b, u_i) = (0, 0.38)$ and $(b, u_i) = (0.38, 0)$. For all other ITNs-IRS combinations outside this region, insecticide resistance is not effectively managed (Fig. 3(c)–(d)). Furthermore, the disease is not effectively controlled for all ITNs coverage levels below 95%, regardless of the size of the IRS coverage in the community.

5.3.3. Effect of increasing ITNs coverages for fixed low IRS coverage in moderate transmission setting

Since IRS coverage levels are generally low (especially in moderate transmission settings) [48], it is instructive to assess the impact of increasing ITNs coverage on disease burden for malaria-endemic communities with low IRS coverage. Consequently, the model (2.5) is simulated, for a moderate malaria transmission setting with 10% IRS coverage, to assess the impact of increasing the ITNs coverage in the community. The three ITNs coverage levels discussed in Section 5.3.1 (namely, $b = 0.22$, $b = 0.35$ and $b = 0.72$) will be used for these simulations (it is worth mentioning that these three ITNs coverage rates are reasonably attainable in moderate malaria transmission settings [29], [48]). For these simulations, which were run for a period of 10 years, the values of all other parameters of the model are as given in Table 2, with the parameters Π_H, r_{SS}, r_{RS}, r_{RR}, K_V, and $\beta_{\max}$ taking their corresponding values for the high malaria transmission setting). For the first set of simulations with ITNs coverage at 22%, it is shown that, within the high-risk human population (i.e., those who do not use ITNs consistently and correctly), the proportion of infectious humans increases from the initial 8% to 24% during the first 150 days, and then decreases to 18% for the next 550 days (and remains at 18% for the rest of the 10-year period).

Similarly, for the low-risk human population (i.e., those who use ITNs consistently and correctly), the proportion of infectious humans increases from the initial 8% to 20% during the first 150 days, and then decreases to 11% in the next 500 days (and remains at 11% for the rest of the 10-year duration) (Fig. 4(a)). The total proportion of infectious humans increases from the initial 8% to 20% in the first 150 days, and then decreases to 14% in the next 850 days (and remains at 14% for the rest of the 10-year period) (Fig. 4(b)). Furthermore, the R-allele frequency decreases from the initial value of $p = 0.375$ (and drops slowly to zero) during the first 200 days (and remains at zero for the rest of the 10-year period). Similarly, the S-allele frequency increases from the initial value of $q = 0.625$ (and reaches

$q = 1$ slowly) during the first 200 days (and remains at $q = 1$ for the rest of 10-year period) (Fig. 4(c)).

The frequency of the *SS*-genotype decreases (from the initial 0.5) to 0.4 in the first 40 days, then increases slowly and reaches 1 in the first 160 days (and remains constant at 1 for the rest of the 10-year period). The frequency of *RS*-genotype increases from initial 0.25 to 0.42 in the first 20 days, and decreases to zero slowly in the next 180 days (and remains at zero for the rest of the 10-year duration). The frequency of the *RR*-genotype decreases to zero (from initial 0.25) in the first 150 days, and remains at zero for the rest of the 10-year duration (Fig. 4(d)). In summary, these simulations show that, for moderate malaria transmission setting, the combined use of these low levels of IRS (at 10%) and ITNs (at 22%) coverage can reduce the proportion of infectious humans (by about 14%, for the 10-year control period), while effectively managing insecticide resistance.

When the ITNs coverage is increased to 35% (while retaining IRS at 10% coverage level), these simulations show that the total proportion of infectious humans increases from the initial 8% to as high as 31% during the 10-year control period (hence, in this case, the disease is not effectively controlled (Fig. 4(e)–(f))) and insecticide resistance is not effectively managed (with insecticide resistance at 100%; Fig. 4(g)–(h)). Thus, these simulations show that an increase in ITNs coverage from 22% to 35% (with IRS coverage fixed at 10%) can induce a negative (detrimental) population-level impact in terms of increasing disease burden and vector insecticide resistance in the community. When the ITNs coverage is further increased to 72% (i.e., $b = 0.72$), with the IRS coverage still fixed at 10%, it is shown that, while the disease is effectively controlled, insecticide resistance is not effectively managed (Figs. 4(i)–(l)).

