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Assessing the impact of insecticide-treated nets in the face of insecticide resistance on malaria control

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ABSTRACT

The mosquito-borne disease, malaria, continues to impose a devastating health and economic burden worldwide. In malaria-endemic areas, insecticide-treated nets (ITNs) have been useful in curtailing the burden of the disease. However, mosquito resistance to insecticides, decay in ITN efficacy, net attrition, etc., undermine the effectiveness of ITNs in combatting malaria. In this study, mathematical models that account for asymptomatic infectious humans (through a partially immune class or a separate asymptomatic infectious class), insecticide resistance, and decay in ITN efficacy are proposed and analyzed. Analytical and numerical results of the models when ITN efficacy is constant show that there are parameter regimes for which a backward bifurcation occurs. Local and global sensitivity analyses are performed to identify parameters (some of which are potential targets for disease control) with the most significant influence on the control reproduction (R_c) and disease prevalence. These influential parameters include the maximum biting rate of resistant mosquitoes, ITN coverage, initial ITN efficacy against sensitive mosquitoes, the probability that an infectious mosquito (human) infects a susceptible human (mosquito), and the rate at which adult mosquitoes develop (lose) resistance to insecticides. Simulations of the models show that accounting for asymptomatic infectious humans through a separate class, or not accounting for the decay in ITN efficacy leads to an underestimation of disease burden. In particular, if the initial efficacy of ITNs against sensitive and resistance mosquitoes is 96%, the minimum ITN coverage required to reduce R_c below one (and hence, contain malaria) is approximately 11% (27%) lower when ITN efficacy is averaged (constant) for a model with a separate asymptomatic class. For the model with a partially immune class and decaying ITN efficacy, reducing R_c below one is impossible even if the entire populace uses ITNs. The study shows that replacing ITNs before their prescribed lifespans, or designing ITNs with longer lifespans is important for malaria control. Furthermore, the study shows that piperonyl butoxide (PBO) ITNs (which inhibit or reverse insecticide resistance) outperform regular ITNs in malaria control. Hence, prospects for effectively controlling malaria are enhanced by widespread use of high quality ITNs (e.g. PBO ITNs), especially if the useful lifespans of the ITNs are long enough and the ITNs are replaced before the end of their useful lifespans.

1. Introduction

Malaria continues to wreak havoc on human health and economies around the world, especially in sub-Saharan Africa (SSA) (World Health Organization, 2021; Gallup and Sachs, 2001; Sachs and Malaney, 2002). In 2020, it was implicated for about 241 million clinical illness episodes (representing a 6.2% increase from 2019) and 627,000 deaths (representing a 12.4% increase from 2019) worldwide (World Health Organization, 2021). Disruptions in malaria control programs caused by the 2019 coronavirus (COVID-19) pandemic accounted for an estimated 68% of the additional malaria-related deaths reported in 2020 (World Health Organization, 2021). These staggering figures suggest that the global gains in the fight against malaria and the progress made towards achieving the Global Technical Strategy (GTS) for malaria's goal of at least a 90% reduction in malaria incidence and mortality by 2030 are being reversed, especially in high-burden malaria countries.

Insecticide-treated nets (ITNs), i.e., long-lasting insecticidal nets (with an average lifespan of three years World Health Organization, 2011; World Health Organization et al., 2013) and natural nets that have been treated with insecticides have been instrumental in the fight against malaria (Lengeler, 2004a; Trape et al., 2011; Bhatt et al., 2015; Lindsay et al., 2021). In particular, ITNs have contributed in reducing the number of malaria cases by approximately 68% since 2000 (Bhatt et al., 2015). They shield those who sleep underneath

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them from mosquito-bites (by preventing mosquitoes from reaching them). Pyrethroids (i.e., the main insecticide that is commonly used on ITNs) can kill mosquitoes that come in contact with ITNs even at low doses. By killing adult mosquitoes (thereby limiting the available adult mosquito population), the protection received by individuals who sleep beneath ITNs within a community is extended to other members of the community, especially in communities with high ITN-use (Maxwell et al., 2002; Killeen and Smith, 2007). Also, high ITN-coverage can force mosquitoes that are unable to feed on humans to turn to other sources for blood meals (Takken and Verhulst, 2013; Iwashita et al., 2014; Stone and Gross, 2018). In 2020, 229 million ITNs were distributed to malaria-endemic nations, with approximately 91% going to SSA (World Health Organization, 2021). Furthermore, over 65% of SSA homes owned at least one ITN and approximately 43% of the population slept beneath an ITN in 2020 (World Health Organization, 2021). The protective efficacy of new ITNs is over 90%, but, this can fall below 70% over the effective lifespan of the ITNs and to about 50% for untreated nets or when all the insecticide in the net is lost (N'Guessan et al., 2007; Clarke et al., 2001). Although, ITNs have been embraced for malaria control and mitigation in many malaria endemic regions (owing to their cost-effectiveness and ease of use), their efficacy is threatened by several factors including decay in ITN efficacy, net attrition (Pulkki-Brännström et al., 2012; Briët et al., 2012; Diema et al., 2017), and mosquito resistance to insecticides used in ITNs (World Health Organization, 2013; Mawejje et al., 2013; Churcher et al., 2016; Ranson and Lissenden, 2016; Namias et al., 2021).

Resistance of mosquitoes to pyrethroid and other insecticides used in ITNs poses a significant problem to the long-term management and control of malaria (World Health Organization, 2013; Brogdon and McAllister, 1998.; Mawejje et al., 2013). According to the 2021 World Health Organization Report on Malaria, resistance to pyrethroids is widespread globally and nearly three-quarters of nations reporting resistance to pyrethroids experienced high intensity resistance in 2020 (World Health Organization, 2021). Resistance enables mosquitoes to evade or overcome vector control measures that rely on the use of insecticides. In particular, as the efficacy of ITNs decays, mosquitoes modify their behavior to evade the repelling and killing effect of pesticides used in the nets, thereby enhancing malaria transmission (Ngonghala et al., 2020). Decay in ITN efficacy, net attrition, mosquito resistance to insecticides, coupled with the decline in access to, and ITN-use in SSA since 2017 (World Health Organization, 2021) undermine the GTS and decade-long achievement in malaria control. This necessitates extensive research to have a better understanding of mosquito resistance to insecticides and to inform effective mosquito and insecticide resistance management strategies (Brooke, 2008; Namias et al., 2021). Synergists such as piperonyl-butoxide (PBO), which are combined with pyrethroids in the new pyrethroid-PBO nets are useful in managing insecticide resistance. Pyrethroid-PBO nets are designed to overcome pyrethroid-resistance and to improve the ability of ITNs to kill pyrethroid resistant mosquitoes. Hence, including PBO in ITNs improves their capability of killing resistant mosquitoes. Pyrethroid-PBO nets have been shown to lower malaria prevalence by reducing (increasing) mosquito blood feeding (mortality) in high pyrethroid resistant environments (Gleave et al., 2018; Martin et al., 2021). Exposure to synergists has been employed to boost the effectiveness of some insecticides (Bingham et al., 2011; Dadzie et al., 2017). Also, the use of pyrethroid-PBO nets has been able to restore insecticide susceptibility in mosquitoes in some countries (World Health Organization, 2021).

The impact of ITNs and the decay in ITN efficacy on the control of malaria have been assessed through mathematical models (Killeen et al., 2007; Chitnis et al., 2010; Okell et al., 2012b; Briët et al., 2012; Agusto et al., 2013; Ngonghala et al., 2014, 2016). Also, mathematical models to assess the effects of mosquito resistance to insecticides have been proposed and analyzed (Barbosa and Hastings, 2012; Birget and Koella, 2015; Barbosa et al., 2018; Mohammed-Awel et al., 2018, 2020; Ngonghala et al., 2020). Although there is overwhelming evidence of asymptomatic malaria transmission (i.e., transmission of the malaria disease by humans with malaria parasite burden, but who do not exhibit clinical symptoms of malaria) in different parts of the world (Bousema et al., 2004; Eke et al., 2006; Lindblade et al., 2013; Lopez-Perez et al., 2015; Sáenz et al., 2017; Tiono et al., 2014; Jiram et al., 2019; Chaumeau et al., 2019; Ramaswamy et al., 2020; Sumner et al., 2021), only few mathematical models have attempted to quantify the impact of asymptomatic infection on malaria spread and persistence through a separate asymptomatic human carrier class (e.g., Filipe et al. (2007) and Aguilar and Gutierrez (2020)). The existence of asymptomatic infectious humans complicates disease control efforts. Specifically, since asymptomatic infectious humans do not exhibit clinical symptoms of malaria and hence, cannot be detected through fever-based methods (Galatas et al., 2016; Ramaswamy et al., 2020), they serve as hidden reservoirs for malaria parasites that can be picked up my mosquitoes and conveyed to other humans. Hence, they are critical in the spread and persistence of malaria (Alves et al., 2002; Bousema et al., 2004; Eke et al., 2006; Lindblade et al., 2013; Dal-Bianco et al., 2007; Laishram et al., 2012). In particular, according to Lindblade et al. (2013), four to five times more asymptomatic than symptomatic malaria cases occur in malaria endemic regions. Also, Okell et al. (2012a), pointed out that subpatent cases (that are common in areas where malaria transmission is low) can account for up to half of all malaria transmissions. Thus, understanding the impact of asymptomatic infection on the dynamics of malaria in the face of decaying ITN efficacy and insecticide resistance is important for malaria control.

In this study, a mathematical model that accounts for asymptomatic infectious humans through a separate class, decay in ITN efficacy over time, and mosquito resistance to insecticides is proposed and analyzed rigorously. The model is used to assess the effects of (regular and PBO) ITNs, decay in ITN efficacy over time, disease transmission by asymptomatic infectious humans, and how mosquito resistance to insecticides affects malaria control efforts in endemic regions. Furthermore, the model is compared with one which fails to account for asymptomatic human transmission and one with partially immune individuals who transmit malaria, albeit a lower extent. To our knowledge, this is the first study that accounts for interactions between the decay in ITN efficacy over time and mosquito resistance to insecticides, as well as a separate asymptomatic infectious human class in a single framework.

2. The model with an infectious partially immune human class

In this section a susceptible–exposed–infectious–recovered – susceptible model for the dynamics of malaria that accounts for ITN-use as a control measure, mosquito resistance to insecticides, and a partially immune human class that contributes in disease transmission is proposed and studied. The model consists of an autonomous system of differential equations with no separate asymptomatic infectious class.

2.1. Model formulation

The human population is split into susceptible (S_h), exposed (E_h), infectious (I_h), and partially immune (R_h) classes, so that the total human population (N_h) is given by $N_h = S_h + E_h + I_h + R_h$. Partially immune humans are recovered individuals, who are protected from severe infection (e.g., through natural immunity acquired from repeated exposure to malaria), but not fully protected from mild infection and hence contribute in spreading malaria. The mosquito population is split into sensitive susceptible (S_s), resistant susceptible (S_r), sensitive exposed (E_s), resistant exposed (E_r), sensitive infectious (I_s), and resistant infectious (I_r) classes, so that the total mosquito population (N_v) is $N_v = S_s+E_s+I_s+S_r+E_r+I_r$. The flow-diagram of the model is presented

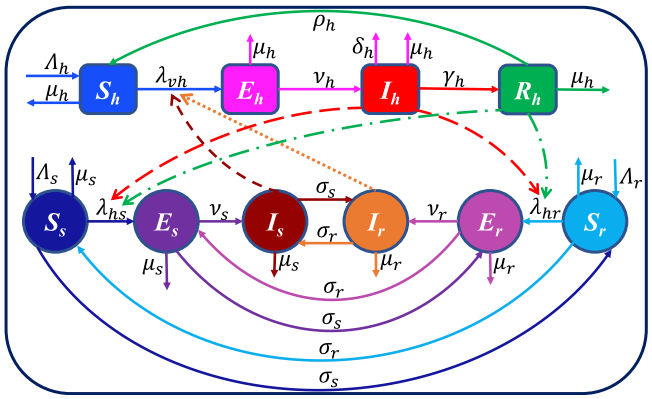

Fig. 1. Conceptual framework of the model depicting transitions of humans and mosquitoes between different epidemiological stages (solid lines) and interactions between humans and mosquitoes that result in infectious and partially immune humans infecting susceptible mosquitoes (long dashed and dash-dotted lines, respectively) and infectious sensitive and resistant mosquitoes infecting susceptible humans (short dashed and dotted lines, respectively). The human population is split into susceptible (S_h) exposed (E_h), infectious (I_h), and partially immune (R_h) compartments, while the mosquito population comprises susceptible sensitive and resistant (S_s and S_r), exposed sensitive and resistant (E_s and E_r), and infectious sensitive and resistant (I_s and I_r) compartments. The parameter $\Lambda_s = (1-\theta)\Lambda_v$ and $\Lambda_r = \theta\Lambda_v$. Descriptions of the parameters are presented in the text and in Table 1.

in Fig. 1. Using the schematics in Fig. 1, the variable descriptions, and the parameter descriptions in Table 1 yields the model:

$$\begin{aligned}
\dot{S}_h &= \Lambda_h + \rho_h R_h - (\lambda_{vh} + \mu_h)S_h,\\
\dot{E}_h &= \lambda_{vh} S_h - (\mu_h + \nu_h)E_h,\\
\dot{I}_h &= \nu_h E_h - (\delta_h + \mu_h + \gamma_h)I_h,\\
\dot{R}_h &= \gamma_h I_h - (\mu_h + \rho_h)R_h,\\
\dot{S}_s &= (1-\theta)\Lambda_v + \sigma_r S_r - (\lambda_{hs} + \sigma_s + \mu_s)S_s,\\
\dot{E}_s &= \lambda_{hs} S_s + \sigma_r E_r - (\sigma_s + \mu_s + \nu_s)E_s,\\
\dot{I}_s &= \nu_s E_s + \sigma_r I_r - (\sigma_s + \mu_s)I_s,\\
\dot{S}_r &= \theta\Lambda_v + \sigma_s S_s - (\lambda_{hr} + \sigma_r + \mu_r)S_r,\\
\dot{E}_r &= \lambda_{hr} S_r + \sigma_s E_s - (\sigma_r + \mu_r + \nu_r)E_r,\\
\dot{I}_r &= \nu_r E_r + \sigma_s I_s - (\sigma_r + \mu_r)I_r,
\end{aligned} \tag{2.1}$$

where $\Lambda_s = (1-\theta)\Lambda_v$, $\Lambda_r = \theta\Lambda_v$, and the dynamics of the total human and mosquito populations are given by:

$$\dot{N}_h = \Lambda_h - \mu_h N_h - \delta_h I_h, \quad \dot{N}_v = \Lambda_v - \mu_s(S_s + E_s + I_s) - \mu_r(S_r + E_r + I_r). \tag{2.2}$$

