Journal of Mathematical Biology (2023) 87:28
https://doi.org/10.1007/s00285-023-01949-x

Mathematical Biology

Can insecticide resistance increase malaria transmission? A genetics-epidemiology mathematical modeling approach

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Received: 27 September 2021 / Revised: 7 May 2023 / Accepted: 5 June 2023

Abstract

The great successes recorded in the fight against malaria over the last two decades, resulting from the wide scale implementation of insecticide-based interventions in malaria-endemic areas, has prompted a renewed global effort to eradicate malaria. The widespread emergence of insecticide resistance in the population of adult female malaria mosquitoes is considered to pose a potential challenge to such effort. In this study, we address one of the key questions in malaria ecology, namely whether or not insecticide resistance increase malaria transmission. We developed a genetics-epidemiology modeling framework that incorporates a detailed genotype structure of the gene that confers insecticide resistance in mosquitoes, malaria epidemiology in mosquitoes and humans (stratified based on whether or not they are protected by Long-lasting insecticide-treated nets (LLINs) indoors), genotype-specific mosquito repellance property of LLINs and mosquito biting behavior (indoor and outdoor bites). Conditions for the existence and local asymptotic stability of the various disease-free equilibria (by genotype) of the resulting genetic-epidemiology model are derived. This study identifies four parameters of the model that play a crucial role on quantifying the impact of insecticide resistance on malaria transmission, namely the parameters related to the level of the dominance of the resistant allele in heterozygous mosquitoes, the coverage of long-lasting insecticidal nets in the community, the probability of endophilic mosquitoes to successfully take a bloodmeal indoors and the proportion of new adult mosquitoes that are endophilic. We showed that, depending on the values of these four identified parameters, insecticide resistance can increase, decrease, or have no effect on malaria transmission. Our simulations show that malaria eradication can indeed be achieved using the currently-available chemical insecticides, even in

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the wake of the prevailing widespread insecticide resistance in malaria-endemic areas, if the insecticide-based interventions implemented can result in the attainment of the optimal values of the four identified parameters in malaria-endemic areas.

Keywords Insecticide resistance · LLINs · Mosquito genotype · Mosquito biting behavior · Reproduction number

Mathematics Subject Classification 92D30

1 Introduction

Malaria is one of the deadliest infectious diseases of humans. Caused by protozoan *Plasmodium* parasites, the disease is spread between humans *via* the bite of infected adult female *Anopheles* mosquitoes (Baton and Ranford-Cartwright 2005; WHO 2016, 2017). Malaria is endemic in many parts of the world, particularly the tropical and subtropical regions [over 2.5 billion people live in areas whose local epidemiology permits transmission of *P. falciparum*, responsible for most of the life-threatening form of malaria (Gething et al. 2011; Johnston et al. 2013)]. Data from the 2022 World Malaria Report of the World Health Organization (WHO) shows that malaria caused 241 million infections and 619,000 deaths (with majority of the deaths occurring in children under the age of five) globally in 2021 (WHO 2022a). With 95% of malaria cases and 96% of malaria deaths in 2021, the WHO African Region carries a disproportionately high share of the global malaria burden (WHO 2022a). Of major concern is that, while malaria cases and mortality have been declining globally, malaria burden in the 10 highest burden countries have been increasing over the past few years [and malaria remains a major public health burden and public health challenge for about half of the world's population (Gething et al. 2016; WHO 2012, 2015b, 2018)].

Since about the year 2007, numerous important global efforts, such as the Roll Back Malaria initiative and the United Nations Millennium Development Goals (MDGs) (Huijben and Paaijmans 2017; WHO 2015a), have embarked on malaria eradication. These efforts resulted in a dramatic reduction of malaria incidence and mortality in sub-Saharan Africa by 42% and 66%, respectively (Riveron et al. 2018). Although multiple factors, such as early diagnosis, improved drug therapy and better public health infrastructure, have contributed to such success, the major reason for the extraordinary success is believed to be large-scale use of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) of insecticides (Riveron et al. 2018). Specifically, it has been estimated that the combined use of bednets and IRS in malaria-endemic areas accounted for about 81% of the reduction of malaria burden recorded globally during the period 2000–2015 (with most of the benefits due to bednets) (Bhatt et al. 2015). There are now renewed global efforts, through programs such as The Global Technical Strategy for Malaria 2016–2030 (WHO 2015a) and the $ZeroX40$ (Gates Foundation 2019; Willis and Hamon 2018), aimed at eradicating malaria by 2030 or 2040. These efforts are heavily focused on the use of insecticide-based vector control interventions, such as *Pyrethroids*-based LLINs and IRS (Barbosa and Hastings 2012;

Huijben and Paaijmans 2017; Mohammed-Awel et al. 2017; Okumu and Moore 2011; WHO 2015c).

Unfortunately, the aforementioned widespread and heavy use of insecticide-based interventions has resulted in the emergence of vector resistance to nearly every currently-available chemical agent embedded in LLINs and IRS, thereby potentially posing challenges to the malaria eradication effort (Alout et al. 2017b; Dondorp et al. 2009; Imwong et al. 2017; Kabula et al. 2014; WHO 2022b). Mosquitoes (or disease vectors in general) are said to be *resistant* to insecticides if the ability of the insecticides to kill them on contact is greatly reduced or eliminated (Mohammed-Awel et al. 2020). Given the dominant role of LLINs in malaria mortality reductions, any threat to their efficacy *via* resistance is of foremost importance. Indeed, Pyrethroid resistance is now widely observed across the African continent (Hemingway et al. 2016). Although *Anopheles* Pyrethroid resistance, as a phenotype in the context of commonly used laboratory assays (e.g., 1-hour or 24-hour survival), is now common, it is not clear that this has translated into an increase in malaria transmission or burden (Alout et al. 2017a, b; Huijben and Paaijmans 2017; Kleinschmidt et al. 2018; Ochomo et al. 2017).

Insecticide resistance traits have commonly been observed to incur a fitness cost in resistant mosquitoes, which could undermine malaria transmission, particularly if the cost comes in the form of decreased adult mosquito survival. Insecticide resistance may also deleteriously affect male mating success (Berticat et al. 2002; Platt et al. 2015), fecundity (Assogba et al. 2015), development time (Assogba et al. 2015; Bourguet et al. 2004), lower energetic reserves (Rivero et al. 2011), and wing length (Bourguet et al. 2004). These costs arise as a result of target site point mutations impacting the function of the gene, or as a result of up-regulation of resistance associated enzymes, which could be costly to overproduce (Assogba et al. 2015). Further, the life-cycles of the adult male and female *Anopheles* vary markedly (most importantly, only females seek bloodmeal from humans and are thus more likely to get into contact with insecticides). Moreover, insecticide exposure even to highly “resistant” mosquitoes under laboratory survival assays may still result in behavioral changes (e.g., reduced host-seeking) or delayed mortality that undermine the vectorial capacity of these insects.

A major open question in the mosquito ecology and the wider malaria control community is whether or not insecticide resistance actually impacts malaria epidemiology. A recent and very large observational cohort study across five countries found that, while LLINs users had lower rates of malaria infection and disease, no relationship between laboratory-assessed insecticide resistance and malaria epidemiology was detected (Kleinschmidt et al. 2018). In contrast, some data suggest that resistance can undermine the control of malaria. One recent study suggests that insecticide resistance has led to a rebound in malaria incidence in South Africa (Alout et al. 2017b; Maharaj et al. 2005). A large, factorial randomized clinical trial (Protopopoff et al. 2018) comparing LLINs, LLINs treated with a piperonyl butoxide (PBO) synergist, and IRS, showed benefit to malaria control with either IRS or a PBO synergistic in addition to an LLINs, suggesting that Pyrethroid resistance decreased the efficacy of the standard LLINs alone. A recent experimental hut trial (Toe et al. 2018) also suggested benefit to LLINs with PBO synergists in an area with highly Pyrethroid-resistant *Anopheles*. Consequently, due to these inconsistencies, there is urgent need to use mathematical modeling efforts, coupled with empirical data analytics, to uncover the relation, if any, between insecticide resistance and malaria transmission, and to determine if existing vector control resources can be optimally used to achieve the malaria eradication objective.

A number of mathematical modelling studies, that incorporate the population genetics of *Anopheles* mosquitoes, have been conducted to assess the impact of insecticide resistance on malaria epidemiology (Barbosa and Hastings 2012; Barbosa et al. 2018; Birget and Koella 2015; Briet et al. 2013; Brown et al. 2013; Levick et al. 2017; South and Hastings 2018). For instance, using a population genetics model, Barbosa and Hastings (Barbosa and Hastings 2012) emphasized the importance of selection coefficients, fitness cost of resistance and dominance of resistant allele on the spread of resistance. Using a population genetics model for the spread of insecticide resistance in a population where insecticide-treated nets (ITNs) and larvicides are used, Birget and Koella (2015) show that the use of indoor ITNs leads to less selection pressure in comparison to the application of larvicides. Brown et al. (2013) showed that fitness costs of resistance are key to quantifying optimal resistance management strategies. Barbosa et al. (2018) used a mosquito stage-structured deterministic model, that stratifies the mosquito population by genotype, and showed that relatively low degrees of resistance can lead to the failure of insecticide-based intervention (with insecticide resistance evolving faster when mosquitoes at the immature stages are exposed to the larvicides). Using an individual-based stochastic simulation model, Briet et al. (2013) showed that bednets (standard and long-lasting insecticidal nets) are cost effective against malaria even in communities with widespread insecticide (Pyrethroid) resistance.

Although the aforementioned mathematical modeling studies have incorporated population genetics of the malaria vector, they did not include the components or dynamics of malaria at population level. Based on this, it is clear that in order to realistically assess the impact of insecticide resistance on malaria transmission, it is necessary to develop a new modeling framework that combines the population genetics of the malaria vector with malaria epidemiology (in humans and mosquitoes at population) and backed by empirical data. The main objective of the current study is to use this novel modeling framework to address the crucial question on whether or not insecticide resistance increases malaria transmission and burden. Preliminary attempts for designing such a framework were conducted by the authors (see, for instance, Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2018, 2020; Mohammed-Awel and Gumel 2023). Although these genetics-epidemiology malaria modeling studies allowed for the assessment of the population-level impact of mosquito insecticide resistance on malaria transmission dynamics in human and mosquito populations (in the presence of wide scale use of ITNs, IRS and their combination), they did not incorporate important features, such as, mosquito biting behavior (indoors and outdoors), bednet repellance property by genotype and detailed mosquito-host contacts process. Further, the key question on whether resistance increases malaria transmission was not explicitly considered in the studies reported in Mohammed-Awel and Gumel (2019), Mohammed-Awel et al. (2018), Mohammed-Awel et al. (2020), Mohammed-Awel and Gumel (2023).

A few other malaria modeling efforts have focused on assessing the impact of mosquito biting behavior and the repellance property of the bednet. For instance, Tsanou et al. (2020) developed a simple mathematical model for malaria transmission that incorporate nonlinear functions for the human-mosquito contact that depends on bednet usage and repellance rate. They showed that ITN usage can effectively control malaria disease, and the usage of ITN with high lethal rate, but low repellance rate, is better than the use of ITN with high repellance and low lethal rates. This study did not include insecticide resistance in mosquitoes. Field study conducted by Sherrard-Smith et al. (2020) showed that, on average, 21% of mosquito bites are caused by malaria mosquito that are outdoors.

The effect of the increase in outdoor biting behavior of malaria mosquitoes on malaria epidemiology need be understood in order to implement appropriate outdoor vector control strategies (since by selecting to bite outdoors, *Anopheles* mosquitoes are essentially evading the insecticide-based pressure indoors, such as the use of ITNs or LLINs) (Sherrard-Smith et al. 2020). Mathematical models have been used to study the population-level impact of mosquito indoor/outdoor biting behavior (Mohammed-Awel et al. 2018; Birget and Koella 2015). Specifically, Birget and Koella (2015) extended the classical Ross-MacDonald model for malaria transmission (Ross 1910) by stratifying the human population based on whether or not they are protected by the bednets indoors, in addition to mosquito indoor/outdoor biting behavior. They showed that ITNs can effectively reduce malaria transmission in the community, however, a conflict between barrier/physical protection, offered by repellance property of the ITNs, and community-wide protection, which relies on the killing efficacy of the ITNs was observed (Birget and Koella 2015). Insecticide-resistance in mosquito was not incorporated in their modeling study. Using a deterministic model that stratifies the mosquito population in terms of their sensitivity or resistance to the chemical insecticides used for vector control and their feeding preferences (indoors or outdoors), Mohammed-Awel et al. (2018) obtained an optimal ITNs-IRS strategy that could lead to the effective control of malaria, while insecticide resistance is effectively managed, in a malaria-endemic setting. The model developed in Mohammed-Awel et al. (2018) was based on the simplifying assumption that mosquito insecticide resistance is determined by a single gene with one allele in a locus (the repellance property of the insecticide-treated bednets was also not included in the model) (Mohammed-Awel et al. 2018).

In the current study, we will develop a new genetics-epidemiology mathematical modeling framework that incorporates the detailed genotype structure of the gene that confers insecticide resistance in mosquitoes, malaria epidemiology in mosquitoes and humans (stratified based on whether or not they are protected by LLINs indoors). The model to be developed further incorporates genotype-specific mosquito repellance property of LLINs and mosquito biting behavior (indoor and outdoor bites). A nonlinear function for genotype specific mosquito-human contact rate that incorporates the possibility of multiple mosquito bite attempts to obtain successful bloodmeal from human hosts is derived. The model structure allows for the simultaneous investigation of malaria transmission dynamics (in humans and mosquitoes) and the evolution of insecticide resistance in mosquitoes. In particular, we will conduct numerical simulations to explore several scenarios to realistically answer the key question on whether insecticide resistance causes an increase or a decrease in malaria transmission in a malaria-endemic area.

The paper is organized as follows. The model is formulated in Sect. 2. Its basic qualitative properties are also analysed. Rigorous results for the existence and asymptotic stability of the various disease-free equilibria of the model are derived in Sect. 3. Numerical simulations of the model, using data relevant to malaria transmission dynamics in Jimma zone of Ethiopia (an area of high malaria transmission), are reported in Sect. 4. Finally, discussion and concluding remarks are presented in Sect. 5.

2 Formulation of mathematical model

In order to formulate the mathematical model, it is convenient to let $N_V(t)$ represent the total population of adult female *Anopheles* mosquitoes at time t. Further, let $N_V^{(in)}(t)$ represent the total population of these mosquitoes that are indoors (i.e., endophilic mosquitoes) and $N_V^{(out)}(t)$ represent the total population of mosquitoes that are outdoors (exophilic). In this study, mosquitoes are classified according to their genotype with respect to insecticide resistance, namely homozygote sensitive (SS), heterozygote (RS) and homozygote-resistant (RR) (Kuniyoshi and Santos 2017; Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020; Mohammed-Awel and Gumel 2023). Let $N_i^{(in)}(t)$ represents the total sub-population of indoor mosquitoes of i-genotype (with $i = \{SS, RS, RR\}$) and let $N_i^{(out)}(t)$ be the total sub-population of mosquitoes of i-genotype that are outdoor. The total population of indoor (outdoor) mosquitoes of i-genotype is further stratified according to disease status. Specifically, we split these sub-populations into compartments for indoor(outdoor) susceptible (denoted by $S_i^{(in)}(t)(S_i^{(out)}(t))$), exposed indoor (outdoor) $(E_i^{(in)}(t)(E_i^{(out)}(t)))$ and infectious indoor (outdoor) $(I_i^{(in)}(t)(I_i^{(out)}(t)))$, so that:

$$\begin{aligned} N_i^{(in)}(t) &= S_i^{(in)}(t) + E_i^{(in)}(t) + I_i^{(in)}(t) \text{ and} \\ N_i^{(out)}(t) &= S_i^{(out)}(t) + E_i^{(out)}(t) + I_i^{(out)}(t). \end{aligned} \tag{2.1}$$

Furthermore,

$$\begin{aligned} N_V^{(in)}(t) &= N_{SS}^{(in)}(t) + N_{RS}^{(in)}(t) + N_{RR}^{(in)}(t) \text{ and} \\ N_V^{(out)}(t) &= N_{SS}^{(out)}(t) + N_{RS}^{(out)}(t) + N_{RR}^{(out)}(t), \end{aligned} \tag{2.2}$$

$$N_{SS}^V = N_{SS}^{(in)} + N_{SS}^{(out)}, \;\; N_{RS}^V = N_{RS}^{(in)} + N_{RS}^{(out)} \text{ and } N_{RR}^V = N_{RR}^{(in)} + N_{RR}^{(out)}, \tag{2.3}$$

and,

$$N_V(t) = N_V^{(in)}(t) + N_V^{(out)}(t). \tag{2.4}$$

In this study, we assume mosquito reproduction is based on random mating between mosquitoes (Kuniyoshi and Santos 2017; Mohammed-Awel and Gumel 2019;

Mohammed-Awel et al. 2020; Mohammed-Awel and Gumel 2023). Let $q(t)$ and $p(t)$ represent the frequency of the sensitive allele (S) and resistant (R) allele in the adult mosquito population (Birget and Koella 2015; Hastings 1997; Kuniyoshi and Santos 2017; Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020; Mohammed-Awel and Gumel 2023). It follows (see Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020; Mohammed-Awel and Gumel 2023 for detailed derivation) that

$$q(t) = \frac{N_{SS}^V(t) + \frac{1}{2}N_{RS}^V(t)}{N_V(t)} \text{ and } p(t) = \frac{N_{RR}^V(t) + \frac{1}{2}N_{RS}^V(t)}{N_V(t)}. \tag{2.5}$$

Following (Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020; Mohammed-Awel and Gumel 2023), the following logistic growth birth functions, denoted by B_i^V, are used for the production of new adult mosquitoes by genotype:

$$\begin{aligned}
B_{SS}^V(t) &= q^2(t) b_{SS} N_V(t)\left(1 - \frac{N_V(t)}{K_V}\right),\\
B_{RS}^V(t) &= 2p(t)q(t) b_{RS} N_V(t)\left(1 - \frac{N_V(t)}{K_V}\right),\\
B_{RR}^V(t) &= p^2(t) b_{RR} N_V(t)\left(1 - \frac{N_V(t)}{K_V}\right).
\end{aligned} \tag{2.6}$$

In (2.6), $b_i > 0$ represents the production (birth) rate of new adult female mosquitoes of i-genotype for $i = \{SS, RS, RR\}$, $K_V > 0$ is the environmental carrying capacity of adult mosquito (note that, to ensure the positivity of the birth functions, we assume $N_V(t) < K_V$ for all t).

Let $N_H(t)$ denotes the total human population at time t. This population will further be stratified according to whether or not individuals use bednets. Specifically, we split this population into those who are “protected" (i.e., those who sleep under bednet, use bednets consistently and correctly) and those who are “unprotected" (i.e., those who do not sleep under a bednet). To account for disease status, the total human population is subdivided into the sub-populations of susceptible protected (unprotected) $S_{H_p}(t)$ ($S_{H_u}(t)$), exposed protected (unprotected) $E_{H_p}(t)$ ($E_{H_u}(t)$), infectious protected (unprotected) $I_{H_p}(t)$ ($I_{H_u}(t)$), and recovered protected (unprotected) $R_{H_p}(t)$ ($R_{H_u}(t)$) humans, so that:

$$\begin{aligned}
N_H(t) = {} & S_{H_p}(t) + S_{H_u}(t) + E_{H_p}(t) + E_{H_u}(t) + I_{H_p}(t)\\
& + I_{H_u}(t) + R_{H_p}(t) + R_{H_u}(t).
\end{aligned} \tag{2.7}$$

Finally, it is convenient to define the total number of unprotected and protected human hosts, at time t, by $N_{H_p}(t)$ and $N_{H_u}(t)$, respectively. That is,

$$\begin{aligned}
N_{H_p}(t) &= S_{H_p}(t) + E_{H_p}(t) + I_{H_p}(t) + R_{H_p}(t) \text{ and}\\
N_{H_u}(t) &= S_{H_u}(t) + E_{H_u}(t) + I_{H_u}(t) + R_{H_u}(t).
\end{aligned} \tag{2.8}$$

2.1 Derivation of genotype-specific probabilities of successfully taking bloodmeal and malaria transmission rates

2.1.1 Probability of endophilic mosquito of *i*-genotype contacting and successfully taking a bloodmeal from protected hosts indoors

Let C_B be the proportion of individuals in the community who consistently sleep under a bednet (LLINs). That is, $C_B = N_{H_p}(t)/N_H(t)$ represents the LLINs coverage in the community (it is shown in Theorem 2.1 that, for the model $\{(2.29)–(2.31)\}$, C_B is a constant for all time t). Furthermore, let ρ_c^{SS} be the probability that an SS-genotype endophilic mosquito is killed by the insecticide (*Pyrethroid*) embedded in the bednet upon contact with the bednet. Moreover, let $0 \leq g^i \leq 1$ (with $i = \{SS, RS, RR\}$) be a modification parameter that accounts for the reduction in insecticide-induced mortality of resistant mosquitoes (homozygotes or heterozygotes), in comparison to insecticide-sensitive mosquitoes. That is, $g^{SS} = 1$, $g^{RS} = (1-hu)$ and $g^{RR} = (1-u)$, where $0 \leq h \leq 1$ is a modification parameter accounting for the measure of the dominance of the resistant allele over the sensitive allele (i.e., $h = 1$ models the case where the resistant allele is dominant, and $h = 0$ represents the case when it is recessive) and $0 \leq u \leq 1$ is a modification parameter accounting for the assumed decrease in the insecticide-induced mortality of the RR-genotype mosquitoes, in comparison to the insecticide-induced mortality of the $SS-$genotype mosquitoes. Hence, the quantity $(1-hu)$ is a measure of the reduction of the efficacy of insecticides to kill adult mosquitoes of RS-genotype (Bourguet et al. 2000). Therefore, $\rho_c^i = \rho_c^{SS} g^i$ is the probability that an i-genotype ($i = \{SS, RS, RR\}$) endophilic mosquito killed by the insecticide chemical embedded in the bednet upon contact with the bednet. Furthermore, let r^i be the efficacy of the bednet to repel (or to deter) an endophilic mosquito of i-genotype from contacting the host (i.e., r^i measures the combined effect of the barrier property of the bednet to deter endophilic mosquitoes from encountering the protected human host as well as the *excito* repellance property of the *Pyrethroid* to repel the mosquito from the human host (protected by the LLINs)). It is worth stating that when an endophilic mosquito is repelled (by the bednet), the mosquito can either return to make another attempt on a protected human host or contact an unprotected human host.