5.3.4. Effect of level of dominance of resistant allele: moderate malaria transmission setting

As stated in Section 5.2, there is uncertainty in the level of resistance allele dominance. Prior simulations were carried out using a baseline value of $h = 0.25$. In this section, the effect of such uncertainty on the simulation results (for the moderate malaria transmission setting) will be monitored by simulating the model with various values of h (namely, $h = 0.5$, $h = 0,75$, and $h = 1.0$). The simulations will be based on fixing the IRS coverage at 10%, and using the ITNs coverage rate ($b = 0.22$) discussed in Section 5.3.1. The results obtained from these simulations are depicted in Fig. 5 (it should, first of all, be recalled from Fig. 4 that, for the case with $h = 0.25$ and IRS coverage at 10% with 22% ITNs coverage, the proportion of

infectious humans reduced to 14%, and insecticide resistance was effectively managed (Fig. 4(a)–(d))).

Our simulations for the case where the allele dominance parameter is increased to $h = 0.5$ show that the proportion of infectious humans rises to as high as 35% (i.e., the disease is not effectively controlled using this strategy) and insecticide resistance is not effectively managed (Fig. 5(a)–(d)). The implication of these simulations is that, for this low level of IRS and ITNs coverages (at 10% and 22%, respectively) in a moderate malaria transmission setting, increasing the level of resistant allele dominance (h) from $h = 0.25$ to $h = 0.5$ induces a negative population-wide consequence (both in terms of increasing disease burden and failing to effectively manage insecticide resistance). Similar dynamics (with respect to disease burden and/or management of insecticide resistance) was obtained when the allele dominance parameter (h) was further increased to $h = 0.75$ (Figs. 5(e)–(h)) or $h = 1.0$ (Figs. 5(i)–(l)), *albeit*, some variability in the distribution of the insecticide allele and genotype distributions were recorded.

5.3.5. Effect of decreasing fitness costs of insecticide resistance: moderate transmission setting

The effect of decreasing the parameters associated with the fitness costs of insecticide resistance (namely, α_{RS}, α_{RS}, θ_{RS}, θ_{RR}, η_{RS} and η_{RS}) is assessed by simulating the model (2.5) for the moderate malaria transmission setting. To do this, the parameters are reduced (from their baseline values given in Table 2) to $\alpha_{RS} = 1.15$, $\alpha_{RS} = 1.25$, $\theta_{RS} = 1.2$, $\theta_{RR} = 1.4$, $\eta_{RS} = 1.15$ and $\eta_{RS} = 1.25$, respectively. The simulation results obtained, depicted in Fig. 6, show that ITNs coverage level of at least 76% (regardless of the level of IRS coverage) will be needed to effectively control the disease (Fig. 6(a)–(b)). However, for this (moderate) transmission setting, insecticide resistance is effectively managed only if the ITNs-IRS coverage level lie in the region below the straight line joining the points $(b, u_i) = (0, 0.17)$ and $(b, u_i) = (0.17, 0)$ (in the $b - u_i$ plane (for all other ITNs-IRS coverage levels outside this region, the combined ITNs-IRS control strategy fails to manage insecticide resistance (Fig. 6(c)–(d))).

The disease is not effectively controlled for ITNs coverage levels below 76%, regardless of the size of IRS coverage. On the other hand, for ITNs coverage levels below 76%, simulations show that although the disease is not effectively controlled, the proportion of infectious humans can be drastically reduced (for

values of ITNs coverage close to the 76% cut-off, such as $b\varepsilon(0.72, 0.75)$) regardless of the level of IRS coverage (and it fails to effectively manage insecticide resistance). Thus, these simulations show that a decrease in the parameters associated with the fitness costs of resistance can induce a negative (detrimental) population-level impact in terms of increasing disease burden and mosquito insecticide resistance (if the ITNs coverage in the community is below 76%). That is, in moderate malaria transmission, our simulations show that the impact of insecticide resistance on the disease burden is high if the fitness costs of insecticide resistance is low.

6. Discussion and conclusions

Over 2.5 billion people live in areas whose local epidemiology permits transmission of *Plasmodium falciparum*, the protozoan parasite responsible for most of the life-threatening form of malaria [24], [30]. Malaria is endemic in 91 countries, and caused 216 million cases and 445,000 deaths in 2016 [52]. While the use of bednets (ITNs) and IRS has resulted in a significant reduction of global malaria burden over the past 15 years (with most of the benefits resulting from the use of bednets) [9], this widespread and heavy use of insecticides has, unfortunately, also resulted in the emergence of vector resistance to nearly every currently available agent (*pyrethroids*, organochlorines, organophosphates and carbamates) used in IRS or ITNs [3]. Given this, and the dominant role ITNs play in reduction of malaria burden (cases and mortality), any threat to the efficacy of these chemical agents *via* resistance is of foremost importance. Thus, it is instructive to design effective strategies, based on using currently-available insecticides, that reduces malaria burden in the study area while effectively managing insecticide resistance.