For notational convenience, we set

$$\begin{aligned}
&A_1 = \mu_h + \nu_h, A_2 = \delta_h + \mu_h + \gamma_h, A_3 = \mu_h + \rho_h, B_s = \sigma_s + \mu_s,\\
&\tilde{B}_s = B_s + \nu_s, B_r = \sigma_r + \mu_r, \tilde{B}_r = B_r + \nu_r.
\end{aligned} \tag{2.3}$$

The forces of infection (λ_{vh} and $\lambda_{hj}, j \in \{r,s\}$) are modeled as in Ngonghala et al. (2014, 2016, 2020), with the assumption that humans are bitten by sensitive and resistant mosquitoes at rates β_s and β_r, respectively, Wat'senga et al. (2018) and Fuseini et al. (2019). Thus,

$$\lambda_{vh} = \frac{p_{vh}(\beta_s I_s + \beta_r I_r)}{N_h} \quad \text{and} \quad \lambda_{hj} = \frac{p_{hv}\beta_j(I_h + \epsilon R_h)}{N_h}, \ j \in \{r,s\}, \tag{2.4}$$

where $\beta_j = \beta_{j1} - (\beta_{j1} - \beta_{j0})\epsilon_{\beta_j} b_0$ is the biting rate of resistant and sensitive mosquitoes, $0 \le b_0 \le 1$ is the ITN coverage (i.e., the fraction of persons who sleep under ITNs), $0 \le \epsilon_{\beta_j} \le 1$ is the personal protective efficacy of ITNs against sensitive and resistant mosquitoes, i.e., the potential of ITNs to shield humans underneath them from sensitive mosquito bites ($j = s$) or resistant mosquito bites ($j = r$). The parameters $p_{vh}, p_{hv}, \beta_{j1}, \beta_{j0}, j \in \{r,s\}$ are described in Table 1. It should be mentioned that the biting rate of mosquitoes is maximum (i.e., $\beta_j = \beta_{j1}$) if $b_0 = 0$ or $\epsilon_{\beta_j} = 0$ and minimum (i.e., $\beta_j = \beta_{j0}$) if $b_0 = 1$ and $\epsilon_\beta = 1$. As in Ngonghala et al. (2014, 2016), the mortality rates $\mu_j, j \in \{r,s\}$ are given by $\mu_j = \mu_{j0} + \mu_{j1}\epsilon_{\mu_j} b_0$, where $0 \le \epsilon_{\mu_j} \le 1$ is the sensitive ($j = s$) and resistant ($j = r$) mosquito killing efficacy of ITNs (i.e., the potential of ITNs to kill sensitive or resistant mosquitoes that land on them) and $\mu_{jk}, k \in \{0,1\}$ are as defined in Table 1. The mosquito death rate is minimum (i.e., $\mu_j = \mu_{j0}$) if $b_0 = 0$ or $\epsilon_{\mu_j} = 0$ and maximum (i.e., $\mu_j = \mu_{j0} + \mu_{j1}$) if $b_0 = 1$ and $\epsilon_{\mu_j} = 1$. For simplicity, we set $\epsilon_{\beta_j} = \epsilon_{\mu_j} = \epsilon_{j0}$, where ϵ_{j0} is constant in Sections 2 and 3.

2.2. Analytical results

In this section, we establish the well-posedness, positivity, and boundedness of solutions of the model system (2.1), compute the control reproduction number and hence the basic reproduction number, and establish the existence and stability of equilibrium points, as well as the existence of a sub-critical (backward) bifurcation.

2.2.1. Well-posedness, positivity, and boundedness of solutions

For a full description of the model (2.1), initial conditions of the form $X(0) = (S_h(0), E_h(0), I_h(0), R_h(0), S_s(0), E_s(0), I_s(0), S_r(0), E_r(0), I_r(0))$, where $N_h(0) = S_h(0) + E_h(0) + I_h(0) + R_h(0)$ and $N_v(0) = S_s(0) + E_s(0) + I_s(0) + S_r(0) + E_r(0) + I_r(0)$ must be prescribed in an epidemiologically-feasible region. Since the state variables (S_h, E_h, I_h, R_h, S_s, E_s, I_s, S_r, E_r, and I_r) represent human and mosquito populations, both the state variables and the corresponding initial conditions $X(0) = (S_h(0), E_h(0), I_h(0), R_h(0), S_s(0), E_s(0), I_s(0), S_r(0), E_r(0), I_r(0))$ are non-negative. Hence, with given initial conditions of the form $X(0)$ in the epidemiologically-feasible region:

$$\begin{aligned}
\Omega = \{(S_h, E_h, I_h, R_h, S_s, E_s, I_s, S_r, E_r, I_r) \in \mathbb{R}^{10}_+ : 0 \le S_h + E_h + I_h + R_h\\
\le \Lambda_h/\mu_h, 0 \le S_s + E_s + I_s + S_r + E_r + I_r \le \Lambda_v/\mu_v\},
\end{aligned}$$

where $\mu_v = min(\mu_s, \mu_r)$, it can be verified (using the approach in Ngonghala et al. (2020) and methods in Jordan and Smith (2007) and Agarwal and O'Regan (2008)) that the model (2.1) is mathematically well-posed within the epidemiologically feasible region (Ω). That is, it can be verified that the model (2.1) has a unique solution that satisfies the initial conditions $\forall t > 0$, and that $N_h(t) = 0$ ($N_v(t) = 0$) $\forall t$ if $N_h(0) = 0$ ($N_v(0) = 0$), and $N_h(t) > 0$ ($N_v(t) > 0$) $\forall t$ if $N_h(0) > 0$ ($N_v(0) > 0$).

Since the dynamics of the total human population is described by the equation $\dot{N}_h = \Lambda_h - \mu_h N_h - \delta_h I_h, \dot{N}_h \le \Lambda_h - \mu_h N_h$. Using an integrating factor or separating variables, we obtain: $N_h(t) \le \frac{\Lambda_h}{\mu_h} + \left(N_h(0) - \frac{\Lambda_h}{\mu_h}\right)e^{-\mu_h t}$, where $N_h(0)$ is the initial total human population. On the other hand, if $\mu_v = min(\mu_s, \mu_r)$, then the population dynamics of the total mosquito population described by the second equation of Eqs. (2.2) becomes: $\dot{N}_v \le \Lambda_v - \mu_v N_v$. Therefore, $N_v(t) \le \frac{\Lambda_v}{\mu_v} + \left(N_v(0) - \frac{\Lambda_v}{\mu_v}\right)e^{-\mu_v t}$, where $N_v(0)$ is the initial total mosquito population. Clearly, $N_h(t) \le \Lambda_h/\mu_h$ and $N_v(t) \le \Lambda_v/\mu_v$ as $t \to \infty$. Hence, the epidemiologically feasible region $\Omega = \{(S_h, E_h, I_h, R_h, S_s, E_s, I_s, S_r, E_r, I_r) \in \mathbb{R}^{10}_+ : 0 \le S_h + E_h + I_h + R_h \le \Lambda_h/\mu_h, 0 \le S_s + E_s + I_s + S_r + E_r + I_r \le \Lambda_v/\mu_v\}$ is positively invariant and attracting with respect to the model system (2.1). That is, any solution of Eqs. (2.1) with initial condition within Ω remains trapped within Ω for $t > 0$.

2.2.2. Disease-free equilibrium and the control reproduction number

The disease-free equilibrium (S_h^0, E_h^0, I_h^0, R_h^0, S_s^0, E_s^0, I_s^0, S_r^0, E_r^0, I_r^0), of the model (2.1), obtained by setting the left-hand sides (LHS) and the disease related variables of Eqs. (2.1) to zero is

$$(S_h^0, E_h^0, I_h^0, R_h^0, S_s^0, E_s^0, I_s^0, S_r^0, E_r^0, I_r^0) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, \frac{B_1}{B_3}, 0, 0, \frac{B_2}{B_3}, 0, 0\right), \tag{2.5}$$

where $B_1 = \Lambda_s B_r + \Lambda_r \sigma_r$, $B_2 = \Lambda_r B_s + \Lambda_s \sigma_s$, and $B_3 = B_s B_r - \sigma_r \sigma_s = \mu_r \mu_s + \mu_r \sigma_s + \mu_s \sigma_r$. Local asymptotic stability of the disease-free equilibrium is established using the next generation matrix operator, which doubles as the process for deriving the reproduction number

Table 1
Table of parameter values and ranges used for the simulations of System (2.1). The dimension H, D, and M represent human, day, and mosquito, respectively. Dimensions are enclosed in parentheses at the end of parameter descriptions and excluded for dimensionless parameters.

Parameter	Description of parameter (dimension)	Value	Range	Reference
Λ_h	Recruitment rate of humans (HD^{-1})	5.1×10^{-2}	$[3.65, 9.13]\times10^{-2}$	The world fact book (2022a)
μ_h	Human natural mortality rate (D^{-1})	4.1×10^{-5}	$[3.3, 5.5]\times10^{-5}$	The world fact book (2022b)
ν_h	Rate at which exposed humans become infectious (D^{-1})	7.1×10^{-2}	$[6.7, 20]\times10^{-2}$	Mehlhorn (2001) and Chitnis et al. (2008a)
γ_h	Recovery rate of infectious humans (D^{-1})	1.3×10^{-2}	$[1.4, 17]\times10^{-3}$	Kakkilaya (2022) and Chitnis et al. (2008a)
δ_h	Malaria-induced death rate for infectious humans (D^{-1})	9.0×10^{-5}	$[0, 4.1]\times10^{-4}$	Chitnis et al. (2008b)
ρ_h	Rate at which partially immune humans loss immunity (D^{-1})	8.3×10^{-3}	$[5.5, 1100]\times10^{-5}$	Ngonghala et al. (2014) and Chitnis et al. (2008a)
θ	Proportion reduction in sensitive mosquito recruitment due to resistance.	1.0×10^{-1}	$[0, 1]$	
Λ_v	Mosquito recruitment rate (MD^{-1})	83.3	$[0.333, 1.4]\times10^{3}$	Ngonghala et al. (2020)
ν_s	Rate at which exposed sensitive mosquitoes become infectious (D^{-1})	7.7×10^{-2}	$[2.9, 33]\times10^{-2}$	Macdonald et al. (1957) and Chitnis et al. (2008a)
ν_r	Rate at which exposed resistant mosquitoes become infectious (D^{-1})	7.7×10^{-2}	$[2.9, 33]\times10^{-2}$	Macdonald et al. (1957) and Chitnis et al. (2008a)
σ_s	Mutation rate of sensitive mosquitoes (D^{-1})	6.0×10^{-1}	$[0, 1]$	Teboh-Ewungkem et al. (2009)
σ_r	Mutation rate of resistant mosquitoes (D^{-1})	5.0×10^{-1}	$[0, 1]$	Wang and Zhao (2008a) and Chitnis et al. (2006)
μ_{r0}	Natural death rate of resistant mosquitoes (D^{-1})	2.5×10^{-2}	$[1.2, 14]\times10^{-2}$	Osoro et al. (2022), Davidson and Draper (1953) and Giles and Warrel (1993)
μ_{s0}	Natural death rate of sensitive mosquitoes (D^{-1})	3.3×10^{-2}	$[1.5, 14]\times10^{-2}$	Osoro et al. (2022), Davidson and Draper (1953) and Giles and Warrel (1993)
μ_{r1}	ITN death rate of resistant mosquitoes (D^{-1})	2.5×10^{-2}	$[1.2, 14]\times10^{-2}$	Osoro et al. (2022) and Lines et al. (1987)
μ_{s1}	ITN death rate of sensitive mosquitoes (D^{-1})	3.3×10^{-2}	$[1.5, 14]\times10^{-2}$	Osoro et al. (2022) and Lines et al. (1987)
p_{hv}	Human to mosquito transmission probability	4.8×10^{-1}	$[7.2, 64]\times10^{-2}$	Chitnis et al. (2008b), Boyd (1949), Smalley and Sinden (1977) and Nedelman (1984)
p_{vh}	Mosquito to human transmission probability	2.2×10^{-2}	$[1.0, 27]\times10^{-2}$	Chitnis et al. (2008b) and Nedelman (1985)
ϵ	Immune human to mosquito transmission probability modification factor	0.1	$[0, 1]$	Chitnis et al. (2008b)
β_{s1}	Maximum sensitive mosquito biting rate (D^{-1})	2.0×10^{-1}	$[0, 2]$	Molineaux et al. (1979), Chitnis et al. (2008b), Gupta et al. (1994) and Bhatt et al. (2015)
β_{r1}	Maximum resistant mosquito biting rate (D^{-1})	6.0×10^{-1}	$[0, 2]$	Molineaux et al. (1979), Chitnis et al. (2008b), Gupta et al. (1994) and Bhatt et al. (2015)
β_{s0}	Minimum sensitive mosquito biting rate (D^{-1})	1.0×10^{-2}	$[1.0, 100]\times10^{-3}$	Mwangangi et al. (2013)
β_{r0}	Minimum resistant mosquito biting rate (D^{-1})	3.0×10^{-2}	$[1.0, 100]\times10^{-3}$	Mwangangi et al. (2013)
b_0	ITN coverage, i.e., the proportion of humans who are protected from mosquito-bites by ITNs	4.3×10^{-1} Varies	$[1.0, 100]\times10^{-2}$ $[1.0, 100]\times10^{-2}$	World Health Organization (2021) World Health Organization (2021)
ε_{s0}	Efficacy of ITNs against sensitive mosquitoes	Varies	$[1.0, 100]\times10^{-2}$	N'Guessan et al. (2007)
ε_{r0}	Efficacy of ITNs against resistant mosquitoes	Varies	$[1.0, 100]\times10^{-2}$	
p	Modification factor the efficacy ε_{r0}	0.5	$[0, 1]$	N'Guessan et al. (2007)
T	Useful life of ITNs	3×365	$[0.5, 3]\times365$	World Health Organization (2011) and Pulkki-Brännström et al. (2012)

of the model (2.1) (Diekmann et al., 1990; Driessche and Watmough, 2002). The matrices of new infections ($\mathscr{F}$) and transitions ($\mathscr{V}$), and the next generation matrix ($\mathscr{F}\mathscr{V}^{-1}$) are given in Section S1.1 of the online supplementary information (SI). If we set $B_4 = (\sigma_r+\mu_r+\nu_r)(\mu_s+\nu_s)+\sigma_s(\mu_r+\nu_r)$, $B_5 = (B_r\nu_s+\tilde{B}_s\nu_r)\sigma_r$, $B_6 = (B_s\nu_r+\tilde{B}_r\nu_s)\sigma_s$, $B_7 = B_r\tilde{B}_r\nu_s+\nu_r\sigma_r\sigma_s$, $B_8 = B_s\tilde{B}_s\nu_r+\nu_s\sigma_s\sigma_r$, $B_0 = \beta_s^2B_1B_7+\beta_r^2B_2B_8+\beta_r\beta_s(B_1B_6+B_2B_5)$, $\beta_j = \beta_{j1}-(\beta_{j1}-\beta_{j0})\epsilon_{j0}b_0$, and $\mu_j = \mu_{j0}+\mu_{j1}\epsilon_{j0}b_0, j\in\{r,s\}$, then the control reproduction number of the model (2.1), i.e., the spectral radius of the next generation matrix ($\mathscr{F}\mathscr{V}^{-1}$) is:

$$R_c = \sqrt{\frac{p_{hv}p_{vh}\mu_h\nu_hB_0(A_3+\epsilon\gamma_h)}{\Lambda_hA_1A_2A_3B_3^2B_4}}. \tag{2.6}$$

The control reproduction number (R_c) quantifies the average number of new malaria cases created by an infectious individual in a population in which a portion of the humans is protected by ITNs. It becomes the basic reproduction number (R_0) in the absence of ITN-usage (i.e., when $b_0 = 0$) and other malaria control and mitigation measures. In particular, if $b_0 = 0$, then $\beta_j = \beta_{j1}, \mu_j = \mu_{j0}$, $B_0 = \beta_{s1}^2B_1B_7+\beta_{r1}^2B_2B_8+\beta_{r1}\beta_{s1}(B_1B_6+B_2B_5)$, and $B_j = \sigma_j+\mu_{j0}, j\in\{r,s\}$. The following result is derived from Theorem 2 of Driessche and Watmough (2002):

Theorem 2.1. *The disease-free equilibrium of the model system given by Eqs. (2.1) is locally-asymptotically stable if the reproduction number (R_c) is less than one and unstable if the reproduction number is greater than one.*

According to Theorem 2.1, a slight increase in malaria cases will not result in malaria establishing itself in a community provided R_c is kept below unity and there is no backward (sub-critical) bifurcation.