It is convenient to define $q^i_{m_{(in)}}$ ($q^i_{m_{(out)}}$) as the probability that the endophilic (exophilic) i-genotype mosquito successfully takes a bloodmeal upon contact with a human host (protected or unprotected). We assume that this mosquito is killed by the indoor [outdoor] human host, upon contact, with probability $(1-q^i_{m_{(in)}})[(1-q^i_{m_{(out)}})]$. That is, if the mosquito is not repelled (with probability $1 - r^i$) and not killed by the chemical embedded in the bednet (with probability $(1 - \rho_c^i)$, then either the mosquito successfully takes a bloodmeal from a human host indoors (with probability $q^i_{m_{(in)}}$) or from a human host outdoors (with probability $q^i_{m_{(out)}}$) or get killed by humans indoors or outdoors (with probability $(1 - q^i_{m_{(in)}})$ or $(1 - q^i_{m_{(out)}})$, respectively). In our formulation, when a mosquito contacts a human host only two things can happen: (a) either the mosquito successfully takes a bloodmeal [with probability $q^i_{m_{(in)}}$ ($q^i_{m_{(out)}}$) for indoors (outdoors)] or (b) is killed by the human host (with probability $(1-q^i_{m_{(in)}})$

Table 1 Description of the state variables of the model {(2.29)–(2.31)}

State variable, $i = \{SS, RS, RR\}$	Interpretation
$S_{H_p}(S_{H_u})$	Number of protected (unprotected) susceptible humans
$E_{H_p}(E_{H_u})$	Number of protected (unprotected) exposed (infected but not yet infectious) humans
$I_{H_p}(I_{H_u})$	Number of protected (unprotected) infectious (symptomatic) humans
$R_{H_p}(R_{H_u})$	Number of protected (unprotected) recovered humans
$S_i^{(in)}(S_i^{(out)})$	Population of adult female endophilic (exophilic) mosquitoes of i-genotype and susceptible to malaria
$E_i^{(in)}(E_i^{(out)})$	Population of adult female endophilic (exophilic) mosquitoes of i-genotype and exposed to malaria
$I_i^{(in)}(I_i^{(out)})$	Population of adult female endophilic (exophilic) mosquitoes of i-genotype and infectious to malaria

$((1 - q^i_{m(out)}))$ for indoors (outdoors)). For simplicity, we do not consider the case where the human host can deter the mosquito from taking a bloodmeal upon contact with the human (in other words, we limit mosquito repellance to be due to contact with the bednet alone).

If the i-genotype endophilic mosquito failed to successfully take a bloodmeal from a protected host, it may return for subsequent attempts on either a protected or unprotected host indoors. Specifically, after n unsuccessful attempts to take a bloodmeal from a protected human host indoors, the mosquito can successfully take the bloodmeal during the $(n+1)^{th}$ attempt. The probability of an unsuccessful attempt is given by the product of the LLINs coverage in the community (C_B), the probability of being repelled (r^i) and the probability of not being killed $(1 - \rho_c^i)$. Hence, the probability of n unsuccessful attempts is $[C_B r^i (1 - \rho_c^i)]^n$. Consequently, the probability of mosquitoes of i-genotype to successfully take a bloodmeal from a protected human host indoors at the $(n+1)^{\text{th}}$ attempt (after n unsuccessful attempts) isnnn given by:

$$\underbrace{C_B}_{\substack{\textbf{targets protected}\\ \textbf{indoor host}}} \underbrace{(1-\rho_c^i)}_{\substack{\textbf{prob. not killed}\\ \textbf{by the bednet}}} \times \underbrace{(1-r^i)}_{\substack{\textbf{prob. not repelled}\\ \textbf{by the bednet}}} \times \underbrace{q^i_{m(in)}}_{\substack{\textbf{prob. successfully}\\ \textbf{taking a bloodmeal}}} \times \overbrace{[r^i C_B (1-\rho_c^i)]^n.}^{\substack{\textbf{prob. of } n \textbf{ failed attempts to take}\\ \textbf{a bloodmeal from protected humans}\\ \text{and not killed during the } n \text{ failed attempts}}} \quad . \tag{2.9}$$

In other words, Equation (2.9) shows that in order for the i-genotype mosquito to successfully take a bloodmeal from a protected human host indoors during the $(n+1)^{th}$ attempt, it has to do all of the following:

(a) Encounter a proportion of the human hosts that are protected (C_B),
(b) Make n failed attempts to take a bloodmeal from the protected hosts (this occurs with probability $[C_B r^i(1-\rho_c^i)]^n$),
(c) Not be killed by the bednet (with probability $(1-\rho_c^i)$),
(d) Not be repelled by the bednet (with probability $(1-r^i)$), and
(e) Successfully take the bloodmeal from the protected host (with probability $q^i_{m_{(in)}}$).

After n unsuccessful attempts on protected human hosts, an endophilic mosquito of i-genotype can return for another attempt and may encounter a protected or unprotected host indoors. If it attempts on a protected host, they can either successfully take a bloodmeal or get repelled (by the bednet) or be killed by the bednet or the human host (as described above). However, if the mosquitoes encounters an unprotected host during this attempt, it can either successfully take a bloodmeal (with probability $q^i_{m_{(in)}}$) or be killed by the unprotected host (with probability $(1-q^i_{m_{(in)}})$). In other words, our formulation does not allow for mosquitoes to be repelled by unprotected hosts (i.e., once they encounter an unprotected host, they either succeed in getting a bloodmeal or they get killed by the unprotected host).

It follows, based on the above derivations, that the overall probability of an endophilic mosquito of i-genotype to successfully take a bloodmeal from a protected host indoors during either the first attempt or during the subsequent n attempts (with $n = 1, 2, \cdots$), denoted by $P^i_{(in)_p}(r^i, C_B, \rho_c^i)$, is given by (the full derivation is given in Equation (A.1) of "Appendix A", where it is also shown that $0 \leq P^i_{(in)_p}(r^i, C_B, \rho_c^i) \leq 1$):

$$P^i_{(in)_p}(r^i, C_B, \rho_c^i) = \frac{C_B(1-\rho_c^i)(1-r^i)q^i_{m_{(in)}}}{1-r^i C_B(1-\rho_c^i)}; \quad i = \{SS, RS, RR\}. \tag{2.10}$$

It follows from Equation (2.10) that if $r^i = 1$, then all endophilic mosquitoes of i-genotype are repelled whenever they attempt to take a bloodmeal from protected hosts. Hence, in this case, the probability that an endophilic mosquito of i-genotype encountering, and successfully taking a bloodmeal from, a protected host is zero (i.e., the probability $P^i_{(in)_p}(r^i, C_B, \rho_c^i)$ is zero in this case). Similarly, if $\rho_c^i = 1$, then all endophilic mosquitoes of i-genotype will be killed upon contact with the bednet. In this case, endophilic mosquitoes of i-genotype have zero chance of encountering, and successfully taking a bloodmeal from, a protected human host (i.e., the probability $P^i_{(in)_p}(r^i, C_B, \rho_c^i)$ is also zero in this case).

2.1.2 Probability of endophilic mosquito of *i*-genotype contacting and successfully taking a bloodmeal from unprotected hosts indoors

Let $P^i_{(in)_u}(r^i, C_B, \rho_c^i)$ represents the probability that an endophilic mosquito of i-genotype makes contact with, and successfully takes a bloodmeal from, an unprotected host indoors. Then, it follows from the derivations in "Appendix B" that $P^i_{(in)_u}(r^i, C_B, \rho^i_c)$ is given by (it has also been shown in "Appendix B" that $0 \leq P^i_{(in)_u}(r^i, C_B, \rho^i_c) \leq 1$):

$$P^i_{(in)_u}(r^i, C_B, \rho^i_c) = \frac{(1 - C_B)q^i_{m_{(in)}}}{1 - r^i C_B(1 - \rho^i_c)}. \tag{2.11}$$

Furthermore, it follows, by adding Equations (2.10) and (2.11), that:

$$P^i_{(in)_p}(r^i, C_B, \rho^i_c) + P^i_{(in)_u}(r^i, C_B, \rho^i_c) = q^i_{m_{(in)}} \left(1 - \frac{C_B \rho^i_C}{1 - r^i C_B \left(1 - \rho^i_C\right)}\right). \tag{2.12}$$

Differentiating $P^i_{(in)_p}(r^i, C_B, \rho^i_c) + P^i_{(in)_u}(r^i, C_B, \rho^i_c)$ partially with respect to the LLINs coverage (C_B) gives:

$$\frac{\partial[P^i_{(in)_p}(r^i, C_B, \rho^i_c) + P^i_{(in)_u}(r^i, C_B, \rho^i_c)]}{\partial C_B} = -\frac{\rho^i_c q^i_{m_{(in)}}}{[1 - r^i C_B(1 - \rho^i_c)]^2} \leq 0, \tag{2.13}$$

from which it follows that the probability of an endophilic mosquito of i-genotype contacting, and successfully taking a bloodmeal from, indoor humans, $[P^i_{(in)_p}(r^i, C_B, \rho^i_c) + P^i_{(in)_u}(r^i, C_B, \rho^i_c)]$, decreases with increasing LLINs coverage (as expected). Similarly, taking partial derivative of $P^i_{(in)_p}(r^i, C_B, \rho^i_c) + P^i_{(in)_u}(r^i, C_B, \rho^i_c)$ with respect to r^i gives:

$$\frac{\partial[P^i_{(in)_p}(r^i, C_B, \rho^i_c) + P^i_{(in)_u}(r^i, C_B, \rho^i_c)]}{\partial r^i} = -q^i_{m_{(in)}} \frac{\rho^i_c (C_B)^2 (1 - \rho^i_c)}{[1 - r^i C_B(1 - \rho^i_c)]^2} \leq 0, \tag{2.14}$$

so that the sum $P^i_{(in)_p}(r^i, C_B, \rho^i_c) + P^i_{(in)_u}(r^i, C_B, \rho^i_c)$ is a decreasing function of r^i. Hence, an increase in repellance (or deterrent) efficacy of the bednet will decrease the overall probability of endophilic mosquitoes of i-genotype to encounter, and successfully take a bloodmeal from, a human host indoors (as expected).

2.1.3 Probability of exophilic *i*-genotype mosquito successfully getting a bloodmeal from a human host outdoors

Let $P^i_{(out)}$ represents a probability of an exophilic mosquito of i-genotype successfully taking a bloodmeal from a human outdoors *per* contact. We assume that exophilic mosquitoes of i-genotype contact humans undeterred (since the outdoor humans are not protected by the bednet or any other physical barrier), and that upon contact with

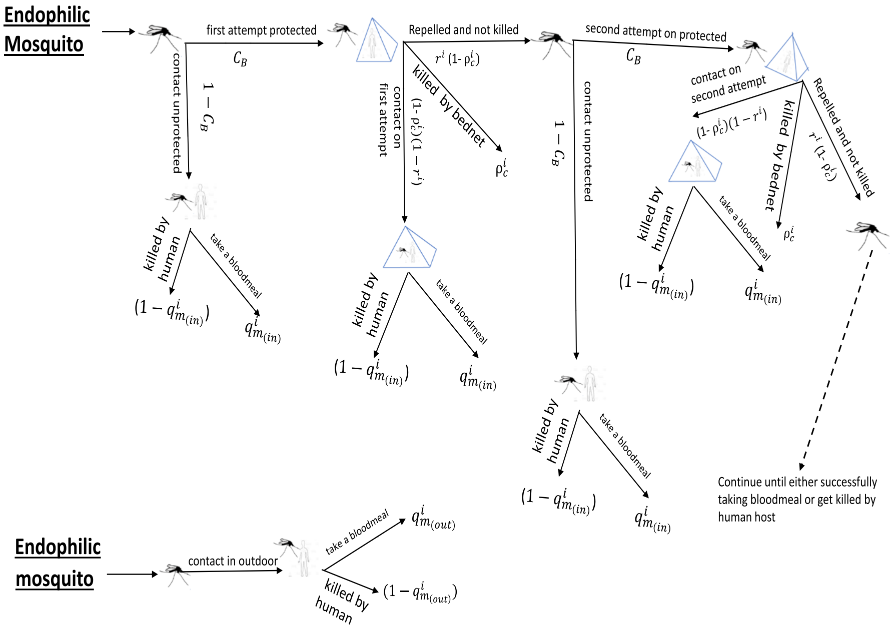

Fig. 1 A flow diagram for the possibilities associated with the adult female mosquito's quest for bloodmeal from humans indoors (endophilic) or outdoors (exophilic). At n^{th} attempt, endophilic adult female mosquitoes seek to bite either a protected host (with probability C_B) or an unprotected host (with probability $1 - C_B$). These (endophilic) mosquitoes have three possible outcomes when they attempt to bite a protected human host,namely either (**a**) they get killed by the insecticide upon contact with the bednet, (**b**) or they get repelled, and not killed, by the bednet, (**c**) or they successfully encounter (or make contact with) the protected human host (with the associated probabilities indicated in the flow diagram). Furthermore, when adult female mosquitoes (either endophilic or exophilic) successfully encounter a human host (protected or unprotected), they either successfully take a bloodmeal or get killed by the human host (with the associated probabilities indicated in the flow diagram)

the humans outdoors, mosquitoes of i-genotype either successfully take a bloodmeal (with probability $q^i_{m_{(out)}}$) or get killed by the humans (with probability $(1 - q^i_{m_{(out)}})$). In other words, since, in this case, the human hosts are not protected (i.e., they are outdoors), the mosquitoes have 100% probability of making contact with the human hosts (so that the mosquitoes either successfully takes a bloodmeal from the outdoor human host or get killed by the human host). Here, too, we make the simplifying assumption that the mosquito is not repelled by the human host. Furthermore, it is assumed that humans outdoors do not use insect repellents or directly (physically) repel or divert the mosquito away upon contact with them. Therefore,

$$\begin{aligned} P^i_{(out)} &= (\text{probability of contacting outdoor host}) \\ &\quad \times (\text{probability of successfully taking a bloodmeal}), \\ &= (1) \times \left(q^i_{m_{(out)}}\right), \\ &= q^i_{m_{(out)}}. \end{aligned} \tag{2.15}$$

Figure 1 depicts a flow diagram of the various probabilities associated with the human-mosquito contact and the adult female mosquito's quest for bloodmeal from humans indoors or outdoors.

2.1.4 Total death rate of endophilic and exophilic mosquitoes

Let μ_M^i represents the natural death rate of adult mosquitoes of i-genotype (with $i = \{SS, RS, RR\}$). It follows from the derivations in "Appendix C" (leading to Equation (C.1)) that the overall probability for an endophilic adult female mosquito of i-genotype to contact the host after infinitely many attempts (during its blood-questing period) is given by ($i = \{SS, RS, RR\}$):

$$\rho_{(ins)}^i = \frac{C_B \rho_c^i}{1 - r^i C_B (1 - \rho_c^i)}. \tag{2.16}$$

Let $\rho_{H_{(in)}}^i$ represents the overall probability for an endophilic adult female mosquito of genotype-i to be killed by a human host indoors (during the duration of its bloodmeal questing period). It follows from the derivations in "Appendix C" (leading to Equation (C.6)) that $\rho_{H_{(in)}}^i$ is given by:

$$\rho_{H_{(in)}}^i = \left(1 - q_{m_{(in)}}^i\right)\left(1 - \frac{C_B \rho_c^i}{1 - r^i C_B (1 - \rho_c^i)}\right); \ i = \{SS, RS, RR\}. \tag{2.17}$$

It is worth mentioning here that, for endophilic mosquitoes, the sum of the probabilities (of successfully taking a bloodmeal, of being killed by the bednet upon contact and of being killed by humans upon contact) is 1 (as expected). That is, the sum of equations (2.12), (2.16) and (2.17) is 1. That is,

$$\begin{aligned}
&\left[P_{(in)_p}^i(r^i, C_B, \rho_c^i) + P_{(in)_u}^i(r^i, C_B, \rho_c^i)\right] + \rho_{(ins)}^i + \rho_{H_{(in)}}^i \\
&= q_{m_{(in)}}^i \left(1 - \frac{C_B \rho_C^i}{1 - r^i C_B \left(1 - \rho_C^i\right)}\right) + \frac{C_B \rho_c^i}{1 - r^i C_B (1 - \rho_c^i)} \\
&+ \left(1 - q_{m_{(in)}}^i\right)\left(1 - \frac{C_B \rho_c^i}{1 - r^i C_B (1 - \rho_c^i)}\right) = 1.
\end{aligned}$$

Let $\delta_{(in)}^i$ (with $i = \{SS, RS, RR\}$) be the death rate for an adult endophilic female mosquito of i-genotype during the entire bloodmeal-questing period due to either insecticide or being killed by human hosts. From the above discussion, the probability of an endophilic female mosquito being killed either by insecticide or humans during a bloodmeal-questing period is $\rho_{(ins)}^i + \rho_{H_{(in)}}^i$. Hence, following the derivation in Birget and Koella (2015), the mortality rate $\delta_{(in)}^i$ is given by:

$$\delta_{(in)}^i = -\ln(1 - \rho_{(ins)}^i - \rho_{H_{(in)}}^i)^{\frac{1}{\tau}}, \tag{2.18}$$

where τ is the average duration for the bloodmeal-questing period for an adult female mosquito.

Thus, it follows that the total death rate [i.e., the sum of the natural death rate and the death rate during the entire bloodmeal-questing period (insecticide-induced death and death by the human host)] of an adult female endophilic mosquito of i-genotype, denoted by $\mu^i_{(in)}$, is given by:

$$\mu^i_{(in)} = \mu^i_M + \delta^i_{(in)}. \tag{2.19}$$

For the exophilic adult female mosquitoes, it is assumed that either they successfully take a bloodmeal from humans outdoors (with probability $q^i_{m_{(out)}}$) or they are killed by the humans outdoors (with probability $(1 - q^i_{m_{(out)}})$). That is, we assume that these mosquitoes are not repelled by the humans outdoors. Therefore, the rate at which exophilic adult female mosquitoes of i-genotype are killed by the human host outdoors, denoted by $\delta^i_{H_{(out)}}$, is given by Birget and Koella (2015):

$$\delta^i_{H_{(out)}} = -\ln\left[1 - \left(1 - q^i_{m_{(out)}}\right)\right]^{\frac{1}{\tau}}. \tag{2.20}$$

Thus, the overall death rate of an adult female exophilic mosquito of i-genotype (denoted by $\mu^i_{(out)}$), which is the sum of the natural death rate of adult female mosquitoes and the death rate due to humans outdoors (given by Equation (2.20)), is given by:

$$\mu^i_{(out)} = \mu^i_M + \delta^i_{H_{(out)}}. \tag{2.21}$$

2.1.5 Genotype-specific malaria transmission rates

Let $\lambda^i_{(VH_p)_{(in)}}$ be the rate at which an infectious adult female endophilic mosquito of i-genotype transmits the disease to a susceptible protected human host indoors. Thus,

$$\lambda^i_{(VH_p)_{(in)}}(t) = \begin{pmatrix}\text{Average number of successful}\\ \text{bites on protected humans}\\ \text{per unit time by endophilic}\\ \text{mosquitoes of } i\text{-genotype}\end{pmatrix} \times \begin{pmatrix}\text{Probability of disease}\\ \text{transmission } \textit{per}\\ \text{successful bite}\end{pmatrix} \times \begin{pmatrix}\text{Probability of}\\ \text{being bitten}\\ \text{by an infectious}\\ \text{endophilic mosquito}\end{pmatrix}$$

Table 2 Transmission rates and biting probabilities for the model {(2.29)–(2.31)}

Transmission rate, $i = \{SS, RS, RR\}$	Description
$\lambda^i_{(VH_p)_{(in)}}(t)$	Mosquito-to-protected-human force of infection for an endophilic mosquito of i-genotype
$\lambda^i_{(VH_u)_{(in)}}(t)$	Mosquito-to-unprotected-human force of infection for an endophilic mosquito of i-genotype
$\lambda^i_{(VH)_{(out)}}(t)$	Mosquito-to-human force of infection for an exophilic mosquito of i-genotype
$\lambda^i_{(H_pV)_{(in)}}(t)$	Protected-human-to-mosquito force of infection for an endophilic mosquito of i-genotype
$\lambda^i_{(H_uV)_{(in)}}(t)$	Unprotected-human-to-mosquito force of infection for an endophilic mosquito of i-genotype
$\lambda^i_{(HV)_{(out)}}(t)$	Human-to-mosquito force of infection for an exophilic mosquito of i-genotype
Biting probabilities, $i = \{SS, RS, RR\}$	**Description**
$P^i_{(in)_p}$	Overall probability of endophilic mosquito of n-genotype successfully taking a bloodmeal from a protected host indoors
$P^i_{(in)_u}$	Overall probability of endophilic mosquito of i-genotype successfully taking a bloodmeal from a unprotected host indoors
$P^i_{(out)}$	Overall probability of exophilic mosquito of i-genotype successfully taking a bloodmeal from a host outdoors

$$= b \times \underbrace{\left(\frac{P^i_{(in)_p}(r^i, C_B, \rho^i_c) N_V^{(in)}(t)}{N_H(t)} \right)}_{\textbf{contact with mosquitoes of } i\textbf{-genotype}} \times \quad (\beta_{VH}) \times \underbrace{\left(\frac{I_i^{(in)}(t)}{N_V^{(in)}(t)} \right)}_{\substack{\textbf{proportion of infectious} \\ \textbf{mosquitoes of } i\textbf{-genotype}}}, \tag{2.22}$$

where b is the average biting rate of mosquitoes *per* person *per* unit time, β_{VH} (β_{HV}) is the transmission probability from infectious mosquito (human) to susceptible human (mosquito). Equation (2.22) can be simplified to:

$$\lambda^i_{(VH_p)_{(in)}}(t) = \frac{b P^i_{(in)_p}(r^i, C_B, \rho^i_c) \beta_{VH} I_i^{(in)}(t)}{N_H(t)}. \tag{2.23}$$