This study presents a new mathematical model, that couples malaria epidemiology (using an SEIR formulation for humans, and an SEI formulation for mosquitoes) and population genetics of the malaria vector, for assessing the population-level impact of the widespread community-wide use of insecticide-treated nets (ITNs) and indoor residual spray (IRS) on the evolution of insecticide resistance in two study areas in Ethiopia (representing a moderate and high malaria transmission setting) [18], [26]). Very few malaria modeling studies (such as the model by Kuniyoshi and Santos [31] and by Luz et al. [32]) have formulated models that couple population-level dynamics and vector population genetics (in the context of insecticide resistance). The novel model developed in the current study extends

the previous malaria epidemiology-genetic models in [31], [32] by incorporating numerous pertinent features associated with malaria transmission dynamics and control, such as: (i) classifying humans into high-risk and low-risk group (based on individuals' behavior on how they use ITNs), (ii) realistically incorporating ITNs and IRS control strategies, (iii) including fitness costs associated with insecticide resistance, such as reducing fecundity (growth rate), increasing rate at which exposed mosquitoes become infectious, and increasing natural mortality (ir the heterozygous and homozygous resistant mosquitoes), and (iv) incorporating the level of resistant allele dominance (h), that measures the relative position of the *RS*-genotype relative to the *SS* and *RR*-genotypes in terms of their sensitivity to the chemical insecticides being used in the community. The primary aim of this study was to use mathematical modeling to provide deeper insight into the role of insecticide resistance on malaria transmission in endemic areas. In particular, a new model was designed and used to determine whether or not the combined use of ITNs and IRS could lead to the effective control of malaria disease, in the endemic setting, while effectively managing insecticide resistance.

The novel epidemiology-genetics model developed in this study, which takes the form of a deterministic system of nonlinear differential equations, has four disease-free equilibria, namely a trivial disease-free equilibrium (where all mosquitoes die out), a non-trivial sensitive-only disease-free boundary equilibrium (that is, $q > 0$ $p = 0$), a non-trivial resistant-only disease-free boundary equilibrium (that is, $q = 0$ and $p > 0$), and a non-trivial co-existence disease-free equilibrium (that is, $q > 0$ and $p > 0$). Rigorous analyses of the model reveal that the three non-trivial disease-free equilibria are locally-asymptotically stable (LAS) when the associated basic reproduction of the model is less than unity. It was further shown that the non-trivial disease-free equilibria of the model are globally-asymptotically stable (GAS) for a special cases (involving an assumption for negligible malaria-induced mortality in the human host population) when the associated basic reproduction of the model is less than unity. The implication of this theoretical result is that, for the case of the model with negligible malaria-induced mortality in the human host population, the combined use of ITNs and IRS in the malaria-endemic settings considered in this study (for high enough ITNs coverage) can lead to the reduction of the associated reproduction numbers of the model (denoted by $\mathscr{R}_0^{0C}$, $\mathscr{R}_0^{0S}$ or $\mathscr{R}_0^{0R}$) to values less than unity, the consequence of which is that the disease can be effectively controlled in (or eliminated from) the malaria-endemic community.

Numerical simulations of the model, using data relevant to malaria dynamics in moderate and high transmission regions of Ethiopia, show that the effective size of ITNs and IRS coverage levels needed for the effective control of the disease (i.e., reduce malaria prevalence), while effectively managing insecticide resistance, depends on the magnitude of the level of resistant allele dominance (h), and several fitness costs associated with insecticide resistance. The results presented in Figs. 2 and 3 revealed that the ITNs-IRS strategy with large coverage of ITNs (and higher fitness costs of insecticide resistance) can lead to the effective control of the disease at equilibrium, although the mosquito population becomes fully (or exclusively) resistant to the insecticide. This finding is consistent with the result on the possible impact of insecticides resistance on the efficacy of ITNs discussed by Thomas and Read [49]. As the ITNs coverage increases, more humans gain protection from mosquito bites, and mosquitoes seeking those hosts are killed by the insecticides. In this situation, if insecticides resistance is developed and the insecticides are completely ineffective, the community still benefits from large physical protection (against contact with mosquitoes) provided by the ITNs, and from the fitness costs associated with resistance in resistant mosquitoes (thereby contributing to reduction in malaria transmission [49]). Furthermore, moderate ITNs coverage can lower the proportion of infectious humans with low (or no) resistance (shown in Figs. 2 and 4((a)–(h))). Our finding also agrees with the result on the effect of intermediate level of ITNs coverage discussed in [49]. Our simulations further show that, in moderate malaria transmission, the impact of insecticide resistance on the disease burden is high if the fitness costs of insecticide resistance is low.