2.2.3. Endemic equilibria and backward bifurcation

Endemic equilibria of the model (2.1) are obtained by setting the LHS of the system to zero and solving for each of the variables in terms of equilibrium values λ_{vh}^* and λ_{hj}^*, of the forces of infection λ_{vh} and λ_{hj}:

$$\begin{aligned}
S_h^* &= \frac{\Lambda_hA_1A_2A_3}{\mu_hA_1A_2A_3+A_4\lambda_{vh}^*}, E_h^* = \frac{\Lambda_hA_2A_3\lambda_{vh}^*}{\mu_hA_1A_2A_3+A_4\lambda_{vh}^*}, I_h^* = \frac{\Lambda_h\nu_hA_3\lambda_{vh}^*}{\mu_hA_1A_2A_3+A_4\lambda_{vh}^*},\\
R_h^* &= \frac{\Lambda_h\gamma_h\nu_h\lambda_{vh}^*}{\mu_hA_1A_2A_3+A_4\lambda_{vh}^*}, N_h^* = S_h^*+E_h^*+I_h^*+R_h^* = \frac{\Lambda_h(A_1A_2A_3+A_5\lambda_{vh}^*)}{\mu_hA_1A_2A_3+A_4\lambda_{vh}^*},\\
S_s^* &= \frac{B_1+\Lambda_s\lambda_{hr}^*}{B_3+B_s\lambda_{hr}^*+(B_r+\lambda_{hr}^*)\lambda_{hs}^*}, E_s^* = \frac{\sigma_rB_2\lambda_{hr}^*+(B_1\tilde{B}_r+B_9\lambda_{hr}^*)\lambda_{hs}^*}{B_4\left[B_3+B_s\lambda_{hr}^*+(B_r+\lambda_{hr}^*)\lambda_{hs}^*\right]},\\
I_s^* &= \frac{B_2B_5\lambda_{hr}^*+(B_1B_7+B_{11}\lambda_{hr}^*)\lambda_{hs}^*}{B_3B_4\left[B_3+B_s\lambda_{hr}^*+(B_r+\lambda_{hr}^*)\lambda_{hs}^*\right]}, S_r^* = \frac{B_2+\Lambda_r\lambda_{hs}^*}{B_3+B_s\lambda_{hr}^*+(B_r+\lambda_{hr}^*)\lambda_{hs}^*},\\
E_r^* &= \frac{\sigma_sB_1\lambda_{hs}^*+(B_2\tilde{B}_s+B_{10}\lambda_{hs}^*)\lambda_{hr}^*}{B_4\left[B_3+B_s\lambda_{hr}^*+(B_r+\lambda_{hr}^*)\lambda_{hs}^*\right]}, I_r^* = \frac{B_1B_6\lambda_{hs}^*+(B_2B_8+B_{12}\lambda_{hs}^*)\lambda_{hr}^*}{B_3B_4\left[B_3+B_s\lambda_{hr}^*+(B_r+\lambda_{hr}^*)\lambda_{hs}^*\right]},
\end{aligned} \tag{2.7}$$

where $A_4 = A_1A_2A_3-\nu_h\rho_h\gamma_h = \mu_h(\rho_h+A_1)A_2+\nu_h\rho_h(\delta_h+\mu_h)$, $A_5 = A_2A_3+\nu_h(\gamma_h+A_3)$, $B_9 = \tilde{B}_r\Lambda_s+\Lambda_r\sigma_r$, $B_{10} = \tilde{B}_s\Lambda_r+\Lambda_s\sigma_s$, $B_{11} = \nu_sB_rB_9+\nu_r\sigma_rB_{10}$, and $B_{12} = \nu_rB_sB_{10}+\nu_s\sigma_sB_9$. Replacing I_h, I_s, I_r, and N_h in the forces of infection λ_{vh} and $\lambda_{hj}, j\in\{r,s\}$ by $I_h^*, I_s^*, I_r^*, N_h^*$ from (2.7) leads to:

$$\lambda_{hj}^* = \beta_jp_{hv}\left(\frac{I_h^*+\epsilon R_h^*}{N_h^*}\right) = \frac{\beta_jp_{hv}\nu_h(A_3+\epsilon\gamma_h)\lambda_{vh}^*}{A_1A_2A_3+A_5\lambda_{vh}^*}, j\in\{s,r\}, \tag{2.8}$$

$$
\begin{aligned}
C_2 &= \frac{A_1A_2A_3\left\{\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)\left[\beta_r\beta_s\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)+2A_5\left(\beta_s B_r+\beta_r B_s\right)\right]+3A_5^2B_3\right\}}{A_5\left\{\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)\left[\beta_r\beta_s\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)+A_5\left(\beta_s B_r+\beta_r B_s\right)\right]+A_5^2B_3\right\}}(1-\mathscr{R}_2)\\
C_1 &= \frac{(A_1A_2A_3)^2\left(\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)\left(\beta_s B_r+\beta_r B_s\right)+3A_5B_3\right)}{A_5\left\{\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)\left[\beta_r\beta_s\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)+A_5\left(\beta_s B_r+\beta_r B_s\right)\right]+A_5^2B_3\right\}}(1-\mathscr{R}_1)\\
C_0 &= \frac{(A_1A_2A_3)^3B_3}{A_5\left\{\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)\left[\beta_r\beta_s\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)+A_5\left(\beta_s B_r+\beta_r B_s\right)\right]+A_5^2B_3\right\}}(1-R_c^2),\\
\mathscr{R}_2 &= \frac{p_{vh}\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)A_4\left[\beta_r\beta_s\left(\beta_s B_{11}+\beta_r B_{12}\right)\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)+A_5B_0\right]}{\Lambda_hA_1A_2A_3B_3B_4\left\{\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)\left[\beta_r\beta_s\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)+2A_5\left(\beta_s B_r+\beta_r B_s\right)\right]+3A_5^2B_3\right\}},\\
\mathscr{R}_1 &= \frac{p_{vh}\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)\left[\beta_r\beta_s\left(\beta_s B_{11}+\beta_r B_{12}\right)\mu_h\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)+\left(A_5\mu_h+A_4\right)B_0\right]}{\Lambda_hA_1A_2A_3B_3B_4\left[\nu_h p_{hv}\left(A_3+\epsilon\gamma_h\right)\left(\beta_s B_r+\beta_r B_s\right)+3A_5B_3\right]},
\end{aligned}
\tag{2.10}
$$

Box I.

$$
\begin{aligned}
\lambda_{vh}^* &= p_{vh}\left(\frac{\beta_s I_s^*+\beta_r I_r^*}{N_h^*}\right)=p_{vh}\frac{1}{N_h^*}\left(\beta_s I_s^*+\beta_r I_r^*\right)\\
&= p_{vh}\frac{\left(\mu_hA_1A_2A_3+A_4\lambda_{vh}^*\right)}{\Lambda_h\left(A_1A_2A_3+A_5\lambda_{vh}^*\right)}\times\left\{\frac{\beta_s\left[B_2B_5\lambda_{hr}^*+\left(B_1B_7+B_{11}\lambda_{hr}^*\right)\lambda_{hs}^*\right]}{B_3B_4\left[B_3+B_s\lambda_{hr}^*+\left(B_r+\lambda_{hr}^*\right)\lambda_{hs}^*\right]}\right.\\
&\quad\left.+\frac{\beta_r\left[B_1B_6\lambda_{hs}^*+\left(B_2B_8+B_{12}\lambda_{hs}^*\right)\lambda_{hr}^*\right]}{B_3B_4\left[B_3+B_s\lambda_{hr}^*+\left(B_r+\lambda_{hr}^*\right)\lambda_{hs}^*\right]}\right\}.
\end{aligned}
\tag{2.9}
$$

Substituting $\lambda_{hj}^*, j\in\{r,s\}$ from Eq. (2.8) into Eq. (2.9) and collecting terms in powers of λ_{vh}^* results in

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

where C_0, C_1, and C_2 are given in Box I. This leads to $\lambda_{vh}^*=0$ (which corresponds to the disease-free equilibrium case), or the cubic equation

$$\lambda_{vh}^{*3}+C_2\lambda_{vh}^{*2}+C_1\lambda_{vh}^*+C_0=0, \tag{2.11}$$

with the coefficients $(C_n, n=0,1,2)$ and the thresholds $(\mathscr{R}_n, n=1,2)$ given by Eqs. (2.10) in Box I. It should be noted that $\lambda_{vh}^*=0$ leads to an unstable disease-free equilibrium solution when $R_c>1$. The possibility of zero, one, or multiple endemic equilibria can be investigated by solving the cubic Eq. (2.11) or by studying the signs of its coefficients using Descartes Rule of Signs. It should be mentioned that the signs of C_0 and $C_n, n\in\{1,2\}$ are determined by the signs of $1-R_c$ and $1-\mathscr{R}_n$, respectively. Specifically, $C_n>(\leq)\,0$ if $\mathscr{R}_n<(\geq)\,1$ and $C_0>(\leq)\,0$ if $R_c<(\geq)\,1$. Hence, the cubic Eq. (2.11) yields the following result:

Theorem 2.2. *Let $C_n, n\in\{0,1,2\}$ be coefficients of the polynomial equation (2.11). Then the model (2.1) has*

(a) *no endemic equilibrium if $C_0\geq 0, C_1\geq 0$, and $C_2\geq 0$;*

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

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

Theorem 2.2(c) indicates that it might be possible for the model (2.1) to have two endemic equilibria when $R_c<1$. This suggests that there is a parameter regime for which the model might exhibit a backward bifurcation (a phenomenon governed by the co-existence of a stable disease-free and a stable endemic equilibrium when $R_c<1$) (Dushoff et al., 1998; Castillo-Chavez and Song, 2004; Gumel, 2012). The Center manifold theory can be used to prove the existence of a backward bifurcation rigorously (Castillo-Chavez and Song, 2004; Gumel, 2012; van den Driessche and Watmough, 2000). The existence of a backward bifurcation implies that although the condition $R_c<1$ is necessary, it is not sufficient for disease elimination (i.e., for reducing the number of malaria cases significantly to essentially very few or no case). Disease elimination in a backward bifurcation scenario is characterized by the initial population size and a second threshold denoted by R_c^{bb}, which is less than R_c. Specifically, in models with backward bifurcations, reducing the control reproduction number slightly below one might not be sufficient for disease elimination (as is the case for models with no backward bifurcations). For disease elimination to be possible in a model with a backward bifurcation, control measures must be applied and sustained until R_c falls below R_c^{bb} (i.e., within the region in which the disease-free equilibrium is globally asymptotically stable).

2.3. Numerical simulation results

The model (2.1) is simulated using the baseline parameter values in Table 1 together with different values of the disease-induced mortality rate (δ_h) to assess the existence of a trans-critical (forward) and a sub-critical (backward) bifurcation. The results obtained, depicted in Fig. 2(a) show a forward bifurcation when the disease-induced mortality rate (δ_h) is smaller than the natural mortality rate (μ_h), i.e., when

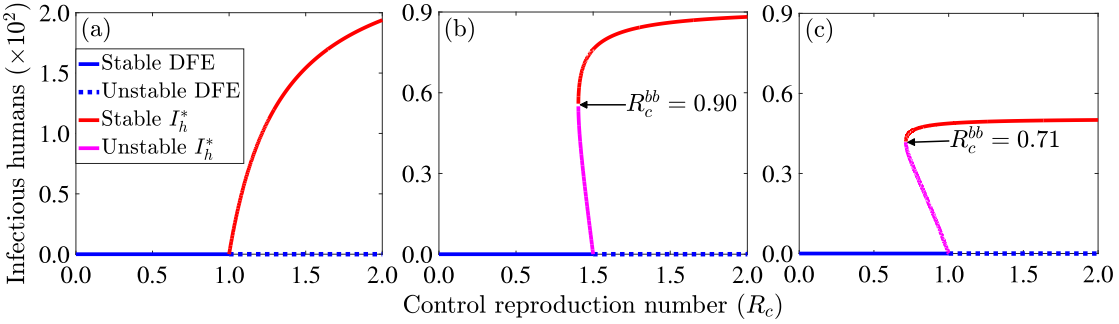

Fig. 2. Simulations of the model (2.1) illustrating: (a) a forward bifurcation when the disease-induced mortality rate $\delta_h=9.0\times10^{-5}<4.1\times10^{-5}=\mu_h$, and a backward bifurcation for (b) $\delta_h=4.5\times10^{-4}>4.1\times10^{-5}=\mu_h$ and (c) $\delta_h=9.0\times10^{-4}$. The other parameters used for the simulations are presented in Table 1.