Table 3 Description of the parameters of the model {(2.29)–(2.31)}related to the probability of successfully taking a bloodmeal

Parameters	Interpretation $i = \{SS, RS, RR\}$	Range (dimensionless)	Baseline (dimensionless)	References
C_B	Proportion of individuals in the community who correctly and consistently use LLINs	$0 - 1$	Varied	
ρ_c^i	Probability of an i-genotype endophilic mosquito killed by the net upon contact the net upon contact	$0 - 1$	$\rho_c^{SS} = 0.85$	Hauser et al. (2019)
			$\rho_c^{RS} = (1 - hu)\rho_c^{SS}$ $\rho_c^{RR} = (1 - u)\rho_c^{SS}$	
$\rho_{(ins)}^i$	Probability for an endophilic mosquito of genotype-i to be killed by the net during the bloodmeal search period		Depends on other parameters	
$\rho_{H(in)}^i \left(\rho_{H(out)}^i\right)$	Probability for an endophilic mosquito of genotype$-i$ to be killed by human host indoors (outdoors) during the bloodmeal search period		Depends on other parameters	
r^i	Efficacy of the bednet to repel an i-genotype endophilic mosquito	0–1	$r^{SS} = 0.18 \times r^{RR}$	Deletre et al. (2019)
			$r^{RS} = 0.6 \times r^{RR}$ $r^{RR} = 0.86$	

Table 3 continued

Parameters	Interpretation $i = \{SS, RS, RR\}$	Range (dimensionless)	Baseline (dimensionless)	References
$q^i_{m_{(in)}}$	Probability of an endophilic i-genotype mosquito successfully taking a complete bloodmeal upon contact with host indoors or outdoors (and survived)	0–1	$q^{SS}_{m_{(in)}} = q^{RR}_{m_{(out)}}/1.25$	Hauser et al. (2019), Nouage et al. (2020)
			$q^{RS}_{m_{(in)}} = q^{RR}_{m_{(in)}}/1.1$ $q^{RR}_{m_{(in)}}$: Varied	
$q^i_{m_{(out)}}$	Probability of an exophilic i-genotype mosquito successfully taking a complete bloodmeal upon contact with host indoors or outdoors (and survived)	0–1	$q^{SS}_{m_{(out)}} = 0.28$	Estimated
			$q^{RS}_{m_{(out)}} = q^{SS}_{m_{(out)}}/1.1$ $q^{RR}_{m_{(out)}} = q^{SS}_{m_{(out)}}/1.25$	

Similarly, the rate at which an infectious adult female endophilic mosquito of i-genotype transmits the disease to an unprotected human host indoors, denoted by $\lambda^i_{(VH_u)_{(in)}}(t)$, is given by:

$$\lambda^i_{(VH_u)_{(in)}}(t) = \frac{bP^i_{(in)_u}(r^i, C_B)\beta_{VH} I_i^{(in)}(t)}{N_H(t)}. \tag{2.24}$$

The rate at which infectious exophilic mosquitoes of i-genotype transmit malaria to a host (outdoors), denoted by $\lambda^i_{(VH)_{(out)}}(t)$, is given by:

$$\lambda^i_{(VH)_{(out)}}(t) = \frac{bP^i_{(out)}\beta_{VH} I_i^{(out)}(t)}{N_H(t)}. \tag{2.25}$$

Infectious protected humans transmit malaria to a susceptible adult female endophilic mosquito of i-genotype at a rate $\lambda^i_{(H_pV)_{(in)}}(t)$, given by:

$$\lambda^i_{(H_pV)_{(in)}}(t) = \frac{bP^i_{(in)_p}(r^i, C_B, \rho^i_c)\beta_{HV} I_{H_p}(t)}{N_H(t)}. \tag{2.26}$$

Similarly, infectious unprotected humans transmit malaria to a susceptible adult female endophilic mosquito of i-genotype at a rate $\lambda^i_{(H_uV)_{(in)}}(t)$, given by:

$$\lambda^i_{(H_uV)_{(in)}}(t) = \frac{bP^i_{(in)_u}(r^i, C_B, \rho^i_c)\beta_{HV} I_{H_u}(t)}{N_H(t)}. \tag{2.27}$$

Finally, infectious humans transmit malaria to a susceptible adult female exophilic mosquito of i-genotype at a rate $\lambda^i_{(HV)_{(out)}}(t)$, given by:

$$\lambda^i_{(HV)_{(out)}}(t) = \frac{bP^i_{(out)}\beta_{HV}[I_{H_p}(t) + I_{H_u}(t)]}{N_H(t)}. \tag{2.28}$$

The aforementioned genotype-specific malaria transmission rates and biting probabilities are tabulated in Table 2. Furthermore, the parameters of the model related to successfully taking a bloodmeal, the use of insecticide resistance and the mosquito-human dynamics are described in Tables 3, 4, 5, respectively.

2.1.6 Equations of the model

Based on the above derivations, the genetic-epidemiology model for the transmission dynamics of malaria mosquitoes (stratified according to biting behavior) in a human population (stratified by whether they are protected by bednets or not) is given by the following deterministic systems of nonlinear differential equations (a schematic

Table 4 Descriptions of the parameters related to the use of insecticides of the model $\{(2.29)–(2.31)\}$

Parameters	Interpretation $i = \{SS, RS, RR\}$	Range (day^{-1})	Baseline (day^{-1})	References
τ	Average duration for an adult female mosquito to quest for a bloodmeal	0–21 days	3 days	Birget and Koella (2015)
$\delta^i_{(in)}$	Rate at which endophilic mosquitoes of i-genotype are killed by insecticides or by humans upon contact		Depends on other parameters	
$\delta^i_{H(out)}$	Rate at which exophilic mosquitoes of i-genotype are killed by humans indoor (outdoor) upon contact per unit time		Depends on other parameters	
h	Level of dominance of R-allele in mosquitoes of RS-genotype ($0 \leq h \leq 1$)	0–1	0.25 (dimensionless)	Birget and Koella (2015), Mohammed-Awel and Gumel (2019), Mohammed-Awel et al. (2020), Mohammed-Awel and Gumel (2023)
u	Modification parameter accounting for the assumed decrease in the mortality rate of the RR-genotype adult mosquitoes due to the insecticides, in comparison to vectors of SS-genotype ($0 \leq u \leq 1$)	0–1	0.9	Mohammed-Awel et al. (2020), Mohammed-Awel and Gumel (2019)
b	The average biting rate of female mosquitoes per person per unit time	0–4	3	Mohammed-Awel et al. (2020), Mohammed-Awel and Gumel (2019)

Table 5 Descriptions of the parameters related to dynamics of adult mosquitoes and humans of the model {(2.29)–(2.31)}

Parameters	Interpretation $i = \{SS, RS, RR\}$	Range (day^{-1})	Baseline (day^{-1})	References
Π_H	Human recruitment rate (due to birth or immigration)	2–5.5	3.18	Mohammed-Awel and Gumel (2019)
μ_H	Natural death rate for humans	$\frac{1}{(50\times365)} - \frac{1}{(70\times365)}$	$1/(60 \times 365)$	Okuneye et al. (2019)
σ_H	Rate of development of clinical symptoms of malaria	$1/17 - 1/14$	1/14	Mohammed-Awel and Gumel (2019), Okuneye et al. (2019)
ξ_H	Rate of loss of natural immunity for humans	$[5.5, 110] \times 10^{-5}$	5.6×10^{-3}	Mohammed-Awel and Gumel (2019)
γ_H	Recovery rate for humans	$1/1500 - 1/100$	1/30	Enahoro et al. (2020), Okuneye et al. (2019)
α	Parameter for the rate of change of behavior with respect to bednet usage		0.02	Estimated
$\alpha \times (1 - C_B)$	Rate at which protected hosts change their behavior and become unprotected hosts		Varied with C_B	
$\alpha \times C_B$	Rate at which unprotected hosts change their behavior and become protected hosts		Varied with C_B	
b_i	Production (birth) rate of new adult female mosquitoes of i- genotype		$b_{SS} = \frac{3}{4} \times 6.353$ $b_{RS} = \frac{3}{4} b_{SS}$ $b_{RR} = \frac{3}{5} b_{SS}$	Mohammed-Awel et al. (2020), Mohammed-Awel and Numfor (2017)

Table 5 continued

Parameters	Interpretation $i = \{SS, RS, RR\}$	Range (day^{-1})	Baseline (day^{-1})	References
K_V	Environmental carrying capacity of mosquitoes		1×10^7 (dimensionless)	Kuniyoshi and Santos (2017), Mohammed-Awel and Gumel (2019)
σ_{SS}	Progression rate of exposed adult mosquitoes of SS-genotype to infectious stage	0–0.1	0.1	Enahoro et al. (2020), Okuneye et al. (2019)
σ_{RS}	Progression rate of exposed adult mosquitoes of RS-genotype to infectious stage	0–0.125	$1.1 \times \sigma_{SS}$	Enahoro et al. (2020), Okuneye et al. (2019), Mohammed-Awel and Gumel (2019)
σ_{RR}	Progression rate of exposed adult mosquitoes of RR-genotype to infectious stage	0–0.175	$1.25 \times \sigma_{SS}$	Enahoro et al. (2020), Okuneye et al. (2019), Mohammed-Awel and Gumel (2019)
μ_M^{SS}	Natural death rate of adult mosquitoes of SS-genotypes	$\frac{1}{21} - \frac{1}{14}$	$\frac{1}{14}$	Ngonghala et al. (2014)
μ_M^{RS}	Natural death rate of adult mosquitoes of RS-genotypes	$\frac{5}{84} - \frac{5}{56}$	$1.1 \times \mu_M^{SS}$	Mohammed-Awel and Gumel (2019), Ngonghala et al. (2014)
μ_M^{RR}	Natural death rate of adult mosquitoes of RR-genotypes	$\frac{7}{84} - \frac{7}{56}$	$1.25 \times \mu_M^{SS}$	Mohammed-Awel and Gumel (2019), Ngonghala et al. (2014)
$f(1-f)$	Proportion of newborn that are endophilic (i.e., that are indoors)	0–1	0.9 (0.1) (dimensionless)	Birget and Koella (2015)
β_{VH}	Transmission probability from infectious mosquitoes to susceptible humans	0.02–0.5	0.48 (dimensionless)	Mohammed-Awel and Gumel (2019)
β_{HV}	Transmission probability from infectious humans to susceptible mosquitoes	0.01–0.5	0.14 (dimensionless)	Mohammed-Awel and Gumel (2019)

diagram of the model is depicted in Fig. 2; the state variables and parameters of the model are described in Table 1 and Tables 2–5, respectively).

Dynamics of adult indoor (endophilic) mosquito of genotype-*i*

$$\begin{aligned}
\frac{dS_{SS}^{(in)}}{dt} &= fB_{SS}^{V}(t) - [\lambda_{(H_pV)_{(in)}}^{SS} + \lambda_{(H_uV)_{(in)}}^{SS} + \mu_{(in)}^{SS}]S_{SS}^{(in)},\\
\frac{dE_{SS}^{(in)}}{dt} &= (\lambda_{(H_pV)_{(in)}}^{SS} + \lambda_{(H_uV)_{(in)}}^{SS})S_{SS}^{(in)} - [\sigma_{SS} + \mu_{(in)}^{SS}]E_{SS}^{(in)},\\
\frac{dI_{SS}^{(in)}}{dt} &= \sigma_{SS}E_{SS}^{(in)} - \mu_{(in)}^{SS}I_{SS}^{(in)},\\
\frac{dS_{RS}^{(in)}}{dt} &= fB_{RS}^{V}(t) - [\lambda_{(H_pV)_{(in)}}^{RS} + \lambda_{(H_uV)_{(in)}}^{RS} + \mu_{(in)}^{RS}]S_{RS}^{(in)},\\
\frac{dE_{RS}^{(in)}}{dt} &= (\lambda_{(H_pV)_{(in)}}^{RS} + \lambda_{(H_uV)_{(in)}}^{RS})S_{RS}^{(in)} - [\sigma_{RS} + \mu_{(in)}^{RS}]E_{RS}^{(in)},\\
\frac{dI_{RS}^{(in)}}{dt} &= \sigma_{RS}E_{RS}^{(in)} - \mu_{(in)}^{RS}I_{RS}^{(in)},\\
\frac{dS_{RR}^{(in)}}{dt} &= fB_{RR}^{V}(t) - [\lambda_{(H_pV)_{(in)}}^{RR} + \lambda_{(H_uV)_{(in)}}^{RR} + \mu_{(in)}^{RR}]S_{RR}^{(in)},\\
\frac{dE_{RR}^{(in)}}{dt} &= (\lambda_{(H_pV)_{(in)}}^{RR} + \lambda_{(H_uV)_{(in)}}^{RR})S_{RR}^{(in)} - [\sigma_{RR} + \mu_{(in)}^{RR}]E_{RR}^{(in)},\\
\frac{dI_{RR}^{(in)}}{dt} &= \sigma_{RR}E_{RR}^{(in)} - \mu_{(in)}^{RR}I_{RR}^{(in)}.
\end{aligned}\tag{2.29}$$

Dynamics of adult outdoor (exophilic) mosquitoes of genotype-*i*

$$\begin{aligned}
\frac{dS_{SS}^{(out)}}{dt} &= (1-f)B_{SS}^{V}(t) - [\lambda_{HV_{(out)}}^{SS} + \mu_{(out)}^{SS}]S_{SS}^{(out)},\\
\frac{dE_{SS}^{(out)}}{dt} &= \lambda_{HV_{(out)}}^{SS}S_{SS}^{(out)} - [\sigma_{SS} + \mu_{(out)}^{SS}]E_{SS}^{(out)},\\
\frac{dI_{SS}^{(out)}}{dt} &= \sigma_{SS}E_{SS}^{(out)} - \mu_{(out)}^{SS}I_{SS}^{(out)},\\
\frac{dS_{RS}^{(out)}}{dt} &= (1-f)B_{RS}^{V}(t) - [\lambda_{HV_{(out)}}^{RS} + \mu_{(out)}^{RS}]S_{RS}^{(out)},\\
\frac{dE_{RS}^{(out)}}{dt} &= \lambda_{HV_{(out)}}^{RS}S_{RS}^{(out)} - [\sigma_{RS} + \mu_{(out)}^{RS}]E_{RS}^{(out)},\\
\frac{dI_{RS}^{(out)}}{dt} &= \sigma_{RS}E_{RS}^{(out)} - \mu_{(out)}^{RS}I_{RS}^{(out)},\\
\frac{dS_{RR}^{(out)}}{dt} &= (1-f)B_{RR}^{V}(t) - [\lambda_{HV_{(out)}}^{RR} + \mu_{(out)}^{RR}]S_{RR}^{(out)},\\
\frac{dE_{RR}^{(out)}}{dt} &= \lambda_{HV_{(out)}}^{RR}S_{RR}^{(out)} - [\sigma_{RR} + \mu_{(out)}^{RR}]E_{RR}^{(out)},\\
\frac{dI_{RR}^{(out)}}{dt} &= \sigma_{RR}E_{RR}^{(out)} - \mu_{(out)}^{RR}I_{RR}^{(out)}.
\end{aligned}\tag{2.30}$$

Disease Dynamics in Humans

$$
\begin{aligned}
\frac{dS_{H_p}}{dt} &= C_B\Pi_H + \xi_H R_{H_p} + C_B\alpha S_{H_u} - \sum_{i=SS,RS,RR}[\lambda^i_{(VH_p)_{(in)}} + \lambda^i_{(VH)_{(out)}}]S_{H_p}\\
&\quad - [(1-C_B)\alpha + \mu_H]S_{H_p},\\
\frac{dE_{H_p}}{dt} &= \sum_{i=SS,RS,RR}[\lambda^i_{(VH_p)_{(in)}} + \lambda^i_{(VH)_{(out)}}]S_{H_p} + C_B\alpha E_{H_u}\\
&\quad - (\sigma_H + (1-CB)\alpha + \mu_H)E_{H_p},\\
\frac{dI_{H_p}}{dt} &= \sigma_H E_{H_p} + C_B\alpha I_{H_u} - (\gamma_H + (1-C_B)\alpha + \mu_H)I_{H_p},\\
\frac{dR_{H_p}}{dt} &= \gamma_H I_{H_p} + C_B\alpha R_{H_u} - (\xi_H + (1-C_B)\alpha + \mu_H)R_{H_p},\\
\frac{dS_{H_u}}{dt} &= (1-C_B)\Pi_H + \xi_H R_{H_u} + (1-C_B)\alpha S_{H_p}\\
&\quad - \sum_{i=SS,RS,RR}[\lambda^i_{(VH_u)_{(in)}} + \lambda^i_{(VH)_{(out)}}]S_{H_u} - (C_B\alpha + \mu)_H S_{H_u},\\
\frac{dE_{H_u}}{dt} &= \sum_{i=SS,RS,RR}[\lambda^i_{(VH_u)_{(in)}} + \lambda^i_{(VH)_{(out)}}]S_{H_u} + (1-C_B)\alpha E_{H_p}\\
&\quad - (\sigma_H + C_B\alpha + \mu_H)E_{H_u},\\
\frac{dI_{H_u}}{dt} &= \sigma_H E_{H_u} + (1-C_B)\alpha I_{H_p} - (\gamma_H + C_B\alpha + \mu_H)I_{H_u},\\
\frac{dR_{H_u}}{dt} &= \gamma_H I_{H_u} + (1-C_B)\alpha R_{H_p} - (\xi_H + C_B\alpha + \mu_H)R_{H_u}.
\end{aligned}
\tag{2.31}
$$

In the model {(2.29)–(2.31)}, the infection rates $\lambda^i_{(VH_p)_{(in)}}$, $\lambda^i_{(VH_u)_{(in)}}$, $\lambda^i_{(VH)_{(out)}}$, $\lambda^i_{(H_pV)_{(in)}}$, $\lambda^i_{(H_pV)_{(in)}}$ and $\lambda^i_{(HV)_{(out)}}$ are given by the equations in {(2.23)–(2.28)}, respectively. Similarly, σ_i represents the progression rate of exposed adult female mosquitoes of i-genotype to the corresponding infectious stage. The parameter f represents the proportion of mosquitoes that are endophilic (and the remaining proportion, $(1-f)$, are exophilic). The parameter Π_H represents the recruitment rate into the community (due to birth or immigration), a proportion, C_B, of these are assumed to be protected (i.e., they consistently sleep under a bednet) and the remaining proportion, $1-C_B$, are unprotected. It is assumed that the proportion of recruited individuals that use bednets follow the same ratio (C_B) for the community (i.e., $C_B\Pi_H$ represents the number of recruited individuals who are protected by the bednets). The parameter ξ_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). It is assumed that protected individuals are protected from getting bitten by endophilic mosquitoes while they are indoors. However, the protected humans can encounter (i.e., be bitten by) exophilic mosquitoes when they are outdoors (this encounter may lead to the acquisition of malaria infection at the rate $\lambda^i_{(VH)_{(out)}}$ (note that protected humans can also acquire malaria transmission from infectious endophilic mosquitoes at the rate $\lambda^i_{(VH_p)_{(in)}}$).

Similarly, unprotected humans can acquire infection while they are indoors $\left(\text{at a rate } \lambda^{i}_{(VH_u)_{(in)}}\right)$ or outdoors $\left(\text{at a rate } \lambda^{i}_{(VH)_{(out)}}\right)$. Natural death occurs in all epidemiological compartments for humans at a rate μ_H. Individuals in the exposed class develop clinical symptoms of malaria at a rate of σ_H. Humans recover at a rate of γ_H. Recovered humans lose natural natural immunity at a rate ξ_H. It is assumed that disease-induced mortality in the human population is negligible. Hence, disease-induced death is not included in the model (this assumption, which helps to make the rigorous analysis more tractable, can be justified considering the fact that in 2021, for example, the global mortality due to malaria was estimated to be 619, 000 (WHO 2022a), which represents 0.0078% of the human population). Furthermore, let α be the rate at which humans change their behavior with respect to sleeping under a bednet. Thus, based on the fact that individuals are more likely to sleep under a bednet if the bednets are widely available in the community, the rate at which protected (unprotected) individuals change their behavior and become unprotected (protected) is $(1 - C_B)\alpha$ $(C_B\alpha)$. In other words, we assume that the decision to change bednet usage behaviour is a linear function of the bednet coverage in the community (it is worth emphasizing that C_B is shown to be a constant, in Theorem 2.1 below, for all time t).

Some of the main assumptions made in the formulation of the model {(2.29)–(2.31)} are:

(i) Insecticide resistance in mosquitoes is determined by a gene of single-locus with two alleles, namely sensitive (S) and resistant (R) allele. Furthermore, reproduction in mosquito population is based on random mating between mosquitoes of opposite sex and of all genotypes (Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020).