Our simulations emphasize the important role parameters related to the level of resistant allele dominance (in mosquitoes with heterozygous genotype) and fitness costs of the insecticide resistance in the vector population play on malaria transmission dynamics and control. There is, currently, very little field/experimental data to be used to determine realistic estimate of these highly important parameters. The absence of such data hampers, to some extent, the effort for the realistic assessment, *via* modeling, of the link between insecticide resistance and malaria epidemiology. This study, consequently, suggests that such field/experimental data needs to be collected and used to realistically estimate these (fitness-related and allele dominance) parameters. In other words, to fully understand the impact of the insecticide-resistance (in mosquitoes) on the global effort to combat malaria, further modeling work needs to be done, with the models fitted using more precise estimates of the parameters associated with the fitness costs of resistance and level of dominance (in fact, some ecological studies indicate

there may be other fitness costs of insecticide resistance, in addition to the ones considered in this study [3], [49]).

Acknowledgements

This work was initiated when JM-A visited AG at Arizona State University (from May 15, 2017 to June 6, 2017). JM-A acknowledges the generous support offered during the visit. AG acknowledges the support, in part, of the Simons Foundation (Award #585022). The authors are very grateful to the anonymous reviewers for their very constructive comments.

Appendix A. Proof of Theorem 3.4

Proof

The proof is based on using comparison theorem.

(a). Let $\mathscr{R}_C > 1$ ($\mathscr{E}_{df} = \mathscr{E}_{0C}$), $\delta_H = 0$ and $\frac{(q^*)^2(\mathscr{R}_C - 1)}{\mathscr{R}_C^2} \geq \frac{1}{4}$. Setting $\delta_H = 0$ in the model (2.5) shows that $\frac{dN_H}{dt} = \Pi_H - \mu_H N_H$. Thus, $N_H(t) \to \frac{\Pi_H}{\mu_H}$, as $t \to \infty$. Hence, from now on, the limiting system with $N_H(t) = N_H^*$ will be used. The equations for the infected components of the model (2.5) can then be written in the form:

$$\frac{d}{dt}\begin{pmatrix} E_H^L(t) \\ I_H^L(t) \\ E_H^H(t) \\ I_H^H(t) \\ E_{SS}^V(t) \\ I_{SS}^V(t) \\ E_{RS}^V(t) \\ I_{RS}^V(t) \\ E_{RR}^V(t) \\ I_{RR}^V(t) \end{pmatrix} = (F - V - S)\begin{pmatrix} E_H^L(t) \\ I_H^L(t) \\ E_H^H(t) \\ I_H^H(t) \\ E_{SS}^V(t) \\ I_{SS}^V(t) \\ E_{RS}^V(t) \\ I_{RS}^V(t) \\ E_{RR}^V(t) \\ I_{RR}^V(t) \end{pmatrix}, \tag{A.1}$$

where the next generation matrices F and V are as given in Section 3.2, and the matrix S is given by

$$S = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & s_{16} & 0 & s_{18} & 0 & s_{1_{10}} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & s_{36} & 0 & s_{38} & 0 & s_{3_{10}} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & s_{52} & 0 & s_{54} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & s_{72} & 0 & s_{74} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & s_{92} & 0 & s_{94} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