$\delta_h = 9.0 \times 10^{-5} < 4.1 \times 10^{-5} = \mu_h$. In this case, there is a globally asymptotically stable disease-free equilibrium when the control reproduction number (R_c) is less than unity and a unique stable endemic equilibrium when $R_c > 1$. More simulation results of the model (2.1) for different ITN coverages (b_0) and initial ITN efficacies against sensitive and resistant mosquitoes (ε_{s0} and ε_{r0}, respectively) that confirm the forward bifurcation scenario and highlight the importance of high usage of highly effective ITNs in the fight against malaria and the impact of other parameters on malaria dynamics are presented in Figs. S1–S2 of the SI. Fig. 2(b)–(c) depict backward bifurcation plots of the model (2.1) when the disease-induced mortality rate is smaller than the natural mortality rate. In this backward bifurcation case, the control reproduction number is less than one and the value of the backward bifurcation threshold quantity R_c^{bb} is 0.90 when $\delta_h = 4.5 \times 10^{-4} > 4.1 \times 10^{-5} = \mu_h$ (Fig. 2(b)). In particular, there is a globally asymptotically stable disease-free equilibrium when $R_c < R_c^{bb}$ and a locally stable disease-free equilibrium co-exists with a locally stable endemic equilibrium when $R_c^{bb} \leq R_c < 1$ (backward bifurcation region). Thus, intervention efforts must be maintained until $R_c < R_c^{bb} = 0.90$. This corresponds to an ITN coverage of ≈88%. If $\delta_h = 9.0 \times 10^{-4}$, this threshold reduces to about $R_c^{bb} = 0.71$, which corresponds to an ITN coverage that is greater than 100% (Fig. 2(c)). For this case, ITNs alone are not enough to contain the disease, even if everyone in the community uses them (see Fig. 2).

3. The model with a separate asymptomatic human carrier class

3.1. Model formulation

In this Section, the model formulated and analyzed in Section 2 will be modified to include a separate asymptomatic human infectious class denoted by I_{ah} and a partially immune class (R_h) that does not contribute to disease transmission. The asymptomatically infectious class consists of (infectious) humans with malaria parasite burden, who do not exhibit clinical symptoms of malaria at the end of the incubation period, and who have not recovered from infection yet. Here, a proportion (m) of exposed humans progress to the symptomatic infectious class (I_{sh}), while the remaining proportion $(1-m)$ progress to the asymptomatic infectious class. Symptomatic (asymptomatic) infectious humans develop immunity at rate γ_{sh} (γ_{ah}). The total mosquito population remains the same, while the total human population is given by $N_h = S_h + E_h + I_{sh} + I_{ah} + R_h$. The force of infection $\lambda_{hj}, j \in \{r, s\}$ of the modified model is given by $\lambda_{hj} = \beta_j p_{hv}(I_{sh} + \epsilon I_{ah})/N_h$, where ϵ is a modification parameter representing the fact that asymptomatic infectious humans are less transmissible. The other functional forms are as defined in Section 2 and the other parameters are as defined in Table 1. Schematics of the modified model are presented in Fig. 3.

The modified model is given by the system of equations:

$$
\begin{aligned}
\dot{S}_h &= \Lambda_h + \rho_h R_h - (\lambda_{vh} + \mu_h) S_h,\\
\dot{E}_h &= \lambda_{vh} S_h - (\mu_h + \nu_h) E_h,\\
\dot{I}_{sh} &= m\nu_h E_h - (\delta_h + \gamma_{sh} + \mu_h) I_{sh},\\
\dot{I}_{ah} &= (1-m)\nu_h E_h - (\gamma_{ah} + \mu_h) I_{ah},\\
\dot{R}_h &= \gamma_{sh} I_{sh} + \gamma_{ah} I_{ah} - (\mu_h + \rho_h) R_h,\\
\dot{S}_s &= (1-\theta)\Lambda_v + \sigma_r S_r - (\lambda_{hs} + \sigma_s + \mu_s) S_s,\\
\dot{E}_s &= \lambda_{hs} S_s + \sigma_r E_r - (\sigma_s + \mu_s + \nu_s) E_s,\\
\dot{I}_s &= \nu_s E_s + \sigma_r I_r - (\sigma_s + \mu_s) I_s,\\
\dot{S}_r &= \theta\Lambda_v + \sigma_s S_s - (\lambda_{hr} + \sigma_r + \mu_r) S_r,\\
\dot{E}_r &= \lambda_{hr} S_r + \sigma_s E_s - (\sigma_r + \mu_r + \nu_r) E_r,\\
\dot{I}_r &= \nu_r E_r + \sigma_s I_s - (\sigma_r + \mu_r) I_r,
\end{aligned}
\tag{3.1}
$$

where $A_s = \delta_h + \gamma_{sh} + \mu_h$, $A_a = \gamma_{ah} + \mu_h$ and A_1, A_3, B_j, and $\tilde{B}_j, j \in \{r, s\}$ are as defined in Eq. (2.3).

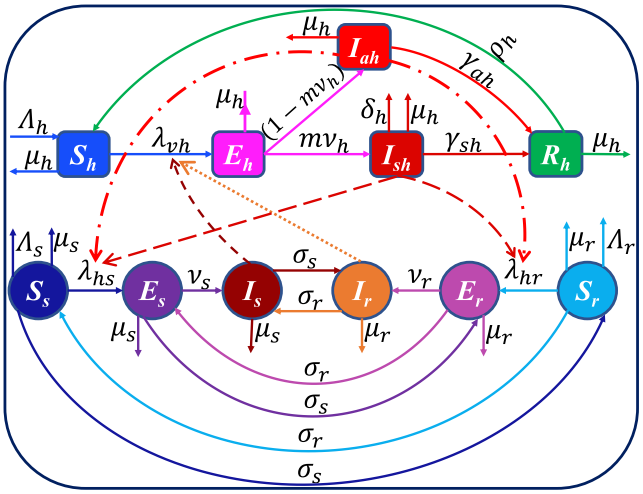

Fig. 3. Schematics of the model depicting transitions of humans and mosquitoes between epidemiological stages (solid lines) and interactions between humans and mosquitoes that result in asymptomatic and symptomatic infectious humans infecting susceptible mosquitoes (long dashed and dash-dotted lines, respectively) and infectious sensitive and resistant mosquitoes infecting susceptible humans (short dashed and dotted lines, respectively).

3.2. Analytical results

It can easily be verified as in Section 2 that the modified model system (3.1) is well-posed within the region

$$
\begin{aligned}
\Omega = \{(S_h, E_h, I_{sh}, I_{ah}, R_h, S_s, E_s, I_s, S_r, E_r, I_r) \in \mathbb{R}_+^{11} : 0 \leq S_h + E_h + I_{sh}\\
+ I_{ah} + R_h \leq \Lambda_h/\mu_h, 0 \leq S_s + E_s + I_s + S_r + E_r + I_r \leq \Lambda_v/\mu_v\},
\end{aligned}
$$

where $\mu_v = min(\mu_s, \mu_r)$ and that this epidemiologically feasible region is positively invariant and attracting with respect to the model (3.1). That is, solutions of (3.1) originating from Ω are trapped in Ω for $t > 0$.

The disease-free equilibrium of the modified model (3.1) is the same as that of the model (2.1) (i.e., Eq. (2.5)), but the reproduction numbers are different. In particular, the reproduction number of Eqs. (3.1) is a function of the proportion of exposed humans who become symptomatically infectious at the end of the incubation period (m). Additionally, the reproduction number of the model (3.1) depends on the parameter groupings $A_s = \delta_h + \gamma_{sh} + \mu_h$ and $A_a = \gamma_{ah} + \mu_h$, since the infectious human class of the model (2.1) is now split into symptomatic and asymptomatic infectious classes, with different recovery rates (γ_{sh} and γ_{ah}). Following the next generation operator approach (see Section S2.1 of the SI for details), the reproduction number of the model (3.1) is

$$
R_c = \sqrt{\frac{p_{hv} p_{vh} \mu_h \nu_h B_0 \left[m A_a + (1-m)\varepsilon A_s\right]}{\Lambda_h A_1 A_a A_s B_3^2 B_4}}. \tag{3.2}
$$

Theorem 3.1 on the stability of the disease-free equilibrium of Eqs. (3.1) follows directly from Theorem 2 in Driessche and Watmough (2002).

Theorem 3.1. *The disease-free equilibrium of the model system given by Eqs. (3.1) is locally-asymptotically stable if $R_c < 1$ and unstable if $R_c > 1$.*

Following the approach in Section 2.2.3, endemic equilibrium values of each of the state variables can be expressed in terms of λ_{vh}^* and $\lambda_{hj}^*, j \in \{r, s\}$, i.e., the equilibrium values of the forces of infection λ_{vh} and λ_{hj}. Using the functional forms of the modified forces of infection leads to a cubic polynomial equation $\lambda_{vh}^{*3} + C_2\lambda_{vh}^{*2} + C_1\lambda_{vh}^* + C_0 = 0$ (see Section S2.2 of the SI for the coefficients $C_n, n \in \{0, 1, 2\}$) that can be used to determine the possible number of endemic equilibria of the modified model (3.1). This analysis leads to the following theorem:

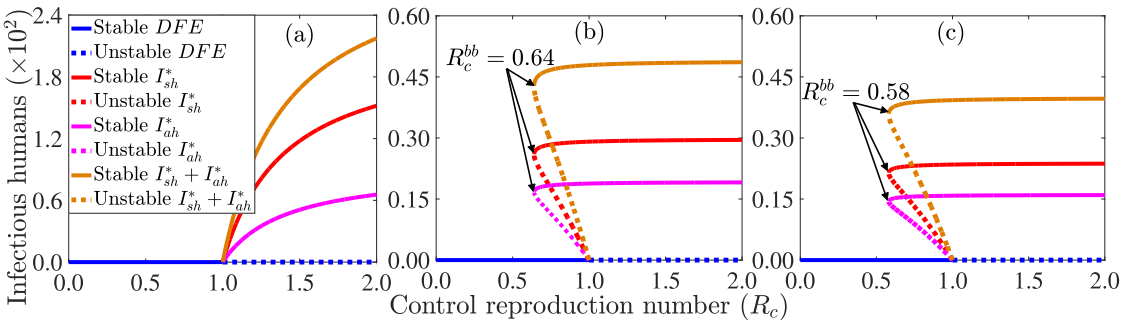

Fig. 4. Simulations of the model (3.1) showing a: (a) forward bifurcation when the recovery rate of asymptomatic infectious humans (γ_{ah}) is 1/80, and a backward bifurcation for (b) $\gamma_{ah}=1/120, \delta_h=9.0\times10^{-5}$ and (c) $\gamma_{ah}=1/120, \delta_h=6.3\times10^{-4}$, where δ_h is the malaria-induced mortality rate. The magenta and red curves represent the equilibrium populations of the asymptomatic infectious (I_{ah}) and the symptomatic infectious (I_{sh}) classes, respectively. The other parameters used for the simulations are presented in Table 1.

Theorem 3.2. *Let $C_n, n \in \{0,1,2\}$ be coefficients of the polynomial Eq. (2.11). Then the model (3.1) has*

(a) *no endemic equilibrium if $C_0 \geq 0, C_1 \geq 0$, and $C_2 \geq 0$;*
(b) *a unique endemic equilibrium if $C_0 < 0, C_1 \geq 0$, and $C_2 \geq 0$, or $C_0 \leq 0, C_1 < 0$, and $C_2 \geq 0$, or $C_0 \leq 0, C_1 \leq 0$, and $C_2 \leq 0$;*
(c) *zero or two possible endemic equilibria if $C_0 \geq 0, C_1 > 0$ and $C_2 < 0$, or $C_0 > 0, C_1 < 0$ and $C_2 \geq 0$, or $C_0 > 0, C_1 \leq 0$ and $C_2 < 0$.*

The case of a unique endemic equilibrium in Theorem 3.2(b) is illustrated in Fig. 4(a) and Fig. S3 of the SI, while the case of a backward bifurcation in Theorem 3.2(c) is illustrated in Fig. 4(b)–(c).

3.3. Numerical simulation results

In this section, simulations of the model (3.1) to assess the impact of malaria intervention measures such as ITNs, the impact of mosquito resistance to insecticides, the impact of asymptomatic transmission, etc., will be performed. Unless otherwise specified, simulations will be performed using the baseline parameter values in Table 1.

3.3.1. Forward versus backward bifurcations

The model (3.1) is simulated to assess the possibility of a forward and a backward bifurcation. The results show that the model exhibits a forward bifurcation when the recovery rate of asymptomatic infectious humans (γ_{ah}) is 1/80 (Fig. 4(a)). In this case, $R_c > 1$. The model exhibits a backward bifurcation when $\gamma_{ah}=1/120, \delta_h=9.0\times10^{-5}$ (Fig. 4(b)) and $\gamma_{ah}=1/120, \delta_h=4.5\times10^{-4}$ (Fig. 4(c)). In this backward bifurcation case, $R_c < 1$ and the backward bifurcation threshold (R_c^{bb}) is 0.64 for Fig. 4(b), which corresponds to an ITN coverage level of ≈95%, and 0.58 for Fig. 4(c). This corresponds to an ITN coverage level of >100%. To contain the disease, control efforts must be sustained until $R_c < R_c^{bb}$. Achieving this using only ITNs is not possible in the case of Fig. 4(c).