(ii) The model does not stratify the human population based on location (indoor or outdoor) at any given time. In most malaria-endemic settings, the human host population is typically large. Hence, there is abundance of human hosts indoors and outdoors for mosquitoes to target (thus, the transition from outdoors to indoors or *vice versa* can be assumed to not be very significant in terms of mosquito feeding/biting probability)

(iii) Mosquitoes do not change their biting behavior (indoors or outdoors). That is, endophilic (exophilic) mosquitoes remain endophilic (exophilic) throughout their lifetime. Furthermore, the bloodmeal questing period is assumed to be the same for endophilic and exophilic mosquitoes.

(iv) It is assumed that endophilic mosquitoes are not repelled by the human host (unprotected and protected) upon contact with the human host. That is, mosquitoes who encounter a human host either successfully take a bloodmeal or are killed by the human host (but they are not directly repelled or physically deterred by the human host). Furthermore, it is assumed that humans do not use insect repellents to repel mosquitoes (i.e., mosquito repellance is limited to be due to the bednet usage alone).

(v) It is assumed that adult female exophilic mosquitoes of all genotypes are not deterred (or repelled) by humans when they encounter them outdoors. In other words, it is assumed that upon contact with humans outdoors, adult female exophilic mosquitoes of all genotypes either successfully take a bloodmeal (with probability $q^i_{m_{(out)}}$) or get killed by the humans (with probability $(1 - q^i_{m_{(out)}})$.

We claim the following result.

Theorem 2.1 *Consider the model {(2.29)–(2.31)}. The proportion of the protected human hosts in the community (C_B) is constant for all time t.*

Proof Let $C_B = \dfrac{N_{H_p}(t)}{N_H(t)}$. Adding the first four equations of the human component of the model (i.e., adding the first four equations of the sub-model (2.31)) gives:

$$\frac{dN_{H_p}}{dt} = C_B \Pi_H + C_B \alpha N_{H_u} - [(1 - C_B)\alpha + \mu_H] N_{H_p}. \tag{2.32}$$

Similarly, adding all eight equations of the sub-model (2.31) gives:

$$\frac{dN_H}{dt} = \Pi_H - \mu_H N_H. \tag{2.33}$$

Differentiating the proportion of protected humans at time t, denoted by $\dfrac{N_{H_p}(t)}{N_H(t)}$, with respect to t gives:

$$\frac{d}{dt}\left(\frac{N_{H_p}(t)}{N_H(t)}\right) = \frac{N_H \dfrac{dN_{H_p}}{dt} - N_{H_P}\dfrac{dN_H}{dt}}{N_H^2} = \frac{1}{N_H}\frac{dN_{H_p}}{dt} - C_B \frac{1}{N_H}\frac{dN_H}{dt}, \tag{2.34}$$

and using equations (2.32) and (2.33), in (2.34), gives:

$$\begin{aligned}\frac{d}{dt}\left(\frac{N_{H_p}(t)}{N_H(t)}\right) &= \frac{1}{N_H}\left[C_B \Pi_H + C_B \alpha N_{H_u} - [(1 - C_B)\alpha + \mu_H] N_{H_p}\right] \\ &\quad - C_B \frac{1}{N_H}\left[\Pi_H - \mu_H N_{H_p}\right], \\ &= \left[\frac{C_B \Pi_H}{N_H} + C_B \alpha (1 - C_B) - [(1 - C_B)\alpha + \mu_H] C_B\right] \\ &\quad - C_B \left[\frac{\Pi_H}{N_H} - \mu_H\right], \\ &= C_B (1 - C_B)(\alpha - \alpha) = 0 \ .\end{aligned} \tag{2.35}$$

Hence, it follows from equation (2.35) that $N_{H_P}(t)/N_H(t)$ is constant. That is, the proportion of protected humans in the community is constant. □

A direct consequence of Theorem 2.1 (where the LLINs coverage in the community, denoted by C_B, is shown to be constant for all time t) is that the model {(2.29)–(2.31)} is autonomous. Theorem 2.1 further imply that, at any time $t \geq 0$, the total human population ($N_H(t)$) is proportional to the total protected ($N_{H_p}(t)$) human population with constant of proportionality, C_B. Similarly, $N_H(t)$ is proportional to $N_{H_u}(t)$ with constant of proportionality, $1 - C_B$.

It is worth mentioning that the genetic-epidemiology malaria model $\{(2.29)–(2.31)\}$ represents an extension of numerous other malaria models that incorporate the population genetics of malaria mosquitoes into the disease epidemiology in humans and mosquitoes, such as the models in Birget and Koella (2015), Tsanou et al. (2020), Kuniyoshi and Santos (2017), Mohammed-Awel and Gumel (2019), Mohammed-Awel et al. (2020), Mohammed-Awel et al. (2018), Mohammed-Awel and Gumel (2023), by, ıinter alia:

(a) Explicitly incorporating the indoor (endophilic) and outdoor (exophilic) feeding and biting behavior of the adult female *Anopheles* mosquito (this is not explicitly accounted for in the models presented in Birget and Koella 2015; Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020; Kuniyoshi and Santos 2017; Tsanou et al. 2020). Adding this important feature allows us to evaluate the population-level impact of *Anopheles* feeding and biting behavior on the evolution of insecticide resistance and the spread and control of malaria in the community.
(b) Explicitly including the effect of change of behavior of humans with respect to sleeping under the bednet. In the formulation of the human component of the model $\{(2.29)–(2.31)\}$, it is assumed that protected humans can change their behavior to become unprotected and *vice-versa* (this feature is not included in the models presented in Tsanou et al. 2020; Kuniyoshi and Santos 2017; Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020, 2018; Mohammed-Awel and Gumel 2023). This feature allows for the assessment of the impact of such behavior change on the evolution of resistance and the spread and control of the disease.
(c) Providing a detailed and explicit derivation of the probabilities of mosquitoes of i-genotype to contact and successfully take a bloodmeal from a protected or unprotected host indoors or outdoors. Incorporating these probabilities into the model allow us to realistically assess the repellance (r^i) and killing efficacies (ρ_c^i), by genotype, of the chemical insecticides embedded in the LLINs [these features are not included in Birget and Koella 2015; Tsanou et al. 2020; Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020, 2018 (Birget and Koella 2015; Tsanou et al. 2020 did not include the population genetics of the mosquito)].
(d) Explicitly accounting for the possibility of adult female *Anopheles* mosquitoes, by genotype, to make multiple unsuccessful attempts to take a bloodmeal from hosts indoors, before successfully taking the bloodmeal (this feature is not included in Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020, 2018). Although this behavior has been incorporated in the models presented in Birget and Koella (2015), Tsanou et al. (2020), these models did not include the population genetics of the mosquito and/or insecticide resistance.

The basic qualitative properties of the autonomous model $\{(2.29)–(2.31)\}$ will now be assessed.

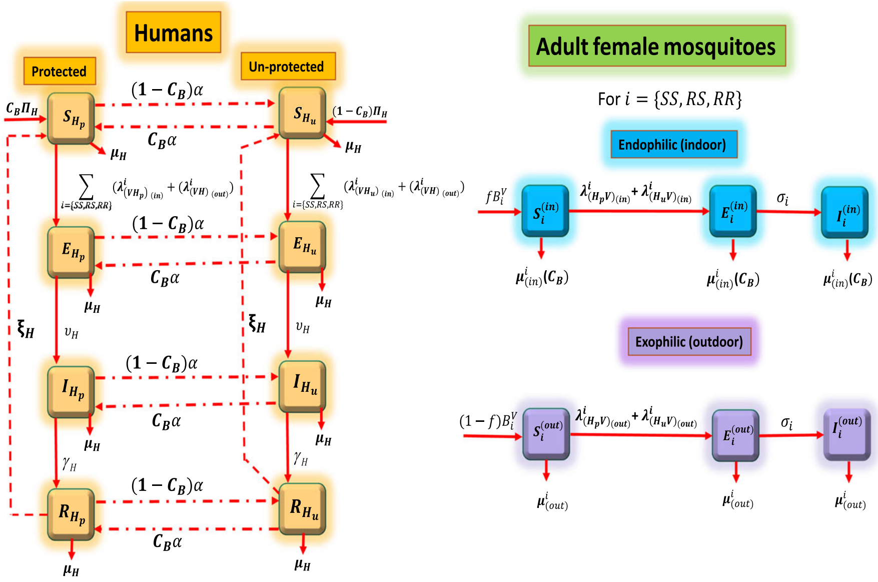

Fig. 2 Schematic diagram of the genetic-epidemiology malaria transmission dynamics model {(2.29)–(2.31)}

2.2 Basic qualitative properties of the model

Since the state variables of the model {(2.29) − (2.31)} represent the populations of humans and adult female mosquitoes, they must all be non-negative for all time t. Furthermore, let

$$\Omega_H = \Big\{ \big(S_{H_p}, E_{H_p}, I_{H_p}, R_{H_p}, S_{H_u}, E_{H_u}, I_{H_u}, R_{H_u}\big) \in \mathbb{R}^8_+ : \\ 0 < (N_H)_{min} \le N_H(t) \le \frac{\Pi_H}{\mu_H} \Big\}, \tag{2.36}$$

where $(N_H)_{min} = min\left(N_H(0), \frac{\Pi_H}{\mu_H}\right)$. It is convenient to define:

$$\mathbb{X} = \Big(S^{(in)}_{SS}, E^{(in)}_{SS}, I^{(in)}_{SS}, S^{(in)}_{RS}, E^{(in)}_{RS}, I^{(in)}_{RS}, \\ S^{(in)}_{RR}, E^{(in)}_{RR}, I^{(in)}_{RR}, S^{(out)}_{SS}, E^{(out)}_{SS}, I^{(out)}_{SS}, S^{(out)}_{RS}, E^{(out)}_{RS}, I^{(out)}_{RS}, \\ S^{(out)}_{RR}, E^{(out)}_{RR}, I^{(out)}_{RR}\Big),$$

and,

$$\Omega_V = \Big\{ \mathbb{X} \in \mathbb{R}^{18}_+ : 0 \le N_V \le K_V(\mathcal{R}_V - 1)/\mathcal{R}_V \Big\}, \tag{2.37}$$

where

$$\begin{aligned} \mu_V &= \min_{i=\{SS,RS,RR\}}\{\mu^i_{(in)}(C_B),\mu^i_M\} = \min_{i=\{SS,RS,RR\}}\{\mu^i_M\} \text{ and} \\ \mathcal{R}_V &= \frac{b_{SS}+b_{RS}+b_{RR}}{\mu_V}. \end{aligned} \tag{2.38}$$

It is worth stating that the quantity $\frac{K_V(\mathcal{R}_V-1)}{\mathcal{R}_V}$ is positive if $\mathcal{R}_V > 1$. It follows from (2.37) that, in a closed environment (where mosquitoes do not fly out of or into the environment from outside sources), the condition $\mathcal{R}_V > 1$ automatically holds if the sum of the growth rates of the mosquitoes by genotype ($b_{SS} + b_{RS} + b_{RR}$) exceeds the minimum natural death rate of mosquitoes by genotype (μ_V). In this case (with $\mathcal{R}_V > 1$), the mosquito population (by genotype) persists in the community (or environment). On the other hand, the mosquito population eventually goes extinct if $\mathcal{R}_V < 1$ (i.e., the mosquito population eventually dies out if the sum of the growth rate of the mosquitoes by genotype is lower than the minimum natural death of the mosquitoes by genotype). For the rest of this study, it is assumed that $\mathcal{R}_V > 1$ (so that mosquitoes always exist in the environment).

The following result can be established for the model {(2.29)–(2.31)} (its proof is fairly standard (Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020), hence not repeated here):

Theorem 2.2 *Let $N_H(0) > 0$. The region $\Omega = \Omega_H \cup \Omega_V$ is positively-invariant and attracts all solutions of the model {(2.29)–(2.31)} in $\mathbb{R}^8_+ \cup \mathbb{R}^{18}_+$.*

3 Existence and stability of disease-free equilibria

In this section, conditions for the existence and asymptotic stability of the disease-free equilibria of the model {(2.29)–(2.31)} will be explored. It is convenient to, first of all, define the following quantities:

$$\begin{aligned} k_1 &= (1-C_B)\alpha+\mu_H,\ \ k_2=\sigma_H+(1-C_B)\alpha+\mu_H, \\ k_3 &= \gamma_H+(1-C_B)\alpha+\mu_H, \\ k_4 &= \xi_H+(1-C_B)\alpha+\mu_H,\ \ k_5=C_B\alpha+\mu_H,\ \ k_6=\sigma_H+C_B\alpha+\mu_H, \\ k_7 &= \gamma_H+C_B\alpha+\mu_H,\ \ k_8=\xi_H+C_B\alpha+\mu_H,\ \ k_9=\mu^{SS}_{in}(C_B), \\ k_{10} &= \sigma_{SS}+\mu^{SS}_{in}(C_B), \\ k_{11} &= \mu^{RS}_{in}(C_B),\ \ ,k_{12}=\sigma_{RS}+\mu^{RS}_{in}(C_B),\ \ k_{13}=\mu^{RR}_{in}(C_B), \\ k_{14} &= \sigma_{RR}+\mu^{RR}_{in}(C_B), \\ k_{15} &= \sigma_{SS}+\mu^{SS}_{(out)},\ \ k_{16}=\sigma_{RS}+\mu^{RS}_{(out)},\ \text{ and, }\ k_{17}=\sigma_{RR}+\mu^{RR}_{(out)}, \\ \mathcal{R}^{(in)}_{SS} &= \frac{b_{SS}}{k_9},\ \ \mathcal{R}^{(in)}_{RS}=\frac{b_{RS}}{k_{11}}, \\ \mathcal{R}^{(in)}_{RR} &= \frac{b_{RR}}{k_{13}},\ \ \mathcal{R}^{(out)}_{SS}=\frac{b_{SS}}{\mu^{SS}_{(out)}},\ \ \mathcal{R}^{(out)}_{RS}=\frac{b_{RS}}{\mu^{RS}_{(out)}}\ \text{ and }\ \mathcal{R}^{(out)}_{RR}=\frac{b_{RR}}{\mu^{RR}_{(out)}}. \end{aligned} \tag{3.1}$$

Furthermore, let

$$\begin{aligned}\mathcal{E}_{df} &= \Big(S_{H_p}, E_{H_p}, I_{H_p}, R_{H_p}, S_{H_u}, E_{H_u}, I_{H_u}, R_{H_u}, S_{SS}^{(in)}, E_{SS}^{(in)}, \\ &\quad I_{SS}^{(in)}, S_{RS}^{(in)}, E_{RS}^{(in)}, I_{RS}^{(in)}, S_{RR}^{(in)}, E_{RR}^{(in)}, I_{RR}^{(in)}, \\ &\quad S_{SS}^{(out)}, E_{SS}^{(out)}, I_{SS}^{(out)}, S_{RS}^{(out)}, E_{RS}^{(out)}, I_{RS}^{(out)}, S_{RR}^{(out)}, E_{RR}^{(out)}, I_{RR}^{(out)}\Big), \\ &= \Big((S_{H_p})^*, 0, 0, 0, (S_{H_u})^*, 0, 0, 0, (S_{SS}^{(in)})^*, 0, 0, (S_{RS}^{(in)})^*, 0, 0, \\ &\quad (S_{RR}^{(in)})^*, 0, 0, (S_{SS}^{(out)})^*, 0, 0, (S_{RS}^{(out)})^*, 0, \\ &\quad 0, (S_{RR}^{(out)})^*, 0, 0\Big), \end{aligned} \tag{3.2}$$

with,

$$(S_{H_p})^* = \frac{C_B \Pi_H}{\mu_H} \text{ and } (S_{H_u})^* = \frac{(1 - C_B)\Pi_H}{\mu_H},$$

represents a general non-trivial disease-free equilibrium of the model {(2.29)–(2.31)} and the non-infected mosquito compartments of the model, evaluated at this general disease-free equilibrium, can be expressed in terms of the corresponding constant frequency of the sensitive allele at this steady-state (denoted by q^*; the derivations of the possible expressions for q^*, for the model {(2.29)–(2.31)}, are given in Lemma 1 of "Appendix D"). It follows, based on the above and the derivations in Lemma 1 of "Appendix D", that the model {(2.29)–(2.31)} has four disease-free equilibria, namely (see also Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020):

(a) A trivial (mosquito-free) disease-free equilibrium (TrivDFE), denoted by $\mathcal{E}_{0T}$, given by:

$$\begin{aligned}\mathcal{E}_{0T} &= \mathcal{E}_{df} \text{ with } (S_{SS}^{(in)})^* = (S_{RS}^{(in)})^* = (S_{RR}^{(in)})^* \\ &= (S_{SS}^{(out)})^* = (S_{RS}^{(out)})^* = (S_{RR}^{(out)})^* = 0,\end{aligned}$$

(b) A non-trivial sensitive-only disease-free boundary equilibrium (NonTrivSens-DFE), denoted by $\mathcal{E}_{0S}$, given by (this equilibrium exists when Condition (ii) of Lemma 1 in "Appendix D" is satisfied; that is, it exists whenever $q^* = 1$ and $p^* = 0$):

$$\begin{aligned}\mathcal{E}_{0S} = \mathcal{E}_{df} &\text{ with } (S_{SS}^{(in)})^* = (S_{SS}^{(in)})^{*S},\ (S_{RS}^{(in)})^* = (S_{RR}^{(in)})^* = 0,\ (S_{SS}^{(out)})^* = (S_{SS}^{(out)})^{*S}, \\ &\text{and } (S_{RS}^{(out)})^* = (S_{RR}^{(out)})^* = 0,\end{aligned}$$

where,

$$\left(S_{SS}^{(in)}\right)^{*S} = f\mathcal{R}_{SS}^{(in)}\left[\frac{K_V(\mathcal{R}_{SS} - 1)}{(\mathcal{R}_{SS})^2}\right] \text{ and}$$

$$\left(S_{SS}^{(out)}\right)^{*S} = (1-f)\mathcal{R}_{SS}^{(out)}\left[\frac{K_V(\mathcal{R}_{SS}-1)}{(\mathcal{R}_{SS})^2}\right], \tag{3.3}$$

(c) A non-trivial resistant-only disease-free boundary equilibrium (NonTrivResDFE), denoted by $\mathcal{E}_{0R}$, given by (this equilibrium exists only when Condition (i) of Lemma 1 in "Appendix D" is satisfied; that is, it exists whenever $p^* = 1$ and $q^* = 0$):

$$\begin{gathered}\mathcal{E}_{0R} = \mathcal{E}_{df} \text{ with } (S_{SS}^{(in)})^* = (S_{RS}^{(in)})^* = 0,\\ (S_{RR}^{(in)})^* = (S_{RR}^{(in)})^{*R},\ (S_{SS}^{(out)})^* = (S_{RS}^{(out)})^* = 0,\\ \text{and } (S_{RR}^{(out)})^* = (S_{RR}^{(out)})^{*R},\end{gathered}$$

where,

$$\begin{aligned}(S_{RR}^{(in)})^{*R} &= f\mathcal{R}_{RR}^{(in)}\left[\frac{K_V(\mathcal{R}_{RR}-1)}{(\mathcal{R}_{RR})^2}\right] \text{ and}\\ \left(S_{RR}^{(out)}\right)^{*R} &= (1-f)\mathcal{R}_{RR}^{(out)}\left[\frac{K_V(\mathcal{R}_{RR}-1)}{(\mathcal{R}_{RR})^2}\right],\end{aligned} \tag{3.4}$$

(d) A non-trivial co-existence disease-free equilibrium (NonTrivCoexDFE), denoted by $\mathcal{E}_{0C}$, given by (this equilibrium exists when Condition (iii) or Condition (iv) of Lemma 1 in "Appendix D" is satisfied; that is, it exists whenever $p^* > 0$ and $q^* > 0$):

$$\begin{aligned}&\mathcal{E}_{0C} = \mathcal{E}_{df} \text{ with } (S_{SS}^{(in)})^* = (S_{SS}^{(in)})^{*C},\ (S_{RS}^{(in)})^* = (S_{RS}^{(in)})^{*C},\\ &(S_{RR}^{(in)})^* = (S_{RR}^{(in)})^{*C},\ (S_{RR}^{(in)})^* = (S_{RR}^{(in)})^{*C},\\ &(S_{SS}^{(out)})^* = (S_{SS}^{(out)})^{*C},\ (S_{RS}^{(out)})^* = (S_{RS}^{(out)})^{*C},\ (S_{RR}^{(out)})^* = (S_{RR}^{(out)})^{*C} \text{ and}\\ &(S_{RR}^{(out)})^* = (S_{RR}^{(out)})^{*C},\end{aligned}$$

where,

$$\begin{aligned}(S_{SS}^{(in)})^{*C} &= f\mathcal{R}_{SS}^{(in)}\left[\frac{(q^*)^2K_V(\mathcal{R}_C-1)}{(\mathcal{R}_C)^2}\right],\\ (S_{SS}^{(out)})^{*C} &= (1-f)\mathcal{R}_{SS}^{(out)}\left[\frac{(q^*)^2K_V(\mathcal{R}_C-1)}{(\mathcal{R}_C)^2}\right],\\ (S_{RS}^{(in)})^{*C} &= f\mathcal{R}_{RS}^{(in)}\left[\frac{2p^*q^*K_V(\mathcal{R}_C-1)}{(\mathcal{R}_C)^2}\right],\\ (S_{RS}^{(out)})^{*C} &= (1-f)\mathcal{R}_{RS}^{(out)}\left[\frac{2p^*q^*K_V(\mathcal{R}_C-1)}{(\mathcal{R}_C)^2}\right],\\ (S_{RR}^{(in)})^{*C} &= f\mathcal{R}_{RR}^{(in)}\left[\frac{(p^*)^2K_V(\mathcal{R}_C-1)}{(\mathcal{R}_C)^2}\right] \text{ and}\end{aligned}$$

$$(S_{RR}^{(in)})^{*C} = (1-f)\mathcal{R}_{RR}^{(out)}\left[\frac{(p^*)^2 K_V(\mathcal{R}_C - 1)}{(\mathcal{R}_C)^2}\right], \tag{3.5}$$

with,

$$\begin{aligned}
\mathcal{R}_{SS} &= f\mathcal{R}_{SS}^{(in)} + (1-f)\mathcal{R}_{SS}^{(out)},\ \ \mathcal{R}_{RS} = f\mathcal{R}_{RS}^{(in)} + (1-f)\mathcal{R}_{RS}^{(out)} \ \text{ and}\\
\mathcal{R}_{RR} &= f\mathcal{R}_{RR}^{(in)} + (1-f)\mathcal{R}_{RR}^{(out)}, &(3.6)\\
\mathcal{R}_C^{(in)} &= (q^*)^2\mathcal{R}_{SS}^{(in)} + 2p^*q^*\mathcal{R}_{RS}^{(in)} + (p^*)^2\mathcal{R}_{RR}^{(in)} \text{ and}\\
\mathcal{R}_C^{(out)} &= (q^*)^2\mathcal{R}_{SS}^{(out)} + 2p^*q^*\mathcal{R}_{RS}^{(out)} + (p^*)^2\mathcal{R}_{RR}^{(out)}, &(3.7)
\end{aligned}$$

and,

$$\mathcal{R}_C = f\mathcal{R}_C^{(in)} + (1-f)\mathcal{R}_C^{(out)}. \tag{3.8}$$