where $\left(S_H^L\right)^* = \frac{\xi \Pi_H}{\mu_H}$, $\left(S_H^H\right)^* = \frac{(1-\xi)\Pi_H}{\mu_H}$, $s_{16} = s_{18} = s_{1_{10}} = \frac{\theta \beta_H b_{Hi}\left(\left(S_H^L\right)^* - S_H^L(t)\right)}{N_H^*}$, $s_{36} = s_{38} = s_{3_{10}} = \frac{\theta \beta_H b_{Hi}\left(\left(S_H^L\right)^* - S_H^L(t)\right)}{N_H^*}$, $s_{52} = s_{54} = \frac{\beta_V b_{Hi}\left(\left(S_{SS}^V\right)^{*C} - S_{SS}^V(t)\right)}{N_H^*}$, $s_{72} = s_{74} = \frac{\beta_V b_{Hi}\left(\left(S_{RS}^V\right)^{*C} - S_{RS}^V(t)\right)}{N_H^*}$ and $s_{92} = s_{94} = \frac{\beta_V b_{Hi}\left(\left(S_{RR}^V\right)^{*C} - S_{RR}^V(t)\right)}{N_H^*}$. Since $S_H^L(t) \leq \left(S_H^L\right)^*$, $S_H^H(t) \leq \left(S_H^H\right)^*$, $S_{SS}^V(t) \leq \left(S_{SS}^V\right)^{*C}$, $S_{RS}^V(t) \leq \left(S_{RS}^V\right)^{*C}$, $S_{RR}^V(t) \leq \left(S_{RR}^V\right)^{*C}$, in $\Omega_C \setminus \{\mathscr{E}_{0T}\}$ (which follows from Lemma 3.3), it follows that the matrix S is non-negative. Hence, Eq. (A.1) can be expressed in terms of the following linear inequality:

$$\frac{d}{dt}\begin{pmatrix} E_H^L(t) \\ I_H^L(t) \\ E_H^H(t) \\ I_H^H(t) \\ E_{SS}^V(t) \\ I_{SS}^V(t) \\ E_{RS}^V(t) \\ I_{RS}^V(t) \\ E_{RR}^V(t) \\ I_{RR}^V(t) \end{pmatrix} \leq (F - V)\begin{pmatrix} E_H^L(t) \\ I_H^L(t) \\ E_H^H(t) \\ I_H^H(t) \\ E_{SS}^V(t) \\ I_{SS}^V(t) \\ E_{RS}^V(t) \\ I_{RS}^V(t) \\ E_{RR}^V(t) \\ I_{RR}^V(t) \end{pmatrix}. \tag{A.2}$$

Since all the eigenvalues of $F - V$ have negative real part for $\overline{\mathscr{R}}_0 < 1$ (from the local stability result in Theorem 3.2), it follows that the linearized system of differential inequality (A.2) is stable if $\overline{\mathscr{R}}_0 < 1$. That is, substituting $E_H^L(t) = 0$,

$I_H^L(t)=0, E_H^H(t)=0, I_H^H(t)=0, E_{SS}^V(t)=0, I_{SS}^V(t)=0, E_{RS}^V(t)=0, I_{RS}^V(t)=0,$
$E_{RR}^V(t)=0, I_{RR}^V(t)=0$ into the equations of the model (2.5) gives:

$$\left(E_H^L(t), I_H^L(t), E_H^H(t), I_H^H(t), E_{SS}^V(t), I_{SS}^V(t), E_{RS}^V(t), I_{RS}^V(t), E_{RR}^V(t), I_{RR}^V(t)\right) \to (0,0,0,0,0,0,0,0,0,0),$$

and,

$$\left(S_H^L(t), R_H^L(t), S_H^H(t), R_H^H(t), S_{SS}^V(t), S_{RS}^V(t), S_{RR}^V(t)\right) \to \left(\left(S_H^L\right)^*, 0, \left(S_H^H\right)^*, 0, \left(S_{SS}^V\right)^{*C}, \left(S_{RS}^V\right)^{*C}, \left(S_{RR}^V\right)^{*C}\right),$$

as $t \to \infty$.

Hence, the NTCDFE ($\mathscr{E}_{0C}$) of the model (2.5), with $\mathscr{R}_C > 1$, $(\mathscr{R}_{SS} - \mathscr{R}_{RS})(\mathscr{R}_{RR} - \mathscr{R}_{RS}) > 0$ or $\mathscr{R}_{SS} = \mathscr{R}_{RS} = \mathscr{R}_{RR}$, $\frac{(q^*)^2(\mathscr{R}_C - 1)}{\mathscr{R}_C^2} \geq \frac{1}{4}$ and $\delta_H = 0$, is GAS in $\Omega_C \setminus \{\mathscr{E}_{0T}\}$ whenever $\overline{\mathscr{R}}_0^{0C} < 1$. Items (b) and (c) can be proved using a similar approach (hence, not repeated here). □

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