3.3.2. Assessing the impact of ITNs, symptomatic transmission, and insecticide resistance on malaria dynamics

The model (3.1) is simulated to assess the impact of ITN efficacy against sensitive mosquitoes (ε_{s0}), the modification factor (p) of ITN efficacy against resistant mosquitoes (ε_{r0}), ITN coverage (b_0), the rate at which adult mosquitoes develop resistance to insecticides (σ_s), the proportion of exposed humans who become symptomatically infectious at the end of the incubation period (m), and the recovery rate of asymptomatic infectious humans (γ_{ah}) on malaria burden, i.e., the total number of infectious humans ($I_{sh}+I_{ah}$). All comparisons will be against the baseline scenario depicted by blue curves in the time series plots. The generated simulation results displayed in Fig. 5, show that reducing the efficacy of ITNs against sensitive mosquitoes from the baseline

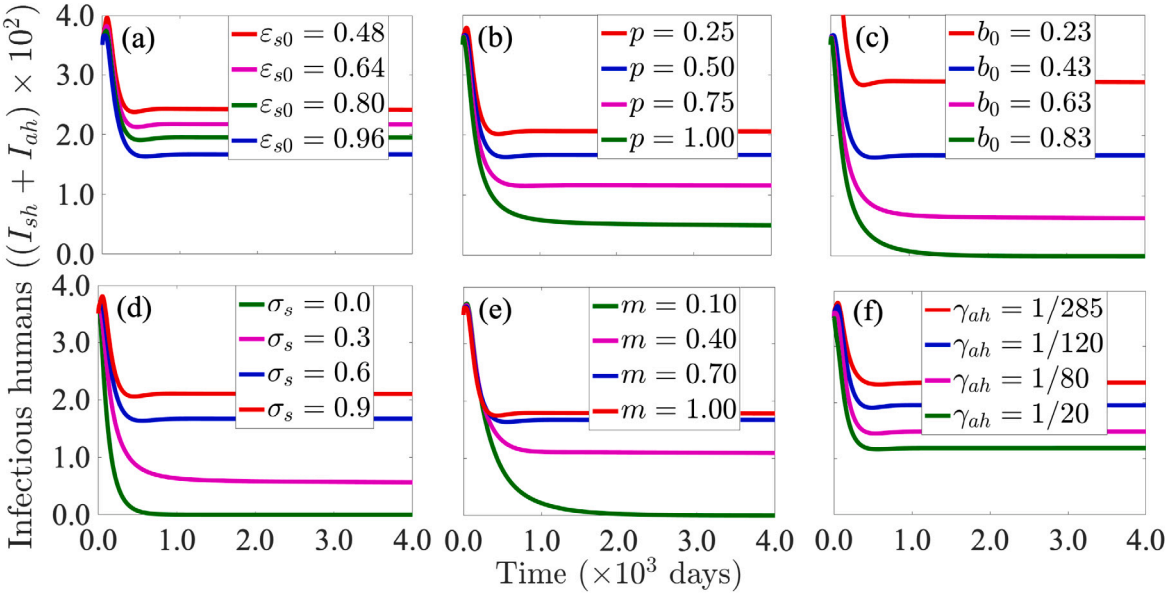

Fig. 5. Simulations of the model (3.1) showing the impact of (a) ITN efficacy against sensitive mosquitoes (ε_{s0}), (b) the modification factor (p) of ITN efficacy against resistant mosquitoes (ε_{r0}), (c) ITN coverage (b_0), (d) the rate at which adult mosquitoes develop resistance to insecticides (σ_s), (e) the proportion of exposed humans who become symptomatically infectious at the end of the incubation period (m), and (f) the recovery rate of asymptomatic infectious humans (γ_{ah}) on the total infectious human population ($I_{sh}+I_{ah}$). The other parameters used for the simulations are given in Table 1.

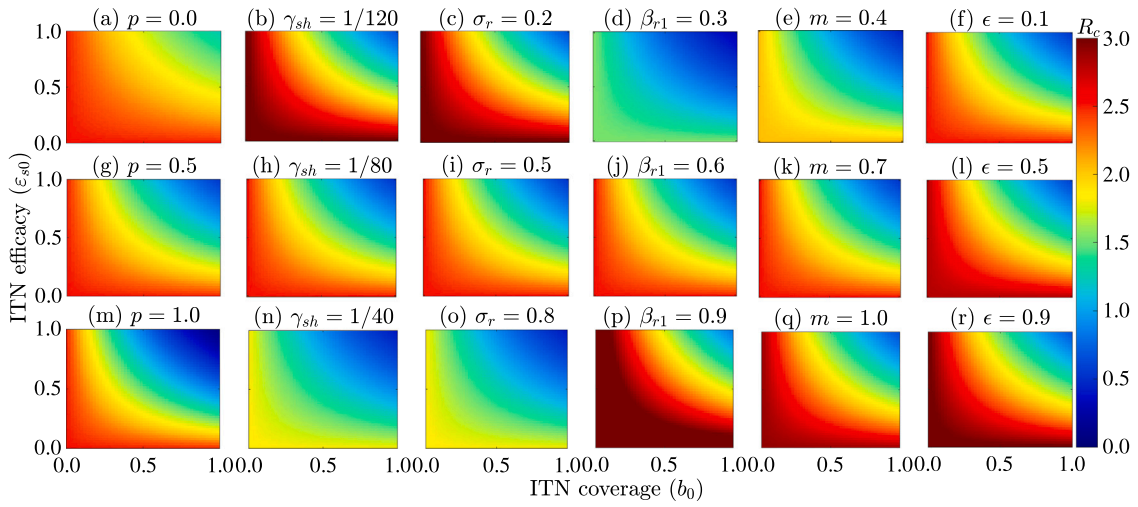

Fig. 6. Heatmaps of the control reproduction number (R_c) of the model (3.1) as a function of ITN coverage (b_0) and the efficacy of ITNs against sensitive mosquitoes (ε_{s0}) for different values of the modification factor for the efficacy of ITNs against resistant mosquitoes, p ((a), (g), and (m)), the recovery rate of symptomatic infectious humans, γ_{sh} ((b), (h), and (n)), the rate at which adult mosquitoes develop resistance to insecticides, σ_s ((c), (i), and (o)), the maximum biting rate of resistant mosquitoes, β_{r1} ((d), (j), and (p)), the proportion of exposed humans who become symptomatic at the end of the incubation period, m ((e), (k), and (q)), and the asymptomatic infectious human-to-mosquito transmission probability adjustment parameter, ϵ ((f), (l), and (r)). Other parameter values of the model are as presented in Tables 1.

value of $\varepsilon_{s0} = 0.96$ (depicted by the blue curve) by 16% (i.e., to $\varepsilon_{s0} = 0.80$), will lead to an ≈17% increase in malaria burden (green curve in Fig. 5(a)). Further reductions in the efficacy will result in higher disease burdens. In particular, if the baseline value of ε_{s0} is halved (i.e., if $\varepsilon_{s0} = 0.48$), the burden of malaria will increase by ≈44% (red curve in Fig. 5(a)). On the other hand, if the modification factor of the efficacy against resistant mosquitoes is halved (i.e., reduced from its baseline value of $p = 0.5$ to $p = 0.25$), an ≈23% increase in disease burden is observed (red curve in Fig. 5(b)), while if the baseline value is doubled (i.e., if $p = 1.0$), an ≈70% reduction in disease burden is observed (green curve in Fig. 5(b)). If the ITN coverage is 20% lower than the baseline value of $b_0 = 0.43$ (i.e., if $b_0 = 0.23$), the burden of malaria witnesses a 75% rise (red curve in Fig. 5(c)), while if the ITN coverage increases by 20% from the baseline value (i.e., if $b_0 = 0.63$), the burden of malaria drops by 62% (magenta curve in Fig. 5(c)). A further increase in ITN coverage by 20%, i.e., increasing the ITN coverage to $b_0 = 0.83$ from the baseline value, can result in malaria elimination (green curve in Fig. 5(c)). Also, if the rate at which adult mosquitoes develop resistance to insecticides increases from the baseline value of $\sigma_s = 0.6$ *per day* to $\sigma_s = 0.9$ *per day*, the burden of malaria increases by 25% (magenta curve in Fig. 5(d)), while if this rate reduces from the baseline value to $\sigma_s = 0.3$ *per day*, the burden of malaria reduces by 66% (green curve in Fig. 5(d)). The diseases can be contained if no mosquito develops resistance to insecticides, i.e., if $\sigma_s = 0.0$ *per day*. The simulation results also indicate that a 30% increase in the proportion of exposed humans who exhibit malaria symptoms at the end of the incubation period from the baseline value of $m = 0.7$ (i.e., $m = 1.0$), will trigger a 7% increase in the burden of malaria (red curve in Fig. 5(e)). A 30% reduction from the baseline value (i.e., $m = 0.4$) will lead to a 35% reduction in the burden of malaria (magenta curve in Fig. 5(e)), while reducing the proportion of exposed humans who develop malaria symptoms at the end of the incubation period from $m = 0.7$ to $m = 0.1$ can result in malaria elimination (green curve in Fig. 5(e)). Furthermore, the simulations show that if the recovery rate of asymptomatic infectious humans is reduced from its baseline value of $\gamma_{ah} = 1/120$ to $\gamma_{ah} = 1/285$ *per day*, the burden of malaria increases by 41% (magenta curve in Fig. 5(f)), while if this rate is increased from the baseline value to $\gamma_{ah} = 1/20$ *per day*, the burden of malaria reduces by 29% (green curve in Fig. 5(f)).

Fig. 6 shows heatmaps of the control reproduction number (R_c) of the model (3.1) as a function of ITN coverage (b_0) and the efficacy of ITNs against sensitive mosquitoes (ε_{s0}) for various values of the modification factor for the efficacy of ITNs against resistant mosquitoes, p (Fig. 6(a), (g), and (m)), the recovery rate of symptomatic infectious humans, γ_{sh} (Fig. 6(b), (h), and (n)), the rate at which adult mosquitoes develop resistance to insecticides, σ_s (Fig. 6(c), (i), and (o)), the maximum biting rate of resistant mosquitoes, β_{r1} ((d), (j), and (p)), the proportion of exposed humans who become symptomatic at the end of the incubation period, m (Fig. 6(e), (k), and (q)), and the asymptomatic infectious human-to-mosquito transmission probability adjustment parameter, ϵ (Fig. 6(f), (l), and (r)). Fig. 6(a), (g), and (m) show that if resistance to insecticides lowers the efficacy of ITNs significantly then higher ITN coverage is required for reducing the control reproduction number significantly. In particular, if the efficacy of ITNs against resistant mosquitoes is zero (i.e., if $p = 0$), reducing the control reproduction number below one will be unattainable even if everybody in the community uses ITNs whose efficacy against sensitive mosquitoes is 100% (Fig. 6(a)). If $p = 0.5$ and $\varepsilon_{s0} = 0.64$ ($\varepsilon_{s0} = 0.96$), then 100% (71%) ITN coverage is required to reduce R_c below one (Fig. 6(g)), while if $p = 1$ (i.e., $\varepsilon_{r0} = \varepsilon_{s0}$), then 86% ITN coverage is required to reduce R_c below one if $\varepsilon_{s0} = 0.48$ (Fig. 6(m)). Furthermore, if $p = 1$ and $\varepsilon_{s0} = 0.64$ ($\varepsilon_{s0} = 0.96$), then 63% (43%) of the populace is required to sleep under ITNs to reduce R_c below one (Fig. 6(m)).

Next, Fig. 6(d), (j), and (p) show that lower ITN coverage is required in communities with low mosquito concentration and biting rates. Specifically, if the maximum biting rate of resistant mosquitoes is $\beta_{r1} = 0.3$, and the efficacy of ITNs against sensitive mosquitoes is only 48% (i.e., $\varepsilon_{s0} = 0.48$), then 61% of the population is required to sleep under ITNs to reduce R_c below one (Fig. 6(d)). But if $\beta_{r1} = 0.3$ and the efficacy of ITNs against sensitive mosquitoes is 64% (96%), then 45% (31%) ITN coverage is required to reduce R_c below one (Fig. 6(d)). If $\beta_{r1} = 0.6$ and $\varepsilon_{s0} = 0.48$, reducing R_c below one will be impossible even if everybody sleeps under an ITN (Fig. 6(j)). However, if $\beta_{r1} = 0.6$ and the efficacy of ITNs is $\varepsilon_{s0} = 0.64$ ($\varepsilon_{s0} = 0.96$), then 98% (65%) ITN coverage is required to reduce R_c below one (Fig. 6(j)). If individuals in a community with high mosquito densities and/or biting rates settle for ITNs of low efficacy to sensitive mosquitoes, it might be impossible to reduce R_c below one (hence, the disease will continue to spread in the population). However, if the populace settle for the baseline case with ITNs of efficacy 96% against sensitive mosquitoes, then at least 90% of the population is required to use ITNs in order to reduce R_c below unity if $\beta_{r1} = 0.9$ (Fig. 6(p)). More outcomes from Fig. 6 are summarized in Table 2, while heatmaps of disease prevalence as a function of ITN coverage and efficacy, and heatmaps of R_c and malaria prevalence as functions of the rate at which adult mosquitoes develop resistance to insecticides (σ_s) and the rate at which resistant mosquitoes lose their resistance (σ_r) are presented in Figs. S4–S6 of the SI.

Table 2
Proportion of humans required to use ITNs to reduce the control reproduction number (R_c) below one for various values of the recovery rate of symptomatic infectious humans (γ_{sh}), various rates at which adult mosquitoes develop resistance to insecticides (σ_s), various proportions of exposed humans who become symptomatic at the end of the incubation period (m), and for various values of the asymptomatic infectious human-to-mosquito transmission probability adjustment factor (ϵ).

ITN	Minimum ITN coverage (b_0)							
efficacy	$\gamma_{sh} = 1/120$	$\gamma_{sh} = 1/40$	$\sigma_r = 0.2$	$\sigma_r = 0.8$	$m = 0.4$	$m = 1.0$	$\epsilon = 0.5$	$\epsilon = 0.9$
$\varepsilon_{s0} = 0.48$	>100%	86%	>100%	88%	100%	>100%	>100%	>100%
$\varepsilon_{s0} = 0.64$	>100%	65%	>100%	65%	76%	>100%	>100%	>100%
$\varepsilon_{s0} = 0.96$	80%	43%	80%	43%	51%	75%	65%	80%

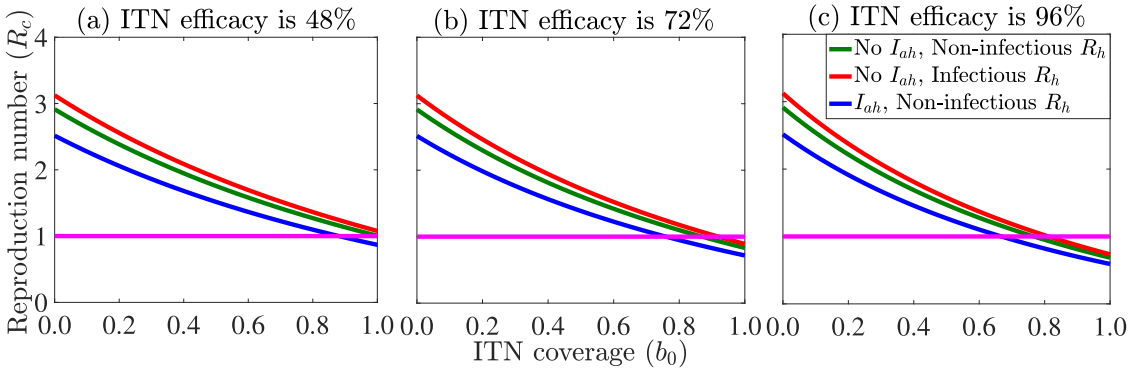

Fig. 7. Profile of the control reproduction number (R_c) as a function of ITN coverage (b_0) for different ITN efficacies (ε_{s0}) and for the case in which there is no asymptomatic infectious class, i.e., $m = 1$ and recovered individuals do not transmit the disease (green curve), there is an asymptomatic infectious class, i.e., $0 < m < 1$ and recovered individuals do not transmit the disease (blue curve), and there is no asymptomatic infectious class, i.e., $m = 1$ and recovered individuals can transmit the disease (red curve). (a) $\varepsilon_{s0} = 0.48$, (b) $\varepsilon_{s0} = 0.72$, and (c) $\varepsilon_{s0} = 0.96$. The other parameters used for the simulation are presented in Table 1.