It follows from Equations (3.3), (3.4) and (3.5) that:

(i) The NonTrivSensDFE ($\mathcal{E}_{0S}$) exists if and only if $\mathcal{R}_{SS} > 1$,
(ii) The NonTrivResDFE ($\mathcal{E}_{0R}$) exists if and only if $\mathcal{R}_{RR} > 1$, and
(iii) The NonTrivCoexDFE ($\mathcal{E}_{0C}$) exists if and only if any of the following holds (see Condition (iii) or Condition (iv) of Lemma 1 in "Appendix D"):
  (a) $\left(\mathcal{R}_{SS}^{(in)} - \mathcal{R}_{RS}^{(in)}\right)\left(\mathcal{R}_{RR}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) \geq 0$, $\left(\mathcal{R}_{SS}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)\left(\mathcal{R}_{RR}^{(out)} - \mathcal{R}_{RS}^{(out)}\right) > 0$ and $\mathcal{R}_C > 1$;
  (b) $\left(\mathcal{R}_{SS}^{(in)} - \mathcal{R}_{RS}^{(in)}\right)\left(\mathcal{R}_{RR}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) > 0$, $\left(\mathcal{R}_{SS}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)\left(\mathcal{R}_{RR}^{(out)} - \mathcal{R}_{RS}^{(out)}\right) \geq 0$ and $\mathcal{R}_C > 1$;
  (c) $\mathcal{R}_{SS}^{(in)} = \mathcal{R}_{RS}^{(in)} = \mathcal{R}_{RR}^{(in)}$, $\mathcal{R}_{SS}^{(out)} = \mathcal{R}_{RS}^{(out)} = \mathcal{R}_{RR}^{(out)}$ and $\mathcal{R}_C > 1$.

Since the trivial disease-free equilibrium (TrivDFE) is not ecologically realistic in a malaria-endemic setting (i.e., it represents the scenario with no mosquitoes in the environment), we do not study its asymptotic stability properties. The local asymptotic stability of the other three disease-free equilibria (NonTrivSensDFE ($\mathcal{E}_{0S}$), NonTrivResDFE ($\mathcal{E}_{0R}$) and NonTrivCoexDFE ($\mathcal{E}_{0C}$) will be explored in Sect. 3.1.

3.1 Local asymptotic stability of the generalized non-trivial disease-free equilibrium ($\mathcal{E}_{df}$)

The linear stability of the generalized non-trivial disease-free equilibrium ($\mathcal{E}_{df}$) of this special case of the model can be established using the next generation operator method (Diekmann et al. 1990; van den Driessche and Watmough 2002). In particular, using the notation in van den Driessche and Watmough (2002), it can be shown that the *basic reproduction number* of the model, denoted by $\mathcal{R}_0^B$, is given by (where the k_i's are as defined in (3.1)):

$$\mathcal{R}_0^B = \sqrt{\left(\mathcal{R}_{HV}^B\right)\left(\mathcal{R}_{VH}^B\right)}, \tag{3.9}$$

where,

$$\mathcal{R}^B_{HV} = \frac{\sigma_H \mu_H b \beta_{HV}}{\Pi_H [k_2 k_6 - C_B(1-C_B)\alpha^2][k_3 k_7 - C_B(1-C_B)\alpha^2]} \text{ and}$$
$$\mathcal{R}^B_{VH} = \left(\mathcal{R}^B_{0_{SS}} + \mathcal{R}^B_{0_{RS}} + \mathcal{R}^B_{0_{RR}}\right),$$

with,

$$\mathcal{R}^B_{0_{SS}} = \frac{b\beta_{VH}\sigma_{SS}\left(a^{SS} + \sqrt{\left(a^{SS}\right)^2 - d^{SS}}\right)}{2k_9 k_{10} k_{15} \mu^{SS}_{(out)}},$$
$$\mathcal{R}^B_{0_{RS}} = \frac{b\beta_{VH}\sigma_{RS}\left(a^{RS} + \sqrt{\left(a^{RS}\right)^2 - d^{RS}}\right)}{2k_{11} k_{12} k_{16} \mu^{RS}_{(out)}}$$
$$\mathcal{R}^B_{0_{RR}} = \frac{b\beta_{VH}\sigma_{RR}\left(a^{RR} + \sqrt{\left(a^{RR}\right)^2 - d^{RR}}\right)}{2k_{13} k_{14} k_{17} \mu^{RR}_{(out)}}, \tag{3.10}$$

and,

$$\begin{aligned}
a^{SS} &= \mu^{SS}_{(out)} k_{15}\left[\eta_1\left(P^{SS}_{(in)_p}\right)^2 + \eta_2 P^{SS}_{(in)_p} P^{SS}_{(in)_u} + \eta_3\left(P^{SS}_{(in)_u}\right)^2\right](S^{(in)}_{SS})^{*C} \\
&\quad + \eta_4 k_9 k_{10}\left(P^{SS}_{(out)}\right)^2 (S^{(out)}_{SS})^{*C}, \\
a^{RS} &= \mu^{RS}_{(out)} k_{16}\left[\eta_1\left(P^{RS}_{(in)_p}\right)^2 + \eta_2 P^{RS}_{(in)_p} P^{RS}_{(in)_u} + \eta_3\left(P^{RS}_{(in)_u}\right)^2\right](S^{(in)}_{RS})^{*C} \\
&\quad + \eta_4 k_{11} k_{12}\left(P^{RS}_{(out)}\right)^2 (S^{(out)}_{RS})^{*C}, \\
a^{RR} &= \mu^{RR}_{(out)} k_{17}\left[\eta_1\left(P^{RR}_{(in)_p}\right)^2 + \eta_2 P^{RR}_{(in)_p} P^{RR}_{(in)_u} + \eta_3\left(P^{RR}_{(in)_u}\right)^2\right](S^{(in)}_{RR})^{*C} \\
&\quad + \eta_4 k_{13} k_{14}\left(P^{RR}_{(out)}\right)^2 (S^{(out)}_{RR})^{*C}, \\
d^{SS} &= 4\eta_5 \mu^{SS}_{(out)} k_9 k_{10} k_{15}\left(P^{SS}_{(out)}\right)^2\left(P^{SS}_{(in)_p} - P^{SS}_{(in)_u}\right)^2 (S^{(in)}_{SS})^{*C} (S^{(out)}_{SS})^{*C}, \\
d^{RS} &= 4\eta_5 \mu^{RS}_{(out)} k_{11} k_{12} k_{16}\left(P^{RS}_{(out)}\right)^2\left(P^{RS}_{(in)_p} - P^{RS}_{(in)_u}\right)^2 (S^{(in)}_{RS})^{*C} (S^{(out)}_{RS})^{*C}, \\
d^{RR} &= 4\eta_5 \mu^{RR}_{(out)} k_{13} k_{14} k_{17}\left(P^{RR}_{(out)}\right)^2\left(P^{RR}_{(in)_p} - P^{RR}_{(in)_u}\right)^2 (S^{(in)}_{RR})^{*C} (S^{(out)}_{RR})^{*C},
\end{aligned} \tag{3.11}$$

where,

$$\eta_1 = C_B\left[C_B(1-C_B)\alpha^2 + k_6 k_7\right], \quad \eta_2 = C_B(1-C_B)\left[(k_2+k_7)\alpha + (k_3+k_6)\alpha\right],$$

$$\begin{aligned}
\eta_3 &= (1-C_B)\left[C_B(1-C_B)\alpha^2 + k_2k_3\right],\\
\eta_4 &= C_B(1-C_B)\left[(k_2+\alpha)\alpha + (k_3+k_6)\alpha\right] + (1-C_B)k_2k_3 + C_Bk_7\left[\alpha(1-C_B)+k_6\right],\\
\eta_5 &= C_B(1-C_B)\left[k_2k_6 - C_B(1-C_B)\alpha^2\right]\left[k_3k_7 - C_B(1-C_B)\alpha^2\right].
\end{aligned}$$

It can be shown that the expressions $k_2k_6 - C_B(1-C_B)\alpha^2$ and $k_3k_7 - C_B(1-C_B)\alpha^2$ (in the formula of $\mathcal{R}^B_{HV}$) are positive. Also, it can be verified that the expression $\left(\left(a^i\right)^2 - d^i\right)$ inside the square root in (3.10) is non-negative for $i = \{SS, RS, RR\}$. In (3.9), the quantity $\mathcal{R}^B_{HV}$ ($\mathcal{R}^B_{VH}$) represents the average number of new cases in mosquitoes (humans) generated by an infectious human (mosquito) if introduced in a susceptible human and vector populations, where a certain proportion of humans (C_B) sleep under a long-lasting insecticidal net. In other words, $\mathcal{R}^B_{HV}$ and $\mathcal{R}^B_{VH}$ represent, respectively, the constituent reproduction number for the transmission of malaria from human-to-vector and vector-to-human.

It is convenient to define the following quantities (obtained by applying the next generation operator method with respect to the sensitive-only ($\mathcal{E}_{0S}$) and the resistant-only ($\mathcal{E}_{0R}$) boundary disease-free equilibrium, respectively. It is convenient to define:

$$\mathcal{R}^B_{0_{SS}}|_{\mathcal{E}_{df}=\mathcal{E}_{0S}} = \mathcal{R}^{SB}_{0_{SS}}, \quad \mathcal{R}^B_{0_{RR}}|_{\mathcal{E}_{df}=\mathcal{E}_{0R}} = \mathcal{R}^{RB}_{0_{RR}},$$

The reproduction numbers associated with the $SS-$only and $RR-$only boundary disease-free equilibria of the model, denoted by $\tilde{\mathcal{R}}^B_{0_{SS}}$ and $\tilde{\mathcal{R}}^B_{0_{RR}}$, are given, respectively, by:

$$\tilde{\mathcal{R}}^B_{0_{SS}} = \sqrt{\left(\mathcal{R}^B_{HV}\right)\left(\mathcal{R}^{SB}_{0_{SS}}\right)} \text{ and } \tilde{\mathcal{R}}^B_{0_{RR}} = \sqrt{\left(\mathcal{R}^B_{HV}\right)\left(\mathcal{R}^{RB}_{0_{RR}}\right)}. \tag{3.12}$$

The results follow from Theorem 2 of van den Driessche and Watmough (2002).

Theorem 3.1 *Consider the model {(2.29)–(2.31)}.*

(i) If $0 < p^*, q^* < 1$ and $\mathcal{R}_C > 1$ (so that the NonTrivCoexDFE ($\mathcal{E}_{0C}$) exists). Then, the NonTrivCoexDFE ($\mathcal{E}_{0C}$) is locally-asymptotically stable if $\mathcal{R}^B_0 < 1$, and unstable if $\mathcal{R}^B_0 > 1$.
(ii) If $\mathcal{R}_{SS} > 1$, then the NonTrivSensDFE ($\mathcal{E}_{0S}$) is locally-asymptotically stable if $\tilde{\mathcal{R}}^B_{0_{SS}} < 1$, and unstable if $\tilde{\mathcal{R}}^B_{0_{SS}} > 1$.
(iii) If $\mathcal{R}_{RR} > 1$, then the NonTrivResDFE ($\mathcal{E}_{0R}$) is locally-asymptotically stable if $\tilde{\mathcal{R}}^B_{0_{RR}} < 1$, and unstable if $\tilde{\mathcal{R}}^B_{0_{RR}} > 1$.

The epidemiological implication of Theorem 3.1 (Item (i)) is that a small influx of infected humans or mosquitoes into the community will not generate a large malaria outbreak in the community if $\mathcal{R}^B_0$ can be brought to (and maintained at) a value less than one. Similarly, Item (ii) of Theorem 3.1 implies that, for the scenario where only the sensitive mosquitoes are present in the environment (i.e., no insecticide-resistant mosquitoes), a small influx of insecticide-sensitive adult female mosquitoes that are infected with malaria will not cause a large outbreak of the disease in the community if the associated threshold quantity, $\tilde{\mathcal{R}}^B_{0_{SS}}$, can be brought to (and maintained at) a value less than one. Furthermore, Item (iii) of this theorem shows that a small influx of insecticide-resistant adult female mosquitoes that are infected with malaria will not generate a significant malaria outbreak in the community if the associated threshold quantity, $\tilde{\mathcal{R}}^B_{0_{RR}}$, is brought to (and maintained) at a value less than unity.

It is worth mentioning that, in the absence of bednets usage (i.e., $C_B = 0$), the control reproduction number ($\mathcal{R}^B_0$) of the model {(2.29)–(2.31)} reduces to

$$\mathcal{R}^B_0|_{C_B=0} = \mathcal{R}_0,$$

where $\mathcal{R}_0$ is the *basic reproduction number* of the model, and is given by:

$$\mathcal{R}_0 = \sqrt{(\mathcal{R}_{HV})\,(\mathcal{R}_{VH})}, \tag{3.13}$$

with,

$$\mathcal{R}^B_{HV}|_{C_B=0} = \mathcal{R}_{HV} \;\text{ and }\; \mathcal{R}_{VH} = \left(\mathcal{R}_{0_{SS}} + \mathcal{R}_{0_{RS}} + \mathcal{R}_{0_{RR}}\right),$$

and,

$$\mathcal{R}^B_{0_{SS}}|_{C_B=0} = \mathcal{R}_{0_{SS}}, \;\; \mathcal{R}^B_{0_{RS}}|_{C_B=0} = \mathcal{R}_{0_{RS}} \;\text{ and }\; \mathcal{R}^B_{0_{RR}}|_{C_B=0} = \mathcal{R}_{0_{RR}}.$$

Similarly, it can be seen that the quantities $\tilde{\mathcal{R}}^B_{0_{SS}}$ and $\tilde{\mathcal{R}}^B_{0_{RR}}$ reduce to

$$\tilde{\mathcal{R}}^B_{0_{SS}}|_{C_B=0} = \tilde{\mathcal{R}}_{0_{SS}} \;\text{ and }\; \tilde{\mathcal{R}}^B_{0_{RR}}|_{C_B=0} = \tilde{\mathcal{R}}_{0_{RR}},$$

respectively, where (with $\mathcal{R}_{HV}$ as defined above)

$$\tilde{\mathcal{R}}_{0_{SS}} = \sqrt{(\mathcal{R}_{HV})\left(\mathcal{R}^S_{0_{SS}}\right)} \text{ and } \tilde{\mathcal{R}}_{0_{RR}} = \sqrt{(\mathcal{R}_{HV})\left(\mathcal{R}^R_{0_{RR}}\right)}, \tag{3.14}$$

with,

$$\mathcal{R}^{SB}_{0_{SS}}|_{C_B=0} = \mathcal{R}^S_{0_{SS}} \;\text{ and }\; \mathcal{R}^{RB}_{0_{RR}}|_{C_B=0} = \mathcal{R}^R_{0_{RR}}.$$

4 Numerical simulations

The model {(2.29)–(2.31)} will now be simulated to, first of all, assess the combined impacts of the LLINs control strategy (both killing efficacy and repellance property of the LLINs) on the population abundance of mosquitoes by genotypes. The impact of mosquito biting behavior (endophilic/exophilic) on the control of malaria disease and on the feasibility of effective management of insecticide resistance in the *Anopheles* population will also be assessed. Specifically, simulations will be carried out to explore the feasibility of the presence of a *control window*, a region in the $C_B - q^{RR}_{m_{in}}$ parameter space within which the disease is effectively controlled (to elimination level) and insecticide resistance is effectively managed. In addition to determining the factors that contribute to the size of the control window, we will also run simulations to determine the feasibility of effective disease control outside the control window, in the presence of widespread insecticide resistance. In other words, these simulations will allow us to explore the all-important question on whether insecticide resistance increases malaria transmission.

The simulations will be carried out using relevant data and parametrization from the Asendabo Health Center of the Jimma Zone in Southwestern Ethiopia, considered to be a region of high malaria transmission (Demissie et al. 2009; Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020). The values of the parameters of the model, as well as the values of the initial sizes of the state variables of the model, are taken to be consistent with those expected or relevant to this region (see Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020. Specifically, based on the data for Jimma Zone (as reported in Demissie et al. (2009), the initial values of the state variables of the model associated with the dynamics of the human population are given by:

$$\begin{aligned}
&S_{H_p}(0) = C_B \times 23,916,\ E_{H_p}(0) = C_B \times 5,977,\\
&I_{H_p}(0) = C_B \times 9,964,\ R_{H_p}(0) = C_B \times 9,962,\\
&S_{H_u}(0) = (1 - C_B) \times 23,916,\ E_{H_u}(0) = (1 - C_B) \times 5,977,\\
&I_{H_u}(0) = (1 - C_B) \times 9,964 \text{ and}\\
&R_{H_u}(0) = (1 - C_B) \times 9,962.
\end{aligned}$$

For the mosquito population, we consider moderate level of frequency of the resistant allele. Following the report in Kuniyoshi and Santos (2017), Mohammed-Awel and Gumel (2019), we consider 37.5% of the local mosquitoes to carry the resistant allele (i.e., $p = 0.375$), while the remaining 62.5% carry the sensitive allele (i.e., $q = 0.625$). In this case, the following initial values for the state variables associated with the mosquito population (by genotype) are chosen to be:

$$\begin{aligned}
&S_{SS}^{(in)}(0) = f \times 25,000,\quad E_{SS}^{(in)}(0) = f \times 12,500,\quad I_{SS}^{(in)}(0) = f \times 12,500,\\
&S_{RS}^{(in)}(0) = f \times 12,500,\quad E_{RS}^{(in)}(0) = f \times 6,250,\quad I_{RS}^{(in)}(0) = f \times 6,250,\\
&S_{RR}^{(in)}(0) = f \times 12,500,\quad E_{RR}^{(in)}(0) = f \times 6,250,\quad I_{RR}^{(in)}(0) = f \times 6,250,\\
&S_{SS}^{(out)}(0) = (1 - f) \times 25,000,\quad E_{SS}^{(out)}(0) = (1 - f) \times 12,500,\\
&I_{SS}^{(out)}(0) = (1 - f) \times 12,500,\\
&S_{RS}^{(out)}(0) = (1 - f) \times 12,500,\quad E_{RS}^{(out)}(0) = (1 - f) \times 6,250,\\
&I_{RS}^{(out)}(0) = (1 - f) \times 6,250,\\
&S_{RR}^{(out)}(0) = (1 - f) \times 12,500,\quad E_{RR}^{(out)}(0) = (1 - f) \times 6,250 \text{ and}\\
&I_{RR}^{(out)}(0) = (1 - f) \times 6,250.
\end{aligned} \tag{4.1}$$

The baseline values of the parameters of the model, tabulated in Tables 3-5, are used to simulate the model. The specific simulations carried out are described in detail below.

4.1 Assessing the combined effect of the dominance of the resistance allele and the probability of mosquitoes successfully taking a complete bloodmeal by genotype on the effectiveness of LLINs intervention: full endophilicity setting

Here, the model $\{(2.29)–(2.31)\}$ is simulated to asses the potential combined impacts of the parameters related to the dominance of the resistance allele in heterozygous mosquitoes (h) and the probability of endophilic mosquitoes successfully taking a complete bloodmeal upon contact with a protected or unprotected host ($q^{i}_{m_{in}};\ i = \{SS, RS, RR\}$) on the effectiveness of the LLINs intervention (as measured in terms of LLINs coverage, C_B) to reduce malaria burden (measured in terms of daily new malaria cases). For this setting, we first consider the scenario where the mosquitoes are fully-endophilic (i.e., 100% of the mosquitoes only take bloodmeal indoors, and not outdoors; so that $f = 1$). Figure 3 depicts heatmaps of equilibrium values of daily new malaria cases, as a function of LLINs coverage (C_B) and the probability of mosquitoes of RR-genotype ($q^{RR}_{m_{in}}$; note that the probability of mosquitoes of SS-genotype and RS-genotype will also vary, according to the description provided in Table 3, as $q^{RR}_{m_{in}}$ is varied), for low, moderate and high levels of the values of the parameter for the dominance of the resistant allele in heterozygous mosquitoes (h), as described in detail below.

4.1.1 Effect of dominance of the resistance allele (*h*)

For simulation purposes, we consider three (arbitrarily-chosen) levels of the dominance of the resistant allele in heterozygous mosquitoes, namely low level (where h is set to 0.25), moderate level (where $h = 0.5$) and high level (where $h = 0.75$) (Mohammed-Awel and Gumel 2019; Mohammed-Awel et al. 2020). We first simulated the model (2.29)–(2.31)}, using the baseline values of the parameters in Tables 3–5, for the case with low level of the dominance of the resistant allele. The simulation results obtained (for this case with $h = 0.25$) show that the average daily new malaria cases is significantly reduced (to elimination levels) if the probability of endophilic mosquitoes successfully taking a bloodmeal upon contact with a human host lie in the range $0 \leq q^{RR}_{m_{in}} \leq 0.4$, regardless of the level of LLINs coverage in the community (Fig. 3a). This result also holds if the dominance of the resistant allele is increased to moderate (Fig. 3c) or high (Fig. 3e) level. Furthermore, for this case with low level of dominance of the resistant allele, the simulations show that insecticide resistance persists in the environment when the values of the LLINs coverage (C_B) and the probability of successfully taking a bloodmeal indoors ($q^{RR}_{m_{in}}$) lie within the region above the straight line connecting the points (0.05, 1) and (1, 0.51) in the $C_B - q^{RR}_{m_{in}}$–plane (Fig. 3b). This result also holds for the moderate level of the dominance of the resistant allele (i.e., $h = 0.5$), but the region for the persistence of insecticide resistance in the environment is much larger (specifically, for this scenario, insecticide resistance persists if the values of C_B and $q_{m_{in}}^{RR}$ lie in the region above the straight line that connects the points (0.05, 1) and (1, 0.15) in the $C_B - q_{m_{in}}^{RR}$−plane, as depicted in Fig. 3d). Finally, simulations for the high level of the dominance of the resistant allele (i.e., $h = 0.75$) show that insecticide resistance persists when the values of C_B and $q_{m_{in}}^{RR}$ lie within the region above the line connecting the points (0.05, 1) and (1, 0.1) in the $C_B - q_{m_{in}}^{RR}$−plane (see Fig. 3f). Thus, the heatmaps depicted in Fig. 3b, d and f show that the size of the region in the $CB - q_{m_{in}}^{RR}$−plane where insecticide resistance persists in the environment increases with increasing levels of the dominance of the resistant allele (h) in heterozygous mosquitoes.

If the probability of successfully taking a bloodmeal is increased to $0.4 < q_{m_{in}}^{RR} \leq 0.55$, our simulations, for the low level of the dominance of the resistant allele (i.e., $h = 0.25$) and a fixed $q_{m_{in}}^{RR}$ chosen from the interval $0.4 < q_{m_{in}}^{RR} \leq 0.55$, show that increasing LLINs coverage (from $C_B = 0$ to a certain threshold value of C_B) causes persistence of the disease (Fig. 3a). For this range of $q_{m_{in}}^{RR}$ values, $0.4 < q_{m_{in}}^{RR} \leq 0.55$, insecticide resistance is effectively managed regardless of the LLINs coverage value (Fig. 3a). For instance, when the probability $q_{m_{in}}^{RR}$ is fixed at 0.5, the simulation results obtained show that increasing the LLINs coverage from $C_B = 0$ to $C_B = 0.2$ causes persistence of the disease (Fig. 3a). The plots in Fig. 3a further show that increasing the LLINs coverage above the threshold $C_B = 0.2$ (up to $C_B = 1$) causes malaria elimination. Furthermore, when the probability $q_{m_{in}}^{RR}$ is fixed at 0.5, the simulation results obtained show that insecticide resistance is effectively managed regardless of the value of LLINs coverage (Fig. 3b).

Furthermore, if the probability $q_{m_{in}}^{RR}$ is further increased to lie within the interval $0.55 < q_{m_{in}}^{RR} \leq 0.8$, our simulations (for $h = 0.25$) show that increasing LLINs coverage from $C_B = 0$ to a certain threshold value of C_B initially causes the persistence of the disease (Fig. 3a). In this case, a further increase in the value of C_B above this threshold, until reaching a second threshold, causes the elimination of the disease (Fig. 3a). For this scenario, for all values of LLINs coverage (from zero to the second threshold) insecticide resistance remains effectively managed (Fig. 3b). A further increase in the value of C_B above the second threshold until $C_B = 1$ causes persistence of the the disease as well as persistence of insecticide resistance (Fig. 3a, b). For example, for $q_{m_{in}}^{RR} = 0.7$, the first threshold value is $C_B = 0.4$ and the second threshold value is $C_B = 0.7$ (Fig. 3a, b). In this case, increasing the LLINs coverage from zero to $C_B = 0.4$ (the first LLINs threshold) causes the persistence of malaria (Fig. 3a). Further increasing the LLINs coverage above $C_B = 0.4$ up to $C_B = 0.7$ causes malaria elimination. In this case, insecticide resistance is effectively managed when LLINs coverage is in the rage $0 \leq C_B \leq 0.7$ (Fig. 3b). In this case, any additional increase in LLINs coverage above $C_B = 0.7$ causes persistence of both malaria and insecticide resistance (see the dashed horizontal lines, corresponding to $q_{m_{in}}^{RR} = 0.7$, and the two thresholds, represented by the magenta dots, at $(C_B, q_{m_{in}}^{RR}) = (0.4, 0.7)$ and $(C_B, q_{m_{in}}^{RR}) = (0.7, 0.7)$, on the $C_B - q_{m_{in}}^{RR}$−plane in (Figs. 3a, b). The same phenomenon is observed for the moderate ($h = 0.5$) and high ($h = 0.75$) level of the dominance of the resistant allele, except that the ranges of $q_{m_{in}}^{RR}$ (and the corresponding thresholds for C_B) change with changing level of the dominance of the resistant allele. Finally, for the low level of the dominance of the resistant allele (i.e., $h = 0.25$)

and with very high probability of endophilic mosquitoes successfully taking a bloodmeal (e.g., $q_{m_{in}}^{RR} > 0.8$), our simulations show that the disease persists regardless of the LLINs coverage level whether insecticide resistance persists or not persists in the community (Fig. 3a). Furthermore, for moderate ($h = 0.5$) and high dominance ($h = 0.75$) of the resistant allele, our simulations show that the disease persists regardless of LLINs coverage and insecticide resistance level in the community if $q_{m_{in}}^{RR} > 0.6$ (Fig. 3c–f).

In summary, the simulations depicted in Fig. 3 show that, for the case when the adult female mosquitoes are fully-endophilic (i.e., $f = 1$) and for each of the three levels of dominance of the resistant allele in heterozygous mosquitoes, persistence of insecticide resistance in the environment is dependent on the level of the LLINs coverage (C_B) in the community and the genotype-specific probability of the adult female mosquito successfully taking a bloodmeal ($q_{m_{in}}^{RR}$). Furthermore, the ability of insecticide resistance to cause an increase in the daily new malaria cases (at equilibrium) depends on the value of the genotype-specific probability of adult female mosquitoes successfully taking a bloodmeal upon contact with the human host. For each of the three levels of the dominance of the resistance allele considered in this study, insecticide resistance could lead to a decrease, an increase or no increase or decrease in malaria burden, depending on the value of the genotype-specific probability of successfully taking a bloodmeal upon contact with a human host.

4.2 Assessing the combined effect of dominance of resistance allele and probability of mosquitoes successfully taking bloodmeal by genotype on effectiveness of LLINs intervention: endophilic-exophilic setting

In this section, the effect of exophilicity (i.e., a certain proportion of mosquitoes are able to bite humans while they are outdoors) on the effectiveness of the LLINs-based strategy will be assessed. For the simulations to be carried out in this section, we assume that 10% of the mosquitoes in the environment are exophilic (i.e., 10% of the local mosquitoes can bite outdoors, so that $f = 0.9$). For these simulations, we vary the probability of successfully taking a bloodmeal for endophilic mosquitoes ($q_{m_{in}}^{RR}$), while keeping the probability of the exophilic mosquitoes to successfully take bloodmeal from humans outdoors ($q_{m_{iout}}^{RR}$) at its baseline value (of 0.05).

The model {(2.29)–(2.31)} is simulated using the parameter and initial settings described (given) in Sect. 4.1 but with $f = 0.9$. Here, too, the simulations are carried out for the three levels (low, moderate and high) of the parameter for the dominance of the resistant allele (h).

4.2.1 Effect of the dominance of the resistance allele (*h*)

We first simulated the model {(2.29)–(2.31)} for the case where the dominance of the resistant allele in heterozygous mosquitoes is low (i.e., $h = 0.25$). The results obtained show that malaria can be eliminated and insecticide resistance effectively managed, regardless of the level of LLINs coverage, if the probability of successfully taking a bloodmeal lies in the range $0 \leq q_{m_{in}}^{RR} \leq 0.35$ (Figs. 4a, b). This result also holds if the

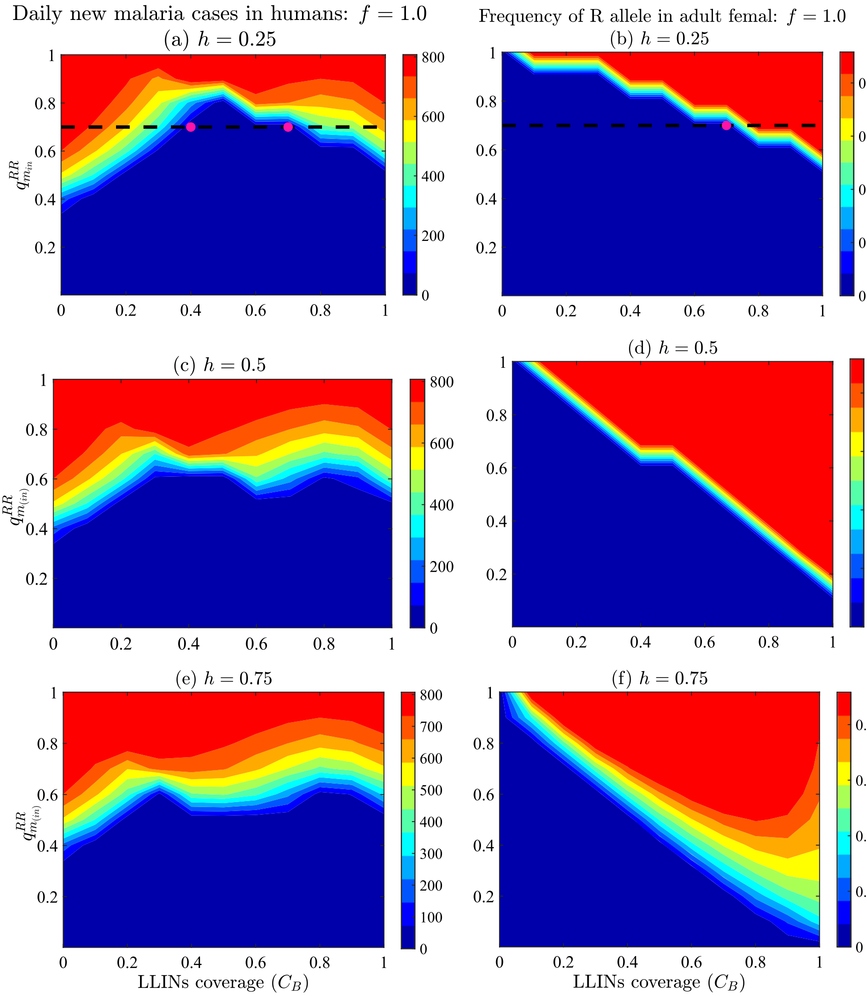

Fig. 3 Heat maps of the model {(2.29)–(2.31)} for LLINs coverage (C_B) *versus* probability of an endophilic RR-genotype mosquito successfully taking a complete bloodmeal (q^{RR}_{min}). Parameter values used are as given by their baseline values in Tables 3–5, with $q^{RS}_{min} = q^{RR}_{min}/1.1$ and $q^{SS}_{min} = q^{RR}_{min}/1.25$ and moderate initial resistant allele frequency given in (4.1). (i) (**a**), (**b**) $f = 1$ & $h = 0.25$, (ii) (**c**), (**d**) $f = 1$ & $h = 0.5$ and (iii) (**e**), (**f**) $f = 1$ & $h = 0.75$. In (a)–(b), the scenario discussed in the above example, for $h = 0.25$, is illustrated by the dashed black horizontal line, corresponding to $q^{RR}_{min} = 0.7$, and the two thresholds for the LLINs coverage (corresponding to magenta dots at $(C_B, q^{RR}_{min}) = (0.4, 0.7)$ and $(C_B, q^{RR}_{min}) = (0.7, 0.7)$)

dominance of the resistant allele is increased to moderate (Fig. 4c, d) or high (Fig. 4e, f) levels. When the probability of successfully taking a bloodmeal is higher (e.g., $0.35 < q^{RR}_{min} \leq 0.72$), and a fixed value of q^{RR}_{min} is chosen from this interval (with the dominance of the resistant allele kept at the low level), the simulation results obtained show that increasing LLINs coverage (C_B), from zero to a certain threshold, causes the persistence of the disease, while insecticide resistance is effectively managed. For this scenario, a further increase in the LLINs coverage above this threshold causes the elimination of the disease, while insecticide resistance is still effectively managed (Fig. 4a, b). For instance, for $q_{m_{in}}^{RR}$ fixed at 0.6, the simulation results show that the disease persists if the LLINs coverage lies in the range $0 \leq C_B \leq 0.32$ (Fig. 4a; for this simulations, $C_B = 0.32$ is the first threshold). In this scenario, insecticide resistance is effectively managed regardless of the value of LLINs coverage (Fig. 4b). Thus, in this scenario (with $q_{m_{in}}^{RR}$ set at 0.6), the disease persists while insecticide resistance is effectively managed if the LLINs coverage is relative low ($C_B < 0.32$), but the disease is eliminated while insecticide resistance remains effectively managed for higher values of LLINs coverage ($C_B > 0.32$). Furthermore, for a fixed value of $q_{m_{in}}^{RR}$ chosen from the interval $0.72 < q_{m_{in}}^{RR} \leq 0.8$ and $h = 0.25$, the simulation results obtained show, initially, the persistence of the disease and insecticide resistance effectively managed for all LLINs coverage levels between $C_B = 0$ and a first threshold value of C_B (Fig. 4a, b). Increasing the LLINs coverage from the first threshold up to a second threshold causes malaria elimination, while insecticide resistance remains effectively managed. The simulations in Fig. 4a, b further show that increasing the LLINs coverage above the second threshold (up to $C_B = 1$) causes persistence of both malaria disease and insecticide resistance in the population. For example, choosing $q_{m_{in}}^{RR} = 0.75$, the simulation results show that the disease persists in the population for LLINs coverage in the range $0 \leq C_B \leq 0.42$ (Fig. 4a) and insecticide resistance is effectively managed for $0 \leq C_B \leq 0.86$ (Fig. 4b). In this case, an increase in LLINs coverage above $C_B = 0.42$ up to $C_B = 0.86$ causes malaria elimination. Furthermore, an additional increase in LLINs coverage above $C_B = 0.86$ causes persistence of both malaria and insecticide resistance (see the solid dashed black horizontal lines, corresponding to $q_{m_{in}}^{RR} = 0.75$, and the two thresholds (corresponding to magenta dots at $(C_B, q_{m_{in}}^{RR}) = (0.42, 0.75)$ and $(C_B, q_{m_{in}}^{RR}) = (0.86, 0.75)$) on the $C_B - q_{m_{in}}^{RR}$–plane in Fig. 4a, b. Similar dynamics are obtained for the moderate ($h = 0.5$) and high ($h = 0.75$) levels of the dominance of the resistant allele. Finally, for the low level of the dominance of the resistant allele (i.e., $h = 0.25$) and with very high probability of endophilic mosquitoes successfully taking a bloodmeal (e.g., $q_{m_{in}}^{RR} > 0.8$), the simulation results obtained show the persistence of the disease regardless of the level of LLINs coverage and regardless of whether insecticide resistance persists or is effectively managed in the community (Fig. 4a). Furthermore, for the case with $h = 0.5$ and $h = 0.75$, the disease persists, regardless of the level of LLINs coverage or persistence (or effective management) of insecticide resistance in the community, if $q_{m_{in}}^{RR} > 0.7$ and $q_{m_{in}}^{RR} > 0.6$, respectively (Fig. 4c–f).

Finally, for the three levels of the dominance of the resistance allele considered in this study, the simulation results depicted in Figs. 3 and 4 show that the size of the region in the $C_B - q_{m_{in}}^{RR}$–plane where insecticide resistance persists decreases as the value of the proportion of newborn that are endophilic (f) decreases from $f = 1$ to $f = 0.9$. The plots in Figs. 3 and 4 further show that, for the three levels of the dominance of the resistance allele, the size of the region in the $C_B - q_{m_{in}}^{RR}$–plane where the disease is eliminated increases as the value of f was decreased from $f = 1$ to $f = 0.9$. Also, as in the case with full endophilicity (i.e., the model with $f = 1$; discussed in Sect. 4.1), the simulations for the case with reduced endophilicity (i.e., $f = 0.9$) show that the

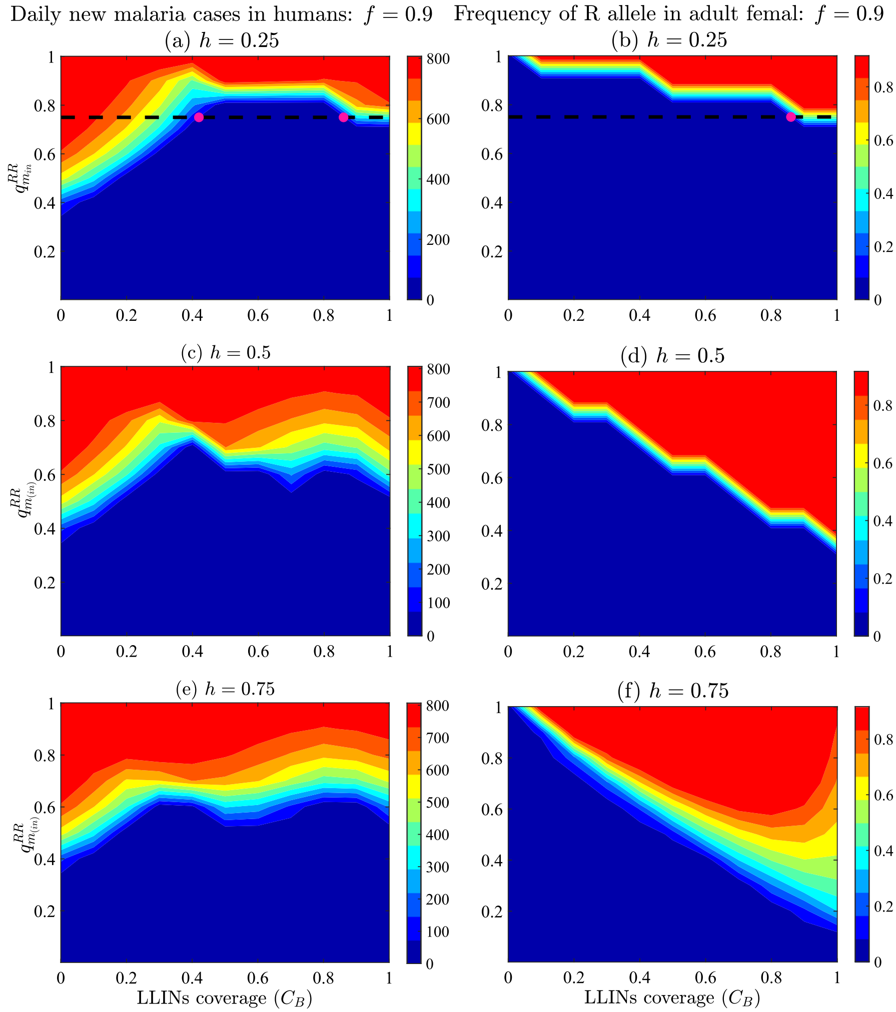

Fig. 4 Heat map of the model {(2.29)–(2.31)} for bednets (LLINs) coverage (C_B) *vs.* probability of an endophilic RR-genotype mosquito successfully taking a complete bloodmeal ($q^{RR}_{m_{in}}$). Parameter values are as given by the baseline values in in Tables 3–5, $q^{RS}_{m_{in}} = q^{RR}_{m_{in}}/1.1$ and $q^{SS}_{m_{in}} = q^{RR}_{m_{in}}/1.25$ with the moderate initial resistant allele frequency given in (4.1). (i) (**a**), (**b**) $f = 0.9$ & $h = 0.25$, (ii) (**c**), (**d**) $f = 0.9$ & $h = 0.5$ and (iii) (**e**), (**f**) $f = 0.9$ & $h = 0.75$. In (**a**), (**b**), the scenario discussed in the above example, for $h = 0.25$, is illustrated by the dashed black horizontal line, corresponding to $q^{RR}_{m_{in}} = 0.75$, and the two thresholds for the LLINs coverage (corresponding to magenta dots at $(C_B, q^{RR}_{m_{in}}) = (0.42, 0.75)$ and $(C_B, q^{RR}_{m_{in}}) = (0.86, 0.75)$)

size of the region in the $CB-q_{m_{in}}^{RR}-$plane where insecticide resistance persists in the environment increases with increasing levels of the dominance of the resistant allele (h) (Figs. 4b, d and f).