3.3.3. *The impact of incorporating a separate asymptomatic infectious class*

Additional simulations of the model (3.1) were performed to assess the impact of incorporating a separate asymptomatic infectious human class. The results obtained (Fig. 7), show that accounting for asymptomatic transmission through a separate asymptomatic infectious human class leads to a model with a smaller control reproduction number. In particular, if the efficacy of ITNs (ε_{s0}) is 48% and a separate asymptomatic infectious human class is incorporated, while partially immune humans do not contribute to disease transmission (i.e., the Model (3.1)), then 89% ITN coverage is required to contain the disease (blue curve in Fig. 7(a)). However, if there is no asymptomatic infectious human class and partially immune humans do not contribute to disease transmission, or if there is no separate asymptomatic infectious human class and partially immune humans contribute to disease transmission (i.e., the Model (2.1)), containing the disease is not possible even if the entire population uses ITNs (green and red curves in Fig. 7(a)). On the other hand, if the efficacy of ITNs against sensitive mosquitoes is 96% and a separate asymptomatic infectious human class is incorporated, then only 67% ITN coverage is required to contain the disease (blue curve in Fig. 7(c)). A higher coverage level is required if asymptomatic infectious humans are not accounted for. In particular, if there is no asymptomatic infectious human class and partially immune humans do not contribute to disease transmission, 77% ITN coverage is required to contain the disease (green curve in Fig. 7(c)), while if there is no asymptomatic infectious human class and partially immune humans contribute to disease transmission, 81% ITN coverage is required to contain the disease (red curve in Fig. 7(c)).

4. The models (2.1) and (3.1) with decaying ITN efficacy

There is overwhelming evidence that the efficacy of ITNs decays over time (N'Guessan et al., 2007; Briët et al., 2012; Obala et al., 2015). In this section, the models (2.1) and (3.1) are extended to account for decaying ITN efficacy and periodic ITN replacement, i.e., $\varepsilon_l, l \in \{\beta_j, \mu_j\}, j \in \{r, s\}$ is now a decreasing function of time over the useful life of an ITN. As in Ngonghala et al. (2014, 2016), we model the (waning of) ITN-efficacy in preventing mosquitoes from reaching humans sleeping beneath them (ε_{β_j}) and in killing mosquitoes that land on them (ε_{μ_j}) through the functional forms:

$$\varepsilon_\beta(t) = \frac{2^n+1}{2^{n+1}}\left(\frac{2^n-1}{2^n+1} + \frac{1}{1+\left(\frac{t \bmod T}{T/2}\right)^n}\right)\varepsilon_{j0},$$
$$\varepsilon_\mu(t) = \frac{2^n+1}{2^n}\left(-\frac{1}{2^n+1} + \frac{1}{1+\left(\frac{t \bmod T}{T/2}\right)^n}\right)\varepsilon_{j0}, \tag{4.1}$$

where $0 \le \varepsilon_{j0} \le 1$ is the initial efficacy of ITNs, T is the useful lifespan of ITNs, and $n > 1$ is a shape constant. It should be mentioned that these functional forms take into account the fact that upon complete waning of insecticides from ITNs, the ITNs provide about half their original protective and killing efficacies (Clarke et al., 2001) and that ITNs are replaced with new ones (a process that restores the original efficacies of the ITNs) after the effective useful lifespan of the ITNs. As in Ngonghala et al. (2014, 2016), $(S_s^*(t), S_r^*(t))$ is the unique globally attractive T-periodic positive solution of the sensitive and resistant susceptible mosquito components of the disease-free system of the non-autonomous versions of the models (2.1) and (3.1), with $\varepsilon_l, l \in \{\beta, \mu\}$ given by Eq. (4.1) (Ngonghala et al., 2014; Nakata and Kuniya, 2010). The disease-free equilibria of the non-autonomous versions of the models (2.1) and (3.1) are $(S_h^*, E_h^*, I_h^*, R_h^*, S_s^*(t), E_s^*(t), I_s^*(t), S_r^*(t), E_r^*(t), I_r^*(t)) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, S_s^*(t), 0, 0, S_r^*(t), 0, 0\right)$ and $(S_h^*, E_h^*, I_{sh}^*, I_{ah}^*, R_h^*, S_s^*(t), E_s^*(t), I_s^*(t), S_r^*(t), E_r^*(t), I_r^*(t)) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, 0, S_s^*(t), 0, 0, S_r^*(t), 0, 0\right)$, respectively. See Ngonghala et al. (2014) for a sample proof of the well-posedness of the non-autonomous versions of the models (2.1) and (3.1) (i.e., the models (2.1) and (3.1) with ε_l given by Eq. (4.1)).

4.1. Results

Unless otherwise specified, the parameter values in Table 1 will be used to simulate the non-autonomous versions of the models (2.1) and (3.1) with $\varepsilon_l, l \in \{\beta, \mu\}$ given by Eq. (4.1) to assess the impact of decay

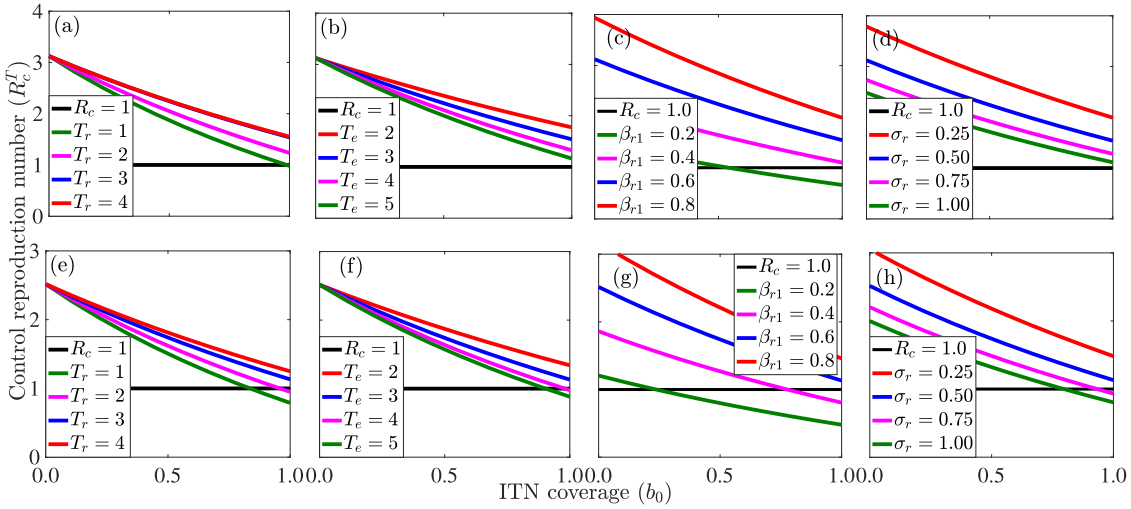

Fig. 8. Profiles of the control reproduction numbers (R_c^T) of the models (2.1) ((a)–(d)) and (3.1) ((e)–(h)) with decaying ITN efficacy and periodic ITN replacement as functions of ITN coverage (b_0) for various values of the ITN replacement times, T_r ((a) and (e)), useful lifespan of ITNs, T_e ((b) and (f)), the maximum biting rate of mosquitoes, β_{r1} ((c) and (g)), and the rate at which mosquitoes lose resistance to insecticides, σ_r ((d) and (h)). The other parameter values are given in Table 1. See Fig. S11 of the SI for more results.

in ITN efficacy, mosquito resistance to insecticides, the useful lifespan of ITNs ($T = T_e$), and the effective replacement time of ITNs ($T = T_r$) on the burden of malaria. The minimum ITN coverage required to reduce the control reproduction number below unity (i.e., the possibility of malaria elimination) under different scenarios will be identified. The numerical technique presented in Wang and Zhao (2008b) and Ngonghala et al. (2014) will be used to compute the reproduction number (R_c^T) of the time-dependent periodic systems as functions of the ITN coverage (b_0). Since the results obtained by comparing the models (2.1) and (3.1) for the case in which ITN efficacy decays over time are similar to those for the case in which ITN efficacy is constant, we focus mostly on the non-autonomous version of the model (3.1) (with decaying ITN efficacy) and present related results for the non-autonomous version of the model (2.1) in the SI (Section S3). The non-autonomous version of the model (3.1) will be referred to as the extended model.

4.1.1. The critical ITN coverage level for containing malaria

We identify the minimum proportion of the human population required to use ITNs to reduce the control reproduction number (R_c^T) of the non-autonomous versions of the models (2.1) and (3.1) with decaying ITN efficacy and periodic ITN replacement below one under different scenarios. These scenarios involve ITN policies that lead to various effective ITN replacement times (T_r), useful lifespans of ITNs (T_e), maximum biting rates of resistant mosquitoes (β_{r1}), and various rates of loss of resistance by adult mosquitoes (σ_r). Fig. 8 depicts plots of R_c^T as functions of ITN coverage (b_0) under various scenarios (involving different values of T_r, T_e, β_{r1}, and σ_r). All other parameters are fixed at their baseline values given in Table 1. The baseline case obtained using the baseline parameter values in Table 1 show that for the non-autonomous version of the model (2.1) ((3.1)) with decaying ITN efficacy and periodic ITN replacement, reducing R_c^T below one only through the use of ITNs is impossible even if the ITN coverage level is 100% (blue curves in Fig. 8). If an ITN policy that relies on replacing ITNs (of prescribed useful lifespan three years) every year is implemented, then it might be possible to reduce R_c^T below one using Model (2.1) ((3.1)), if 99% (83%) of the population use ITNs for personal protection (green curves in Fig. 8(a) and (e)). However, if ITNs (of prescribed useful lifespans of three years) are replaced every four years, then reducing R_c^T below one will never be possible even if everyone in the community uses ITNs for personal protection (red curves in Fig. 8(a) and (d)). On the other hand, if an ITN policy that requires the use of ITNs of shorter useful lifespans is implemented, then more humans will be required to use ITNs. In particular, if the useful lifespan of ITNs is two years (i.e., one year shorter than the baseline useful lifespan prescribed by WHO), it will not be possible to reduce R_c^T below one even if everybody uses ITNs for personal protection (red curves in Fig. 8(b) and (f)). But, if the prescribed lifespan of ITNs is increased from the baseline value of three years to five years, then 90% ITN coverage is required to reduce R_c^T below one for the model (3.1), while reducing R_c^T below one is impossible for the model (2.1) (green curves in Fig. 8(b) and (f)). In communities with lower mosquito densities or biting rates, lower ITN coverage is required to reduce R_c^T below one. In particular, if the maximum biting rate of resistant mosquitoes is $\beta_{r1} = 0.2$, then using Model (2.1) ((3.1)), 54% (23%) ITN coverage is required to reduce R_c^T below unity (green curves in Fig. 8(c) and (g)). Furthermore, if the rate at which adult mosquitoes develop resistance to insecticides is reduced (possibly through the use of synergists that inhibit the development of resistance), lower ITN coverage is required to reduce R_c^T below one. Specifically, if the rate at which resistant mosquitoes lose resistance to insecticides is $\sigma_r = 0.25$ *per day* reducing R_c^T below one will be impossible (red curve in Fig. 8(c)), while if $\sigma_r = 1.0$ *per day*, 80% ITN coverage is required for Model (3.1), while reducing R_c^T below one is impossible for Model (2.1) (green curves in Fig. 8(d) and (h)). Results for the initial ITN efficacies (ε_{s0} and ε_{r0}) and the proportion of exposed humans who are symptomatic at the end of the incubation period (m) are presented in Section 5.

5. Outcomes of the autonomous versus non-autonomous model

In this section, the autonomous and non-autonomous versions of the models (2.1) and (3.1) (i.e., the models (2.1) and (3.1) with constant ITN efficacy and with decaying ITN efficacy and periodic ITN replacement) are analyzed and compared under various scenarios. Since results for the autonomous and non-autonomous versions of the model (2.1) are similar to those of the autonomous and non-autonomous versions of the model (3.1), we present them in the SI (with the exception of Fig. 9, which compares the long-term dynamics of all the models).

5.1. Long-term dynamics of the autonomous and non-autonomous models

Fig. 9 depicts the long-term dynamics of the autonomous and non-autonomous versions of the models (2.1) and (3.1) (i.e., the models (2.1) and (3.1) with constant ITN efficacy and with decaying ITN efficacy and periodic ITN replacement) under different ITN efficacies and ITN coverages. For ITNs with high efficacies and high coverage (e.g., if $\varepsilon_{s0} = 0.96$ and $b_0 = 0.90$), the autonomous models (2.1)

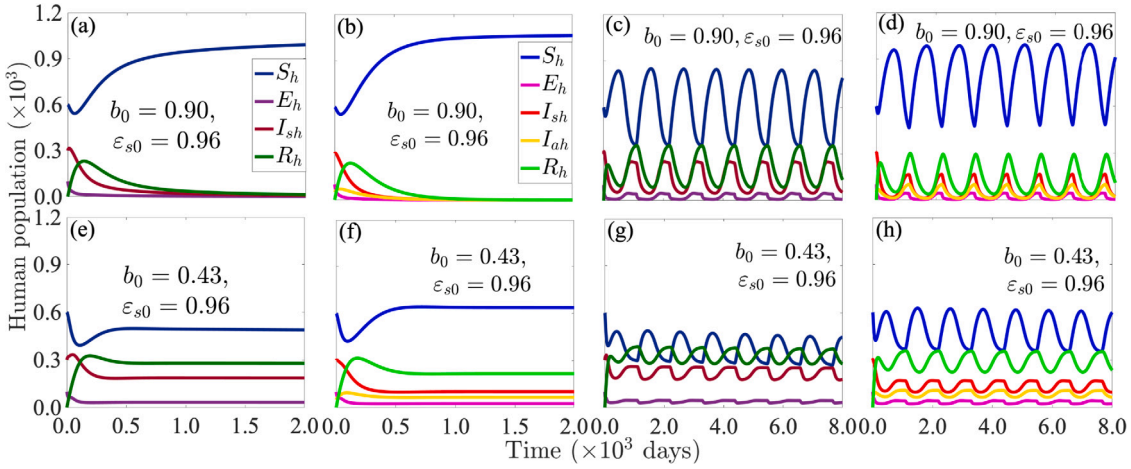

Fig. 9. Long-term dynamics of the model (2.1) with constant ITN efficacy ((a) and (e)), the model (3.1) with constant ITN efficacy ((b) and (f)), the model (2.1) with decaying ITN efficacy ((c) and (g)), and the model (3.1) with decaying ITN efficacy ((d) and (h)) for different values of the initial ITN efficacy against sensitive mosquitoes (ε_{s0}) and ITN coverages (b_0). The other parameter values used for the simulation are presented in Table 1.

and (3.1) relax at the disease-free equilibrium (Fig. 9(a) and (b), respectively), while the non-autonomous models (2.1) and (3.1) exhibit oscillatory dynamics with non-zero infectious populations (Fig. 9(c) and (d), respectively). Thus, although the autonomous systems show that disease elimination is possible for this level of ITN coverage and ITN efficacy (Fig. 9(a)–(b)), the non-autonomous models show that disease elimination is not possible (Fig. 9(c)–(d)). But, for high ITN efficacy and low ITN coverage (e.g., if $\varepsilon_{s0} = 0.96$ and $b_0 = 0.43$), the autonomous models (2.1) and (3.1) relax on an their respective endemic equilibria (Fig. 9(e) and (f), respectively), while the non-autonomous models (2.1) and (3.1) exhibit oscillatory dynamics with period equivalent to the replacement time of ITNs (Fig. 9(g) and (h), respectively). These oscillations are due to the periodic replacement of ITNs after the useful lifespan. Although the autonomous systems show that disease elimination might be possible (Fig. 9(a)–(b)), the non-autonomous models show that disease elimination might not be possible in the same parameter regime due to the added realism from ITN-use implementation (Fig. 9(c)–(d)). This is consistent with results from previous studies (e.g., Ngufor et al. (2011), West et al. (2014) and Protopopoff et al. (2015)) showing that ITN-use or indoor residual spraying as a single intervention is not sufficient for containing malaria; however, combining the two interventions offers better performance in controlling the disease. Studies in Ngufor et al. (2011), Djènontin et al. (2010) and Djènontin et al. (2009) also show that combining the two measures improve insecticide-resistance management (since different insecticides with different modes of action are used at the same location and time). Furthermore, this result is consistent with results from Killeen and Smith (2007), Govella et al. (2010), Bugoro et al. (2011) and Govella and Ferguson (2012) indicating that the possibility of out-door feeding or resting by some mosquitoes can reduce the effectiveness of ITNs in malaria control significantly thereby rendering elimination challenging.