In conclusion, our study shows, based on the simulation results depicted in Figs. 3 and 4, that the impact of insecticide resistance on malaria burden (as measured by the daily new malaria cases) depend on the size of the LLINs coverage (C_B), the level of the dominance of the resistant allele in heterozygote mosquitoes (h), the value of the probability of successfully taking a bloodmeal by endophilic mosquitoes by genotype ($q_{m_{in}}^{RR}$, $q_{m_{in}}^{RS}$ & $q_{m_{in}}^{SS}$) and the endophilicity ($f = 1$) or exophilicity ($f < 1$) of the malaria mosquitoes by genotype. We will explore these interactions in more detail in the simulations to be carried out in Sect. 4.3 below.

4.3 Assessing the combined effect of dominance of resistance allele and probability of mosquitoes successfully taking bloodmeal by genotype on effectiveness of LLINs intervention: comparing levels of mosquito indoor versus outdoor biting behavior

The model {(2.29)–(2.31)} is now simulated, using various values of the LLINs coverage (C_B), the parameter for the dominance of the resistance allele (h) and the probability of successfully taking a complete bloodmeal ($q_{m_{in}}^{i}, i = \{SS, RS, RR\}$), to assess their combined impacts on the daily new malaria cases under fully-endophilic setting (i.e., $f = 1$). For the case of the model with moderate probability of successfully taking a complete bloodmeal (e.g., $q_{m_{in}}^{RR} = 0.45$), moderate level of dominance of the resistant allele in heterozygous mosquitoes ($h = 0.5$) and no LLINs coverage (i.e., $C_B = 0$), the simulation results obtained show that while malaria persists in the population, insecticide resistance is effectively managed at equilibrium (Fig. 5a). However, for this setting, if the LLINs coverage is increased to 50% (i.e., C_B is increased from 0 to 0.5), the disease is significantly reduced (but not eliminated), while insecticide resistance remains effectively managed (Fig. 5b). If the LLINs coverage is further increased (e.g., to $C_B = 0.9$), under this scenario, malaria is essentially eliminated but insecticide resistance now persists in the environment (Fig. 5c). This (latter) case where disease is eliminated while resistance persists show that malaria can, indeed, be eliminated despite widespread insecticide resistance in the population. In other words, for the case where mosquitoes have a moderate probability of successfully taking a bloodmeal (i.e., $q_{m_{in}}^{RR} = 0.45$) coupled with moderate level of the dominance of the resistant allele in heterozygous mosquitoes in the environment (i.e., $h = 0.5$), an LLINs-based vector control strategy with with high coverage (e.g., $C_B \geq 0.9$) will lead to the elimination of malaria, despite widespread insecticide resistance in the environment.

We also ran the same simulations as above, but with the probability of successfully taking a complete bloodmeal $q_{m_{in}}^{RR}$ increased **from** $q_{m_{in}}^{RR} = 0.45$ **to** $q_{m_{in}}^{RR} = 0.6$. The simulation results obtained show that, in the absence of LLINs coverage (i.e., $C_B = 0$), malaria persists in the population, but insecticide resistance is effectively managed (Fig. 5d). For this scenario, when the LLINs coverage is increased to 50%, the number of daily new cases is dramatically reduced to elimination level and insec-

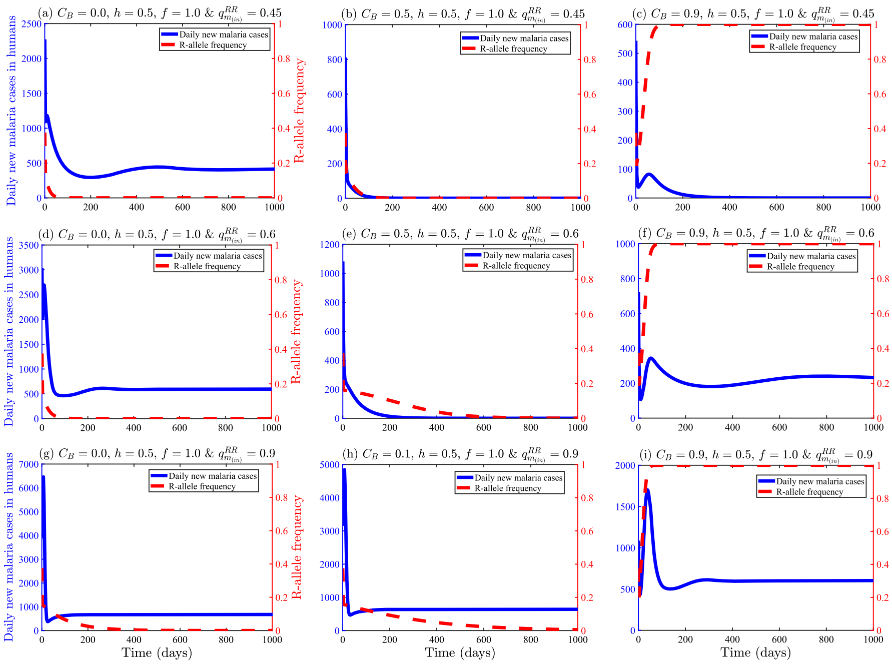

Fig. 5 Simulations of the model {(2.29)–(2.31)} showing daily new malaria cases in humans and distribution of allele frequencies in mosquitoes. Parameter values are as given by the baseline values in in Tables 3–5, $q^{RS}_{m_{in}} = q^{RR}_{m_{in}}/1.1$ and $q^{SS}_{m_{in}} = q^{RR}_{m_{in}}/1.25$ with the moderate initial resistant allele frequency given in (4.1). (i) (**a**) $C_B = 0$, $h = 0.5$, $f = 1.0$ & $q^{RR}_{m_{in}} = 0.45$, (ii) (**b**) $C_B = 0.5$, $h = 0.5$, $f = 1.0$ & $q^{RR}_{m_{in}} = 0.45$, (iii) (**c**) $C_B = 0.9$, $h = 0.5$, $f = 1.0$ & $q^{RR}_{m_{in}} = 0.45$, (iv) (**d**) $C_B = 0$, $h = 0.5$, $f = 1.0$ & $q^{RR}_{m_{in}} = 0.6$, (v) (**e**) $C_B = 0.5$, $h = 0.5$, $f = 1.0$ & $q^{RR}_{m_{in}} = 0.6$, (vi) (**f**) $C_B = 0.9$, $h = 0.5$, $f = 1.0$ & $q^{RR}_{m_{in}} = 0.6$, (vii) (**g**) $C_B = 0$, $h = 0.5$, $f = 1.0$ & $q^{RR}_{m_{in}} = 0.9$, (viii) (**h**) $C_B = 0.1$, $h = 0.5$, $f = 1.0$ & $q^{RR}_{m_{in}} = 0.9$, (ix) (**i**) $C_B = 0.9$, $h = 0.5$, $f = 1.0$ & $q^{RR}_{m_{in}} = 0.9$

ticide resistance is effectively managed (Fig. 5e). However, if the LLINs coverage is further increased to 90%, both malaria and insecticide resistance persist in the population (Fig. 5f). Thus, it follows, by comparing Fig. 5b and f, that, for the scenario with $h = 0.5$, increasing the probability of successfully getting a bloodmeal from a moderate to a relatively high value (e.g., increasing $q^{RR}_{m_{in}}$ from 0.45 to 0.6) could cause a rebound of malaria (from elimination to persistence) and widespread insecticide resistance (in comparison to the case with $C_B = h = 0.5$ and $q^{RR}_{m_{in}} = 0.45$, where insecticide resistance was effectively managed), if the LLINs coverage is increased from the moderate to high levels (e.g., C_B increased from 0.5 to 0.9). In other words, in comparison to Fig. 5b, the scenario with $h = 0.5$, $q^{RR}_{m_{in}} = 0.6$ and $C_B = 0.9$ (depicted in Fig. 5f) show the case where widespread insecticide resistance can cause a rebound of malaria cases from elimination.

We now simulate the case with $h = 0.5$ and the probability of successfully taking a complete bloodmeal in increased from the moderate value of 50% (depicted in Fig. 5d–f) to a high value, such as 90% (i.e., $q^{RR}_{m_{in}} = 0.9$). The simulation results obtained for this scenario show that, in the absence of LLINs coverage, malaria and insecticide resistance persist in the population (Fig. 5g). When the LLINs coverage is increased either to low (e.g., to $C_B = 0.1$) or high (e.g., to $C_B = 0.9$), the disease and insecticide resistance continue to persist in the population (see Fig. 5h, i). Thus, the scenario with $h = 0.5$ and high probability of successfully taking a bloodmeal ($q_{m_{in}}^{RR} = 0.9$) illustrates the case where the disease will persist in the population regardless of the level of LLINs coverage and absence of, or widespread, insecticide resistance. The same results are also observed for low and high values of the value of the parameter for the dominance of the resistant allele in heterozygous mosquitoes (e.g., the same results are observed if h is set to either $h = 0.25$ or $h = 0.75$). Qualitatively similar simulation results are observed under a low exophilicity assumption (i.e., $f = 0.9$).

4.4 Impact of LLINs coverage and repellance: comparing mosquito indoor versus outdoor biting behavior

In this section, the model $\{(2.29)–(2.31)\}$ is simulated to asses the repellance property of the LLINs (as measured by the parameter r^i, with $i = \{SS, RS, RR\}$). For these simulations, the values of r^{RS} and r^{SS} are calculated in terms of the value of r^{RR}, as defined/expressed in Table 3.

We first simulated the case where the mosquitoes are fully-endophilic (i.e., $f = 1$) and with high LLINs coverage ($C_B = 0.9$) and moderate probability of successfully taking a bloodmeal ($q_{m_{in}}^{RR} = 0.5$). Our simulation results show that, for the case where the efficacy of the bednet to repel an endophilic mosquito with RR-genotype is fixed at 0.25 (i.e., we set $r^{RR} = 0.25$), the disease persists and insecticide resistance is not effectively managed (Fig. 6a). However, when the value of r^{RR} is increased to its baseline level (i.e., $r^{RR} = 0.86$), the disease is eliminated and insecticide resistance is not effectively managed (Fig. 6b). Thus, in this case with full endophilicity and moderate probability to successfully take a bloodmeal, this study shows that significantly increasing the value of the repellance property of the bednet (from $r^{RR} = 0.25$ to $r^{RR} = 0.86$) could result in disease elimination even though insecticide is widespread in the environment.

We further simulated the case where the mosquitoes are not fully-endophilic (while keeping all other parameter values the same as in the simulations with $f = 1$ above). Specifically, we consider the scenario where 10% of the new adult mosquitoes bite outdoors (i.e., $f = 0.9$). For this setting, our simulations show persistence of both malaria and insecticide resistance if the repellance property of the net is kept at the low level of $r^{RR} = 0.25$ (Fig. 6c). Furthermore, as observed in the case with full endophilicity, our simulations show that the disease is eliminated when the repellance property of the net was increased to its baseline level of $r^{RR} = 0.86$, while insecticide resistance remains widespread (Fig. 6d).

In conclusion, the simulations in this section (depicted in Fig. 6) show that, in a fully-endophilic or 10% exophilic mosquito environment with high LLINs coverage, both the disease and insecticide resistance persist in the community if the efficacy of the bednet to repel endophilic mosquitoes is low (such as, $r^{RR} = 0.25$). However, for this setting, increasing the efficacy of the repellent property of the bednet to 86% resulted

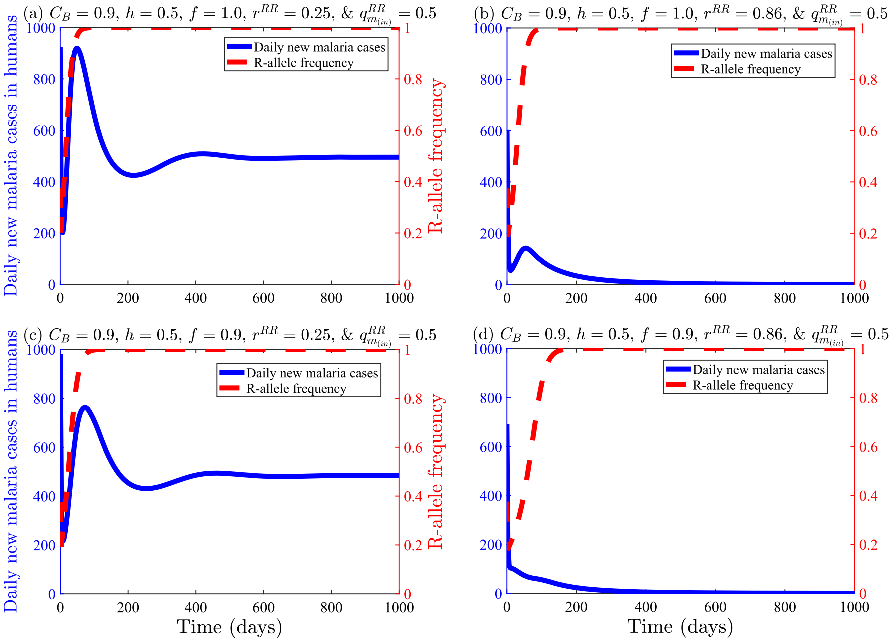

Fig. 6 Simulations of the model {(2.29)–(2.31)} showing daily new malaria cases in humans and distribution of allele frequencies in mosquitoes. Parameter values are as given by the baseline values in in Tables 3, 4, 5, $q^{RS}_{m_{in}} = q^{RR}_{m_{in}}/1.1$, $q^{SS}_{m_{in}} = q^{RR}_{m_{in}}/1.25$, $r^{RS} = 0.6r^{RR}$ and $r^{SS} = 0.18r^{RR}$ with the moderate initial resistant allele frequency given in (4.1). (i) (**a**) $C_B = 0.9$, $h = 0.5$, $f = 1.0$, $r^{RR} = 0.25$ & $q^{RR}_{m_{in}} = 0.5$, (ii) (**b**) $C_B = 0.9$, $h = 0.5$, $f = 1.0$, $r^{RR} = 0.86$ & $q^{RR}_{m_{in}} = 0.5$, (iii) (**c**) $C_B = 0.9$, $h = 0.5$, $f = 0.9$, $r^{RR} = 0.25$ & $q^{RR}_{m_{in}} = 0.5$ and (iv) (**d**) $C_B = 0.9$, $h = 0.5$, $f = 0.9$, $r^{RR} = 0.86$ & $q^{RR}_{m_{in}} = 0.5$

in the elimination of the disease while insecticide resistance remains widespread (at 100% at steady-state). These simulations illustrate the case where an increase in the repellent property of the bednet causes disease elimination, while insecticide resistance persists, when the LLINs coverage in the community is high (such as $C_B = 0.9$).

5 Discussion and conclusions

Malaria is a deadly disease that is spread between humans via the bite of a mosquito (Baton and Ranford-Cartwright 2005; WHO 2016, 2017). It inflicts severe public health and socio-economic burden in geographies inhabited by more than half of the world's population (Gething et al. 2011; Johnston et al. 2013). Mosquito resistance to majority of the currently-available insecticides used in frontline mosquito control products, such as long-lasting insecticidal nets (LLINs), is considered by many to be the most important challenges that will hamper the current global effort to eradicate malaria by 2040 (Mohammed-Awel et al. 2020; Alout et al. 2017b; Dondorp et al. 2009; Imwong et al. 2017; Kabula et al. 2014; WHO 2022b). A major open question in the mosquito ecology and the wider malaria control community is whether or not insecticide resistance actually impacts malaria epidemiology. While some empirical studies suggest that insecticide resistance increases malaria prevalence, other studies show the exact opposite (Kleinschmidt et al. 2018; Alout et al. 2017b; Maharaj et al. 2005; Toe et al. 2018; Protopopoff et al. 2018). Consequently, detailed mathematical modeling can play important role to identify factors that cause the conflicting relation between insecticide resistance and malaria transmission.

In this study, we developed a genetic-epidemiology modeling framework for malaria transmission dynamics. Some of the notable features of the framework is the design of a novel model for malaria transmission dynamics and control that incorporates, *inter alia*, the detailed genotype structure of the gene that confers insecticide resistance in mosquitoes, malaria epidemiology in mosquitoes and in the LLINs-protected and LLINs-unprotected humans. The model further incorporates genotype-specific mosquito repellance property of the LLINs and mosquito biting behavior (i.e., biting humans indoors or outdoors). We also formulated a new nonlinear probability function for the contact between an endophilic *Anopheles* mosquito (of i-genotype) and a human host (protected or otherwise) indoors. In the formulation of the nonlinear probability function, we took into account the fact that the endophilic mosquito (of i-genotype) may succeed in taking a bloodmeal during the first attempt, or after making multiple failed attempts. The model was rigorously analysed to gain insight into its dynamical features. Specifically, conditions for the existence of four associated disease-free equilibria of the model were derived. The expression for the control reproduction number of the model, defined in terms of the constituent reproduction numbers (corresponding to the cases where only insecticide-sensitive or insecticide-resistant or mosquitoes of all three genotypes exist at disease-free equilibrium) was obtained. It was shown that each of the nontrivial disease-free equilibria of the model is locally-asymptotically stable if its associated control reproduction number is less than unity. The ecological and epidemiological implication of this theoretical result is that a small influx of infected humans or adult female *Anopheles* will not generate a large malaria outbreak in the community if the associated control reproduction number is less than one. In other words, malaria can be effectively controlled in, or eliminated from, the community if the value of the associated control reproduction number of the model can be brought to, and maintained at, a value less than unity.

This study identifies, based on the rigorous theoretical analysis and numerical simulations we carried out, four main parameters that play a major role in helping to answer the crucial question of whether or not insecticide resistance increases or decreases malaria transmission in a malaria-endemic setting, namely:

(i) The level of dominance of resistance allele in heterozygous mosquitoes (h);
(ii) The proportion of new adult mosquitoes that bite indoors (f);
(iii) The probability of endophilic mosquitoes to successfully take a bloodmeal from a host ($q_{m_{RR}}^{RR}$ for resistant mosquitoes, which is related to $q_{m_{SS}}^{SS}$ for sensitive mosquitoes and $q_{m_{RS}}^{RS}$ for heterozygous mosquitoes); and
(iv) LLINs coverage in the community (C_B).

We showed that the answer to the above question could be yes or no, depending on the values of the aforementioned four parameters identified in this study. We enumerate the following scenarios.

5.1 Scenarios where insecticide resistance increases malaria transmission

For the case where the level of the dominance of the resistant allele in heterozygous mosquitoes is low (e.g., $h = 0.25$) and the new adult mosquitoes are fully-endophilic (i.e., $f = 1$), there are scenarios where insecticide resistance increases malaria transmission. For example, if the probability of endophilic mosquitoes successfully taking a bloodmeal is moderate (i.e., $q_{m_{RR}}^{RR} = 0.7$) and the LLINs coverage lies in the range $0.4 \leq C_B \leq 0.7$, the daily new malaria cases is at the level of elimination, while insecticide resistance is effectively managed (as shown in Fig. 3a, b). In this case, the simulation results show that an increase in LLINs coverage (e.g., to a value in the range $0.7 < C_B \leq 1$) will cause a rebound of malaria and the inability to effectively manage insecticide resistance (Fig. 3a, b). The same scenario was observed for moderate level of dominance $h = 0.5$ (as depicted in Fig. 5d–f) and for high level dominance ($h = 0.75$) as depicted in Fig. 3e, f. This result is consistent with the empirical studies in Alout et al. (2017b), Maharaj et al. (2005), which showed that insecticide resistance could cause a rebound (or an increase) in malaria incidence.

Furthermore, the scenario where the level of the dominance of the resistant allele is kept low (at $h = 0.25$) but the proportion of new adult mosquitoes that bite indoors is slightly decreased to 90% (i.e., $f = 0.9$) could also cause insecticide resistance to increase malaria transmission. For example (for this case with $h = 0.25$ and $f = 0.9$), if the probability of successfully taking a bloodmeal is moderate (e.g., $q_{m_{RR}}^{RR} = 0.75$) and the LLINs coverage is moderate or high (e.g., $0.42 \leq C_B \leq 0.86$), then the daily new malaria cases is at elimination level and insecticide resistance is effectively managed (Fig. 4a, b). If the LLINs coverage is increased to higher level, within the range $0.86 < C_B \leq 1$, our simulations show a rebound in malaria burden (from the elimination level), and insecticide resistance is now widespread (Fig. 4a, b). This result holds for moderate and high ($h = 0.5$ and $h = 0.75$) levels of the dominance of the resistant allele in heterozygous mosquitoes (as shown in Fig. 4c, d, and e, f, respectively). This result supports the finding reported in the empirical studies in Alout et al. (2017b), Maharaj et al. (2005).

5.2 Scenarios where insecticide resistance reduces malaria transmission

For the case where the dominance of the resistant allele is moderate (e.g., $h = 0.5$) and mosquitoes are fully-endophilic (i.e., $f = 1$), our simulations show that scenarios exist where insecticide resistance could reduce malaria transmission. For example, malaria persists and insecticide resistance is effectively managed if the probability of endophilic mosquitoes successfully taking a bloodmeal is moderate (e.g., $q_{m_{RR}}^{RR} = 0.45$) and bednets are not used in the community ($C_B = 0$ (Fig. 5a). However, in this case, adding bednets-based intervention with very high LLINs coverage (e.g., 90% LLINs coverage, so that $C_B = 0.9$), while causing the persistence of insecticide resistance, resulted in a reduction in the daily new cases to elimination level (as shown in Fig. 5c). The scenario where insecticide resistance causes disease elimination/reduction was observed for low level of the dominance of the resistant allele ($h = 0.25$), as depicted in Fig. 3a and b, and for the high level of the dominance of the resistant allele ($h = 0.75$), as shown in Fig. 3e and f. This result is consistent with the empirical study (based on experimental hut evaluation) in Toe et al. (2018), which showed that the use of LLINs is beneficial even in the presence of widespread *Pyrethroid* resistance.