In both the autonomous and non-autonomous models, the disease burden (i.e., the total infectious human population) for the model (2.1) is greater than the disease burden for the model (3.1). Hence, the model (3.1) underestimates disease burden.

5.2. Assessing the impact of parameters on disease burden through a global uncertainty and sensitivity analysis

The malaria models (2.1) (from Section 2) and (3.1) from Section 3 with constant ITN efficacy together with the non-autonomous versions with decaying ITN efficacy and periodic ITN replacement times described in Section 4 have large numbers of parameters, the estimation of which involves uncertainty and variability. Consequently, it is useful to examine the effect of these uncertainties and variability on the outputs of the model. Specifically, it is critical to identify the model parameters that have the greatest effect on disease dynamics. Here, we consider the model (2.1) with (a) constant ITN efficacy, (b) waning ITN efficacy and periodic ITN replacement time, and the model (3.1) with (c) constant ITN efficacy, and (d) waning ITN efficacy and periodic ITN replacement time. Malaria prevalence in humans is used as the response function. Similar results are obtained for the models (2.1) and (3.1) with constant ITN efficacy when the control reproduction number is used as the response function (Figs. S7 (a) and S12 (a) of the SI). As in Ngonghala et al. (2014, 2016, 2020), global uncertainty and sensitivity analysis will be performed on the response functions of the models utilizing the Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficients (PRCCs) approach (Blower and Dowlatabadi, 1994; Marino et al., 2008). The uncertainty and sensitivity analysis results obtained for the four models are presented in Fig. 10. The analysis shows that for each of the four model scenarios, the maximum biting rate of resistant mosquitoes (β_{r1}) and the ITN coverage (b_0) have the greatest impact on malaria prevalence (Fig. 10(a)–(d)) and the other response function (Figs. S7 and S12 of the SI). The next set of highly influential parameters are the probability that an infectious mosquito (human) infects a susceptible human, p_{vh} (mosquito, p_{hv}), the ITN efficacy for sensitive mosquitoes (ε_{s0}), and the rate at which adult mosquitoes lose (develop) resistance to insecticides, σ_r (σ_s). The strong negative correlation between disease prevalence and the ITN coverage b_0 and/or the efficacy of ITNs against sensitive mosquitoes indicates that high usage of high quality ITNs is important in mitigating the health burden of malaria. This is consistent with studies in Lindsay et al. (2021) calling for an increase in ITN coverage and improvements in the lifetime of active chemicals used in ITNs, as well as the physical integrity of ITNs in order to enhance the impact of ITNs in combating malaria. Also, studies in Clarke et al. (2001), Lengeler (2004b,a), Pryce et al. (2018) and Yang et al. (2018) have shown that ITNs contribute significantly in preventing the spread of malaria. Furthermore, ITNs have been shown to perform better in preventing the spread of malaria than untreated nets (Clarke et al., 2001; Pryce et al., 2018), while PBO ITNs have been shown to contribute more in reducing malaria prevalence in regions with high pyrethroid resistance by killing resistant mosquitoes and reducing the rate at which mosquitoes acquire blood meals (Gleave et al., 2018; Martin et al., 2021) than traditional ITNs. There is a positive correlation between the parameters β_{r1}, p_{vh}, p_{hv}, σ_s and malaria prevalence. Other significantly impactful parameters that correlate negatively with the response function are σ_r, the natural mortality rates of sensitive and resistant mosquitoes (μ_{s0} and μ_{r0}), the recovery rate of symptomatically infectious humans (γ_{sh}), and the

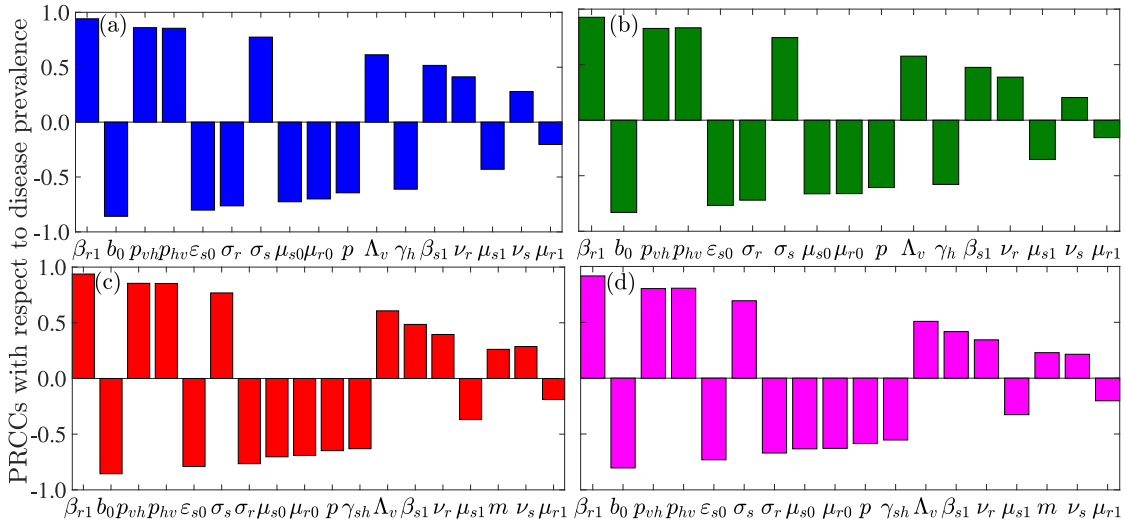

Fig. 10. Partial rank correlation coefficients (PRCCs) showing the contributions of parameters of the model (2.1) with (a) constant ITN efficacy, (b) waning ITN efficacy and periodic ITN replacement, and the model (3.1) with (c) constant ITN efficacy, (d) waning ITN efficacy and periodic ITN replacement to variability in human malaria prevalence $((E_h + I_{sh} + I_{ah})/N_h)$. A positive (negative) PRCC depicts a positive (negative) correlation between malaria prevalence in humans and the corresponding parameter, while the magnitude of the PRCC depicts the strength of the correlation with ± 1 depicting the strongest correlation and zero, depicting no correlation. Parameters with very low significance are not shown. The baseline parameters used for the simulation are presented in Table 1.

modification factor of the efficacy of ITNs for resistant mosquitoes (p), while other significantly impactful parameters that correlate positively with the response function are the mosquito recruitment rate (Λ_v) and the maximum biting rate of sensitive mosquitoes (β_{s1}). Parameters such as the proportion of mosquitoes that develop resistance at birth (θ), the useful lifespan of ITNs (T), and the minimum biting rates of sensitive and resistant mosquitoes (β_{s0} and β_{r0}, respectively,) are among the least influential parameters (and are not shown in Fig. 10). This confirms the minimal malaria risk in places with low mosquito concentrations or where mosquitoes are prevented from biting humans a lot.

5.3. Assessing the impact of ITN efficacy

In this Section, we compute the control reproduction number of the model (3.1) with constant ITN efficacy (R_c), the time-averaged reproduction number of the non-autonomous version of the model (3.1) ($\bar{R}_c$), and the actual reproduction number of the non-autonomous model (3.1) (R_c^T) as functions of ITN coverage (b_0) for various values of the initial ITN efficacies against sensitive and resistant mosquitoes (ε_{s0} and ε_{r0}, respectively). The numerical scheme described in Wang and Zhao (2008b) and Ngonghala et al. (2014) is used to compute the reproduction number (R_c^T). The results obtained and depicted in Fig. 11 show that the model with constant ITN efficacy underestimates

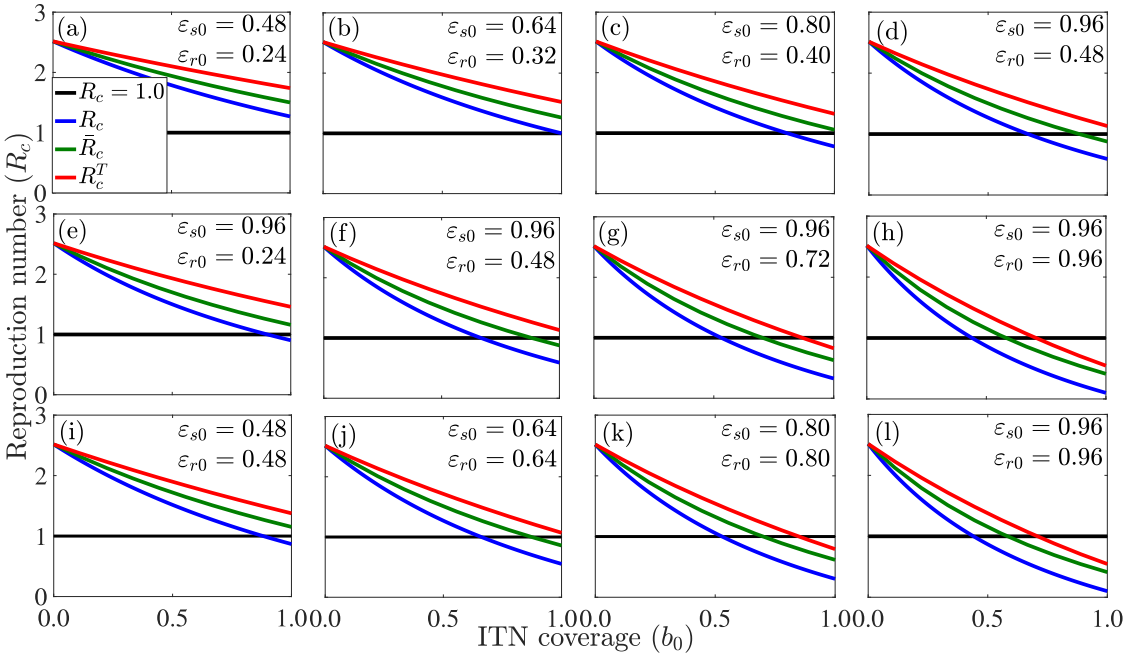

Fig. 11. Profiles of the control reproduction number of the model (3.1) with constant ITN efficacy denoted by R_c (blue curve), time-averaged ITN efficacy denoted by $\bar{R}_c$ (green curves), and periodic ITN efficacy denoted by R_c^T (red curves) as functions of ITN coverage (b_0) for various initial ITN efficacies against sensitive and resistant mosquitoes (ε_{s0} and ε_{r0}, respectively). (a)–(d): The efficacy (ε_{s0}) is varied, while $p = 0.5$. (e)–(h): The efficacy (ε_{r0}) is varied, while ε_{r0} is fixed. (i)–(l): Both ε_{s0} and ε_{r0} are varied with $\varepsilon_{s0} = \varepsilon_{r0}$. The black horizontal line representing a control reproduction number of one is denoted by R_c^1. Other parameter values used are presented in Table 1.

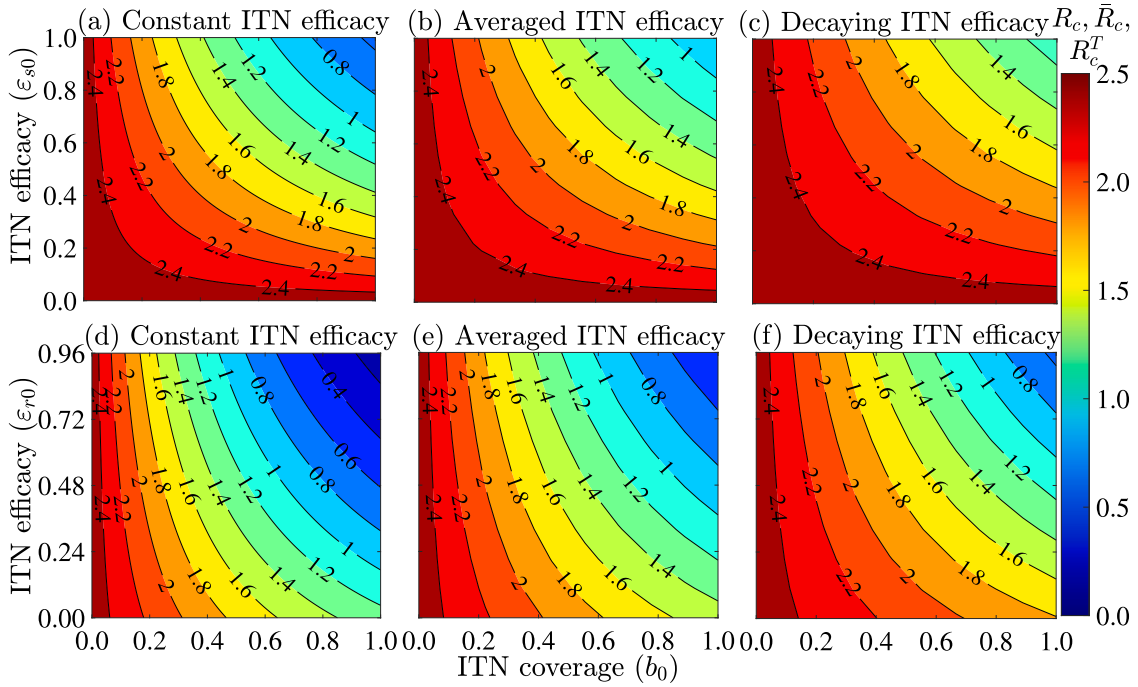

Fig. 12. Contour plots of the control reproduction number of the model (3.1) with constant ITN efficacy (R_c), time-averaged ITN efficacy ($\bar{R}_c$), and periodic ITN efficacy (R_c^T) as functions of ITN coverage (b_0) and initial ITN efficacies against (a)–(d): sensitive mosquitoes (ε_{s0}) and (e)–(h): resistant mosquitoes (ε_{r0}). Values of the other parameters used for generating the contour plots are given in Table 1.