Furthermore, insecticide resistance could reduce malaria transmission in the scenario where the dominance of the resistant allele is kept at moderate value (at $h = 0.5$) but the proportion of mosquitoes that are endophilic is slightly decreased to 90% (i.e., $f = 0.9$). For example, we showed that while malaria persists and insecticide resistance is effectively managed if the probability of endophilic mosquitoes successfully taking a bloodmeal is moderate (e.g., $q_{m_{RR}}^{RR} = 0.5$) and no LLINs coverage ($C_B = 0.0$), increasing the LLINs coverage to a high value $C_B = 0.9$ resulted in a elimination of the daily new malaria cases, but this also resulted in widespread insecticide resistance (Fig. 4c and d). The scenario where insecticide resistance causes disease elimination/reduction was observed for low level of dominance $h = 0.25$ (as depicted in Fig. 3a and b) and for high level dominance ($h = 0.75$) as depicted in Fig. 3e and f. Thus, this study shows that although the large scale use of LLINs is beneficial (in reducing malaria burden), such wide-scale use of LLINs also causes widespread insecticide resistance in the malaria mosquito population in the community.

5.3 Scenarios where insecticide resistance does not increase or reduce malaria transmission

Our study also identified scenarios where the disease persists regardless of the LLINs coverage value or whether insecticide resistance persists or not persists. For example, as depicted in Fig. 3a, b, insecticide resistance has no effect on malaria transmission when the following three conditions hold:

(a) The dominance of the resistant allele is low (i.e., when $h = 0.25$),
(b) Mosquitoes are fully endophilic (i.e., $f = 1$) and
(c) The probability of successfully taking a bloodmeal is moderate or high (e.g., $q_{m_{RR}}^{RR} > 0.8$).

For this case, the disease, as well as insecticide resistance, persists regardless of the LLINs coverage value. Moreover, the same scenario holds, if the above conditions in (a)–(c) are satisfied, for the setting (with $h = 0.25$, but with 10% of the mosquitoes being exophilic (i.e., $f = 0.9$)) (Fig. 4a and b). This result supports the observational cohort study on the implication of insecticide resistance for the control of the malaria vector using LLINs reported in Kleinschmidt et al. (2018), where no relationship between laboratory-assessed insecticide resistance and malaria epidemiology was detected.

For the case where the parameter for the dominance of the resistant allele is moderate (i.e., $h = 0.5$) and mosquitoes are fully-endophilic ($f = 1$), this study show that insecticide resistance has no effect on malaria transmission if the probability of successfully taking a bloodmeal lies within the range $q_{m_{RR}}^{RR} > 0.6$ (Fig. 3c, d). Moreover, if 10% of the mosquitoes are now exophilic (i.e., $f = 0.9$) and the probability of successfully taking a bloodmeal is high **(e.g.,** $q_{m_{RR}}^{RR} > 0.7$), our simulations showed that insecticide resistance does not increase or decrease the daily new malaria cases (Fig. 4c and d). These results are also in agreement with the results reported in Kleinschmidt et al. (2018).

Finally, for the case where the dominant of the resistant allele is high (i.e., $h = 0.75$), mosquitoes are fully-endophilic ($f = 1$), and the probability of endophilic mosquitoes successfully taking a bloodmeal exceeds 60%, our simulations also showed that insecticide resistance has no effect on malaria transmission, regardless of the level of LLINs coverage (Fig. 3e and f). This result holds even if the mosquitoes are not fully-endophilic (e.g., even if $f = 0.9$) but $q_{m_{RR}}^{RR} > 0.6$, as depicted in Fig. 4e and f.

In conclusion, our simulation results showed that insecticide resistance in mosquitoes my increase, decrease or offer no effect on malaria transmission depending on the values or levels of the four key parameters identified in this study, namely the level of the dominance of the resistant allele in heterozygous mosquitoes (h), the LLINs coverage (C_B), the probability of successfully taking a bloodmeal ($q_{m_{in}}^{RR}$) and the proportion of new adult mosquitoes that are endophilic (f). In addition to the four identified parameters, the parameter associated with the repellance property of LLINs (r^i) also plays an important role in a fully-endophilic and exophilic settings (Fig. 6a–d). Our simulation showed that an increase in the repellance property of LLINs can cause an elimination in daily new malaria cases while widespread insecticide resistance in the community when LLINs at high coverage are used (Fig. 6a–d). *In summary, the answer to the key question in the malaria ecology community on whether insecticide resistance increases or reduces malaria transmission is both yes and no, depending on the values of the aforementioned identified four parameters and the parameter associated with the repellance property of the LLINs*. Hence, in order to fully quantify the impact of insecticide resistance (if any) on malaria transmission, it is important that laboratory experiments and field studies are conducted to generate the genotype-specific data that can be used to realistically estimate these parameters. Other fitness cost-related parameters, such as the modification parameter accounting for the assumed decrease in the mortality rate of the RR-genotype adult mosquitoes due to the insecticides, in comparison to vectors of SS-genotype (u), the probability of an i-genotype endophilic mosquito to be killed by the bednet upon contact (ρ_c^i), the probability of an exophilic i-genotype mosquito successfully taking a complete bloodmeal upon contact with host indoors or outdoors ($q_{m_{(in)}}^i$ or $q_{m_{(out)}}^i$, respectively), the production (birth) rate of new adult female mosquitoes of i-genotype (b_i) and the progression rate of exposed adult mosquitoes of i-genotype to infectious stage (σ_i), with $i = \{SS, RS, RR\}$, also need to be realistically estimated from laboratory experiments and field studies. Furthermore, some of the other limitations of our study include the simplifying assumption that mosquitoes are not repelled by the human host upon contact with the human host (i.e., we assumed that either mosquitoes successfully take a bloodmeal upon contact with the human host or are killed by the human host; but they are not directly repelled or physically diverted by the human host). We also assumed that the human hosts do not use insect repellents (i.e., in the formulation of our model, we limited mosquito repellance to be due to the bednet usage alone). In summary, our study showed that the prospect of achieving malaria eradication using currently-available insecticides is promising (despite widespread insecticide resistance in the mosquito population) provided optimal values of the aforementioned four key parameters identified in this study are chosen to lie within the dark blue regions in the $C_B - q_{m_{out}}^i$ parameter space, where malaria is eliminated (as measured by the associated reproduction number of the model being brought to, and maintained at, a value less than unity) and insecticide resistance is effectively managed.

Acknowledgements ABG acknowledges the support, in part, of the National Science Foundation (DMS-2052363). JM-A acknowledges the support, in part, of the National Science Foundation (DMS-2052355 (transferred to DMS-2221794)). The authors are grateful to the anonymous reviewers and the Handling Editor for their very constructive comments.

Appendices

Appendix A: Probability of endophilic mosquito of *i*-genotype encountering and successfully taking a bloodmeal from a protected human host indoors

Let $P^i_{(in)_p}(r^i, C_B, \rho^i_c)$ be the overall probability of an endophilic mosquito of i-genotype to successfully take a bloodmeal from a protected host indoors during either the first attempt or during the subsequent n attempts (with $n = 1, 2, \cdots$). It then follows from (2.9) that

$$P^i_{(in)_p}(r^i, C_B, \rho^i_c) = C_B(1-\rho^i_c)(1-r^i)q^i_{m_{(in)}}\left[\underbrace{1}_{\substack{\textbf{succeedsduring}\\ \textbf{firstattempt}}} + \sum_{n=1}^{\infty}[r^iC_B(1-\rho^i_c)]^n\right],$$

which can further be simplified to,

$$P^i_{(in)_p}(r^i, C_B, \rho^i_c) = \frac{C_B(1-\rho^i_c)(1-r^i)q^i_{m_{(in)}}}{1-r^iC_B(1-\rho^i_c)}, \tag{A.1}$$

from which (upon further simplification) it follows that,

$$\begin{aligned} P^i_{(in)_p}(r^i, C_B, \rho^i_c) &= \frac{C_B(1-\rho^i_c)(1-r^i)q^i_{m_{(in)}}}{1-r^iC_B(1-\rho^i_c)} \\ &= \left[\frac{C_B(1-\rho^i_c) - r^iC_B(1-\rho^i_c)}{1-r^iC_B(1-\rho^i_c)}\right] \times q^i_{m_{(in)}} \\ &\le \left[\frac{1-r^iC_B(1-\rho^i_c)}{1-r^iC_B(1-\rho^i_c)}\right] \times q^i_{m_{(in)}} \\ &= q^i_{m_{(in)}} \le 1, \end{aligned}$$

so that (as expected),

$$0 \le P^i_{(in)_p}(r^i, C_B, \rho^i_c) \le 1.$$

Appendix B: Probability of endophilic mosquito of *i*-genotype encountering and successfully taking a bloodmeal from unprotected hosts indoors

Let $P^i_{(in)_u}(r^i, C_B)$ represents the probability that an exophilic mosquito of i-genotype makes contact with, and successfully takes a bloodmeal from, an unprotected host indoors. There are two possibilities here. Either the mosquito first encounters an unprotected host (during first attempt) and successfully takes a bloodmeal (with probability $(1 - C_B)q^i_{m_{(in)}}$) or the mosquito makes n unsuccessful attempts to encounter a protected host and not be killed during the unsuccessful attempts (with probability $[r^i C_B(1 - \rho^i_c)]^n$) before finally encountering an unprotected host (with probability $(1 - C_B)[r^i C_B(1 - \rho^i_c)]^n$). Hence, the overall probability of an exophilic mosquito of i-genotype encountering, and successfully taking a bloodmeal, from an unprotected host indoors is given by:

$$\begin{aligned} P^i_{(in)_u}(r^i, C_B, \rho^i_c) = &\underbrace{(1 - C_B)}_{\substack{\textbf{proportion of}\\ \textbf{unprotected host indoors}}} \times \underbrace{q^i_{m_{(in)}}}_{\substack{\textbf{probability of successfully}\\ \textbf{taking a bloodmeal}}} \\ &+(1 - C_B)q^i_{m_{(in)}} \sum_{n=1}^{\infty} \overbrace{[r^i C_B(1 - \rho^i_c)]^n}^{\substack{\textbf{prob. of } n \textbf{ failed attempts to take}\\ \text{a bloodmeal from protected humans}\\ \textbf{and not killed during the } n \textbf{ failed attempts}}}, \end{aligned} \tag{B.1}$$

which can be simplified to,

$$P^i_{(in)_u}(r^i, C_B, \rho^i_c) = (1 - C_B)q^i_{m_{(in)}} \sum_{n=0}^{\infty}[r^i C_B(1 - \rho^i_c)]^n, \tag{B.2}$$

from which it follows that,

$$P^i_{(in)_u}(r^i, C_B, \rho^i_c) = \frac{(1 - C_B)q^i_{m_{(in)}}}{1 - r^i C_B(1 - \rho^i_c)}. \tag{B.3}$$

Furthermore, since $(1 - C_B) \leq (1 - r^i C_B(1 - \rho^i_c))$, and $q^i_{m_{(in)}} \leq 1$, it follows that $P^i_{(in)_u}(r^i, C_B, \rho^i_c) \leq 1$.

Appendix C: Total death rate of endophilic and exophilic mosquitoes

Let μ^i_M represent the natural death rate of adult mosquitoes of i-genotype (with $i = \{SS, RS, RR\}$). The probability for an endophilic mosquito of genotype-i to contact the bednet at the $(n + 1)^{\text{th}}$ attempt and killed by the insecticide embedded in the bednet is given by:

$$\underbrace{C_B}_{\substack{\textbf{targets protected}\\ \textbf{indoor host}}} \quad\times\quad \overbrace{[r^i C_B(1-\rho_c^i)]^n.}^{\substack{\textbf{prob. of } n \textbf{ failed attempts to take}\\ \textbf{abloodmeal from protected humans}\\ \textbf{and not killed during the } n \textbf{ failed attempts}}} \quad\times\quad \underbrace{\rho_c^i.}_{\substack{\textbf{Prob. of being killed by}\\ \textbf{the chemical insecticide upon}\\ \textbf{landing on the bednet}}}$$

Therefore, the overall probability for an endophilic mosquito of genotype-i to be killed by the bednet during its bloodmeal-questing period, denoted by $\rho^i_{(ins)}$, is given by ($i = \{SS, RS, RR\}$):

$$\rho^i_{(ins)} = \sum_{n=0}^{\infty} C_B \rho_c^i [r^i C_B(1-\rho_c^i)]^n = \frac{C_B \rho_c^i}{1 - r^i C_B(1-\rho_c^i)}. \tag{C.1}$$

The terms in (C.1) can be interpreted as follows (here, too, it can readily be seen that $0 \leq \rho^i_{(ins)} \leq 1$):

$$\rho^i_{(ins)} = \underbrace{\left(\frac{C_B}{1 - r^i C_B(1-\rho_c^i)}\right)}_{\substack{\textbf{Prob. of landing on}\\ \textbf{insecticide-treatedbednet}\\ \textbf{during the blood-questing period}}} \quad\times\quad \underbrace{\left(\rho_c^i\right)}_{\substack{\textbf{Prob. of being killed by}\\ \textbf{the chemical insecticide upon}\\ \textbf{landing on the bednet}}}. \tag{C.2}$$

Furthermore, endophilic mosquitoes of i-genotype are killed by protected humans with probability:

$$\begin{aligned} & C_B(1-\rho_c^i)(1-r^i)(1-q^i_{m_{(in)}}) \sum_{n=0}^{\infty} [r^i C_B(1-\rho_c^i)]^n \\ & = \frac{C_B(1-\rho_c^i)(1-r^i)(1-q^i_{m_{(in)}})}{1 - r^i C_B(1-\rho_c^i)}. \end{aligned} \tag{C.3}$$

Similarly, endophilic mosquitoes of i-genotype are killed by unprotected humans with probability:

$$(1-C_B)(1-q^i_{m_{(in)}}) \sum_{n=0}^{\infty} [r^i C_B(1-\rho_c^i)]^n = \frac{(1-C_B)(1-q^i_{m_{(in)}})}{1 - r^i C_B(1-\rho_c^i)}. \tag{C.4}$$

It is worth mentioning here that endophilic mosquitoes of i-genotype are killed by the protected as well as by the unprotected humans with probability $\left(1 - q^i_{m_{(in)}}\right)$ upon contact. Hence, the overall probability for an endophilic adult female mosquito of genotype-i to be killed by a human host indoors (during the duration of its bloodmeal questing period), denoted by $\rho^i_{H_{(in)}}$, is given by (obtained by adding the probabilities given by Equations (C.3) and (C.4)):

$$\rho^i_{H_{(in)}} = \left(\underbrace{\frac{C_B(1-\rho^i_c)(1-r^i)}{1-r^i C_B(1-\rho^i_c)}}_{\substack{\textbf{Prob. of contacting}\\ \textbf{a protected human during}\\ \textbf{the blood-questing period}}} + \underbrace{\frac{(1-C_B)}{1-r^i C_B(1-\rho^i_c)}}_{\substack{\textbf{Prob. of contacting}\\ \textbf{an unprotected human during}\\ \textbf{the blood-questing period}}} \right) \times \underbrace{\left(1-q^i_{m_{(in)}}\right)}_{\substack{\textbf{Prob. of being killed by}\\ \textbf{a human upon contact during}\\ \textbf{the blood-questing period}}}, \quad \text{(C.5)}$$

which can be further simplified to:

$$\rho^i_{H_{(in)}} = \left(1-q^i_{m_{(in)}}\right)\left(1-\frac{C_B\rho^i_c}{1-r^i C_B(1-\rho^i_c)}\right). \quad \text{(C.6)}$$

Here too, it can be easily shown that $0 \le \rho^i_{H_{(in)}} \le 1$.

Appendix D: Derivations of possible expressions for the frequency of the sensitive Allele (*S*) at the general disease-free equilibrium (q^*)

The various disease-free equilibria of the model {(2.29)–(2.31)}, described in Sect. 3, are expressed in terms of the steady-state value of the frequency of the sensitive allele (denoted by q^*). In this appendix, the possible expressions for q^* are derived for the model (with $N_V(0) > 0$). It is convenient to recall, first of all, the definitions of the quantities k_i (where $i = 1, 2, \cdots 17$), $\mathcal{R}^{(in)}_j$ and $\mathcal{R}^{(out)}_j$ (where $j = \{SS,\ RS,\ RR\}$) as defined in Equation (3.1) of Sect. 3. The model {(2.29)–(2.31)} has a general disease-free equilibrium (which takes the form $\mathcal{E}_{df}$, defined by Equation (3.2) in Sect. 3), where all the infected components (and, consequently, the recovered compartments) of the model are zero and

$$(S_{H_p})^* = \frac{C_B\Pi_H}{\mu_H} \text{ and } (S_{H_u})^* = \frac{(1-C_B)\Pi_H}{\mu_H}.$$

The allele frequencies for the sensitive (q^*) and resistant (p^*) alleles, at the general disease-free equilibrium ($\mathcal{E}_{df}$), are given, respectively, by:

$$q^* = \frac{\left[\left(S^{(in)}_{SS}\right)^* + \left(S^{(out)}_{SS}\right)^*\right] + \frac{1}{2}\left[\left(S^{(in)}_{RS}\right)^* + \left(S^{(out)}_{RS}\right)^*\right]}{N^*_V}, \quad \text{(D.1)}$$

and,

$$p^* = \frac{\left[\left(S_{RR}^{(in)}\right)^* + \left(S_{RR}^{(out)}\right)^*\right] + \frac{1}{2}\left[\left(S_{RS}^{(in)}\right)^* + \left(S_{RS}^{(out)}\right)^*\right]}{N_V^*}, \tag{D.2}$$

with,

$$N_V^* = \left(S_{SS}^{(in)}\right)^* + \left(S_{RS}^{(in)}\right)^* + \left(S_{RR}^{(in)}\right)^* + \left(S_{SS}^{(out)}\right)^* + \left(S_{RS}^{(out)}\right)^* + \left(S_{RR}^{(out)}\right)^*.$$

To find the expressions for the non-infected mosquito compartments of the model at the general disease-free equilibrium ($\mathcal{E}_{df}$), we set the right side of equations (2.29) & (2.30) zero and replace p^* by $(1 - q^*)$. Using (D.1) & (D.2) and through algebraic calculations, these equations (that correspond to the non-infected mosquito compartments of the model) are reduced into the following cubic polynomial equation in q^* (see also Mohammed-Awel and Gumel 2019):

$$\begin{aligned} q^*(q^* - 1)\Big[\Big\{ & f\left[\left(\mathcal{R}_{SS}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) + \left(\mathcal{R}_{RR}^{(in)} - \mathcal{R}_{RS}^{(in)}\right)\right] \\ & +(1-f)\left[\left(\mathcal{R}_{SS}^{(out)} - \mathcal{R}_{RS}^{(out)}\right) + \left(\mathcal{R}_{RR}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)\right]\Big\} q^* \\ & -\left(f\left(\mathcal{R}_{RR}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) + (1-f)\left(\mathcal{R}_{RR}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)\right)\Big] = 0. \end{aligned} \tag{D.3}$$

The result below follows from the possible solutions of (D.3) (see also Mohammed-Awel and Gumel 2019):

Lemma 1 *Consider the model* {(2.29)–(2.31)} *with* $N_V(0) > 0$. *It follows from the solution of* (D.3), *at the general disease-free equilibrium* ($\mathcal{E}_{df}$; *for the case with* $N_V(0) > 0$) *that* q^* *and* p^*, *given by* (D.1) *and* (D.2), *respectively, have the following possible solutions:*

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

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

(iii) $q^* = \dfrac{f\left(\mathcal{R}_{RR}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) + (1-f)\left(\mathcal{R}_{RR}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)}{f\left[\left(\mathcal{R}_{SS}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) + \left(\mathcal{R}_{RR}^{(in)} - \mathcal{R}_{RS}^{(in)}\right)\right] + (1-f)\left[\left(\mathcal{R}_{SS}^{(out)} - \mathcal{R}_{RS}^{(out)}\right) + \left(\mathcal{R}_{RR}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)\right]}$,
and,
$p^* = \dfrac{f\left(\mathcal{R}_{SS}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) + (1-f)\left(\mathcal{R}_{SS}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)}{f\left[\left(\mathcal{R}_{SS}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) + \left(\mathcal{R}_{RR}^{(in)} - \mathcal{R}_{RS}^{(in)}\right)\right] + (1-f)\left[\left(\mathcal{R}_{SS}^{(out)} - \mathcal{R}_{RS}^{(out)}\right) + \left(\mathcal{R}_{RR}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)\right]}$,
provided that $\left(\mathcal{R}_{SS}^{(in)} - \mathcal{R}_{RS}^{(in)}\right)\left(\mathcal{R}_{RR}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) \geq 0$ *and* $\left(\mathcal{R}_{SS}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)\left(\mathcal{R}_{RR}^{(out)} - \mathcal{R}_{RS}^{(out)}\right) > 0$ *or* $\left(\mathcal{R}_{SS}^{(in)} - \mathcal{R}_{RS}^{(in)}\right)\left(\mathcal{R}_{RR}^{(in)} - \mathcal{R}_{RS}^{(in)}\right) > 0$ *and* $\left(\mathcal{R}_{SS}^{(out)} - \mathcal{R}_{RS}^{(out)}\right)\left(\mathcal{R}_{RR}^{(out)} - \mathcal{R}_{RS}^{(out)}\right) \geq 0$

(iv) Any value q^*, p^* *in* $[0, 1]$, *with* $p^* + q^* = 1$, *if* $\mathcal{R}_{SS}^{(in)} = \mathcal{R}_{RS}^{(in)} = \mathcal{R}_{RR}^{(in)}$ *and* $\mathcal{R}_{SS}^{(out)} = \mathcal{R}_{RS}^{(out)} = \mathcal{R}_{RR}^{(out)}$.

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