the control reproduction number (and hence the burden of the disease) and that reducing the control reproduction number below zero might be impossible if the efficacy of ITNs against sensitive or resistant mosquitoes is very low. In particular, if $\varepsilon_{s0} = 0.48$ or $\varepsilon_{s0} = 0.64$ and $p = 0.5$ (which corresponds to $\varepsilon_{r0} = 0.24$ or $\varepsilon_{r0} = 0.32$), reducing any of the control reproduction numbers ($R_c, \bar{R}_c$, or R_c^T) will never be possible even if everybody sleeps under an ITN (Fig. 11(a)–(b)). For populations that prioritize ITNs of higher efficacies, lower ITN coverage levels are required to reduce $R_c, \bar{R}_c$, or R_c^T below unity. In particular for ITNs that are 80% efficacious against sensitive mosquitoes (i.e., if $\varepsilon_{s0} = 0.80$) and $p = 0.5$ (or $\varepsilon_{r0} = 0.40$), at least 79% of the population is required to use ITNs in order to reduce the reproduction number of the model (3.1) with constant ITN-efficacy below one (blue curve in Fig. 11(c)). However, for the model with periodic ITN efficacy, reducing any of the control reproduction numbers $\bar{R}_c$, or R_c^T below unity under this 80% ITN efficacy scenario is impossible, even if everybody uses ITNs (green and red curves in Fig. 11(c)). Furthermore, if the efficacy of ITNs against sensitive mosquitoes is 96% and $p = 0.5$ (or $\varepsilon_{r0} = 0.48$), at least 66% of the population is required to use ITNs in order to reduce the reproduction number (R_c) below one for the model with constant ITN efficacy (blue curve in Fig. 11(d)), 87% ITN coverage is required for the model with a time-averaged ITN efficacy (green curve in Fig. 11(d)), and reducing R_c^T below one is unattainable even if everyone in the community uses highly efficacious ITNs (red curve in Fig. 11 (d)).

Next, the impact of the efficacy of ITNs against resistant mosquitoes (ε_{r0}) on the three control reproduction numbers ($R_c, \bar{R}_c$, and R_c^T), when the efficacy of ITNs against sensitive mosquitoes (ε_{s0}) is held at its baseline value of 96% is assessed. The results obtained and presented in Fig. 11(e)–(h) show that for a low efficacy of $\varepsilon_{r0} = 0.24$, 90% ITN coverage is required to reduce R_c below one, while reducing $\bar{R}_c$ or R_c^T below one will never be possible (green and red curves in Fig. 11(e)). The case for which $\varepsilon_{r0} = 0.24$ (i.e., Fig. 11(f)) has already been discussed under Fig. 11(d) above. For a moderately high efficacy of $\varepsilon_{r0} = 0.72$, reducing R_c below one requires a 53% ITN coverage (blue curve in Fig. 11(g)), reducing $\bar{R}_c$ below one requires a 70% ITN coverage (green curve in Fig. 11(g)), while reducing R_c^T below one requires a 87% ITN coverage (red curve in Fig. 11(g)). The high efficacy case (i.e., the case when $\varepsilon_{r0} = 0.96$) in Fig. 11(h) is discussed below.

To assess the impact of pyrethroid-PBO nets on malaria control, the control reproduction numbers ($R_c, \bar{R}_c$, and R_c^T) are computed as functions of ITN coverage (b_0) for various values of ITN efficacies when the modification factor (p) of the ITN efficacy against resistance mosquitoes is one (i.e., when $\varepsilon_{s0} = \varepsilon_{r0}$). The results obtained (depicted in Fig. 11(i)–(l)), show that if $\varepsilon_{s0} = \varepsilon_{r0} = 0.48$, at least 89% ITN coverage is required to reduce R_c below one (blue curve in Fig. 11(i)), while reducing $\bar{R}_c$ or R_c^T below one will never be possible even if the entire populace uses ITNs (green and red curves in Fig. 11(i)). On the other hand, if $\varepsilon_{s0} = \varepsilon_{r0} = 0.80$, at least 53% (70%) ITN coverage is required to reduce R_c ($\bar{R}_c$) below one, while reducing R_c^T below one requires 85% of the community to use ITNs (red curve in Fig. 11(i)). Even lower ITN coverages are required for higher efficacies. Specifically, if $\varepsilon_{s0} = \varepsilon_{r0} = 0.96$, reducing R_c below one requires only a 44% ITN coverage (blue in Fig. 11(h) and (l)), while reducing $\bar{R}_c$ below one requires a 60% ITN coverage (blue in Fig. 11(h) and (l)). For this same case in which $\varepsilon_{s0} = \varepsilon_{r0} = 0.96$, R_c^T can be brought below unity, with a 71% ITN coverage (red curve in Fig. 11(h) and (l)). Similar results for the model (2.1) are presented in Figs. S8–S9 of the SI.

In summary, the results depicted in Fig. 11 show a significant reduction of about 46% in the proportion of the population required to use ITNs in order to reduce R_c below one when ITNs of efficacy $\varepsilon_{s0} = \varepsilon_{r0} = 0.96$ compared to ITNs of efficacy $\varepsilon_{s0} = 0.96$ and $\varepsilon_{r0} = 0.24$ are used (comparing the blue curves in Fig. 11(e) and (h)) and that although reducing $\bar{R}_c$ (R_c^T) below one is possible with 60% (71%) ITN coverage, when $\varepsilon_{s0} = \varepsilon_{r0} = 0.96$, reducing $\bar{R}_c$ (R_c^T) below one is impossible when $\varepsilon_{s0} = 0.96$ and $\varepsilon_{r0} = 0.24$ (comparing the green curves in Fig. 11(e) and (h) and the red curves in Fig. 11(e) and (h)). Under the very high (96%) ITN efficacy against sensitive and resistant mosquito scenario, the autonomous model with constant ITN efficacy underestimates the reproduction number of the non-autonomous version by about 27% (comparing the intersection points of the blue and red curves with the black curve in Fig. 11(h) and (l)), while the model with averaged ITN efficacy underestimates the reproduction number of the non-autonomous model by about 11% (comparing the intersection points of the blue and green curves with the black curve in Fig. 11(h) and (l)). The scenario with $\varepsilon_{s0} = \varepsilon_{r0}$ can be associated with control measures involving the use of pyrethroid-PBO nets. Detailed profiles

for various combinations of ITN coverages and ITN efficacies required to reduce the reproduction numbers R_c, $\bar{R}_c$, and R_c^T below unity are depicted by the contour plots in Fig. 12. Results for various values of the useful lifespan of ITNs, the replacement time of ITNs, the proportion of exposed humans who become symptomatic after the incubation period, and the rate at which adult mosquitoes develop resistance to insecticides are depicted in Figs. S11, S13 and S14 of the SI.

5.4. Assessing the impact of waning (decaying) ITN efficacy

In this section, the model (3.1) with constant, time averaged, and waning ITN efficacy are simulated to assess the impact of widespread use of ITNs of different efficacies on the control reproduction number (R_c) of the autonomous version of the model (3.1) with constant ITN efficacy and ($\bar{R}_c$ and R_c^T) of the non-autonomous version of the model (3.1) with waning ITN efficacy as functions of ITN coverage (b_0) for different values of initial ITN efficacies ($\varepsilon_{j0}, j = r, s$), the rate at which adult mosquitoes lose resistance to insecticides (σ_r), and the proportion of exposed humans who become symptomatically infectious at the end of the incubation period (m). The results obtained and depicted in Fig. 13, indicate that for low efficacious ITNs, e.g., if $\varepsilon_{s0} = 0.48$ and $p = 0.5$, reducing the control reproduction number below unity and hence containing the disease is impossible even if everybody in the community uses ITNs (red curves in Fig. 13(a), (e), and (i)). The proportion of the population required to use ITNs in order to reduce the control reproduction number below one reduces in communities that prioritize ITNs of higher efficacies. Specifically, for ITNs of moderately high efficacy (e.g., if $\varepsilon_{s0} = 0.80$ and $p = 0.5$), at least 79% of the population is required to use ITNs in order to reduce R_c below unity (green curve in Fig. 13(a)), while reducing $\bar{R}_c$ or R_c^T below one is impossible (green curves in Fig. 13(e) and (i)). It should be mentioned that for $\varepsilon_{s0} = 0.80$ or $\varepsilon_{s0} = 0.96$, reducing either $\bar{R}_c$ or R_c^T below one is not possible for the model (2.1) (Fig. S8 of the SI). Furthermore, for ITNs of very high efficacy (e.g., if $\varepsilon_{s0} = 0.96$ and $p = 0.5$), a 66% ITN coverage is required to reduce R_c below one for the model (3.1) with constant ITN efficacy (blue curve in Fig. 13(a)), an 87% ITN coverage is required to reduce $\bar{R}_c$ below one for the model (3.1) with time-averaged ITN efficacy (blue curve in Fig. 13(e)), while reducing R_c^T below one is still impossible for the model (3.1) with waning ITN efficacy (blue curve in Fig. 13(i)). On the other hand, for ITNs with very low efficacy against resistant mosquitoes (e.g., if $\varepsilon_{r0} = 0.24$ and $\varepsilon_{s0} = 0.96$), 90% of the population is required to use ITNs to reduce R_c below one (blue curve in Fig. 13(b)), while reducing $\bar{R}_c$ or R_c^T below one is unattainable (blue curves in Fig. 13(f) and (j)). However, for ITNs of very high efficacy against resistant mosquitoes (e.g., if $\varepsilon_{r0} = \varepsilon_{s0} = 0.96$), only 44% of the population is required to use ITNs in order to reduce R_c below one (blue curve in Fig. 13(b)), 60% of the population is required to use ITNs in order to reduce $\bar{R}_c$ below one (blue curve in Fig. 13(f)), while to reduce R_c^T below one requires up to 71% of the population to use ITNs (blue curve in Fig. 13(j)). For the model (2.1) and ITNs of efficacy 96% against resistant mosquitoes, at least 53% ITN coverage is necessary to bring R_c below one, 70% ITN coverage is required to bring $\bar{R}_c$ below one, and 83% ITN coverage is required to bring R_c^T below one (Fig. S8 of the SI). In summary, the model (3.1) with constant ITN efficacy underestimates R_c compared to the model (2.1) with constant ITN efficacy, while the model (3.1) with waning ITN efficacy and periodic ITN replacement time underestimates $\bar{R}_c$ and R_c^T compared to the model (2.1) with waning ITN efficacy and periodic ITN replacement time. Additionally, the model (3.1) with constant ITN efficacy underestimates the control reproduction number compared to the model (3.1) with waning ITN efficacy and periodic ITN replacement time (i.e., $R_c < \bar{R}_c < R_c^T$ always).

To assess the impact of losing resistance to insecticides (or restoring susceptibility of resistant mosquitoes to insecticides), the control reproduction numbers (R_c, $\bar{R}_c$, and R_c^T) of the model (3.1) are studied as functions of ITN coverage (b_0) for different values of the rate at which adult mosquitoes lose resistance to insecticides (σ_r). The results depicted in Fig. 13(c), (g), and (k) show that when more adult mosquitoes lose resistance to insecticides, lower ITN coverage is required for containing the malaria disease. In particular, if the rate at which adult mosquitoes lose resistance to insecticides is as low as $\sigma_r = 0.25$ *per day*, then 87% of the population is required to use ITNs to reduce R_c

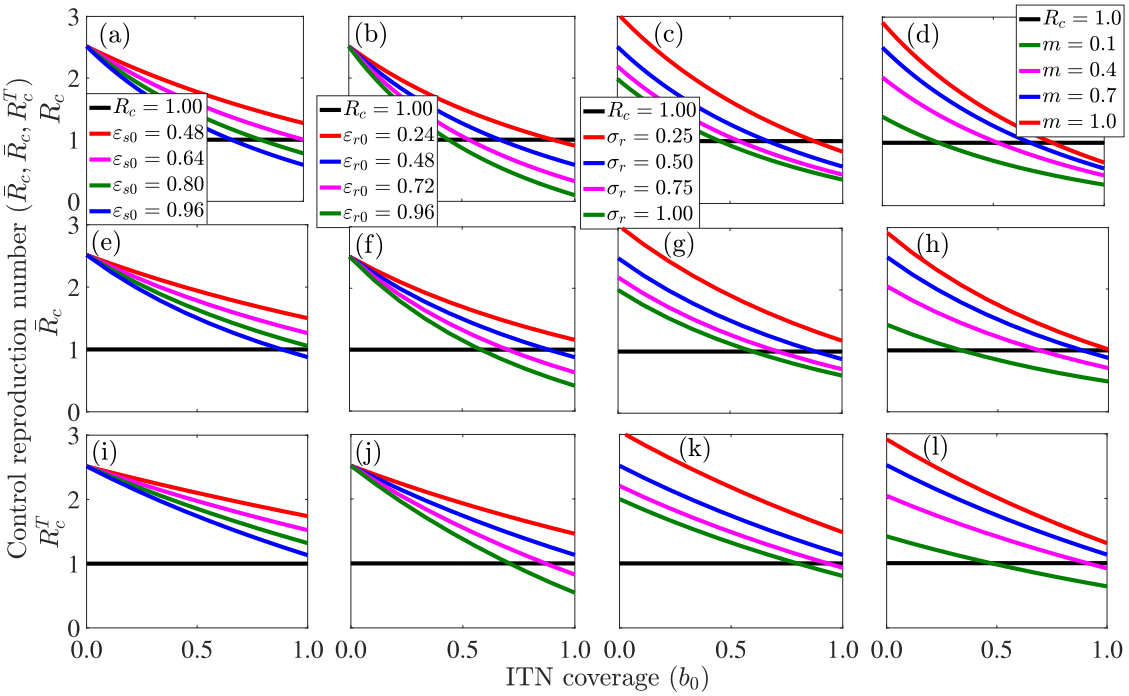

Fig. 13. Profile of the control reproduction number of the model (3.1) with (a)–(d) constant ITN efficacy (R_c), (e)–(h) time-averaged ITN-efficacy ($\bar{R}_c$), and (i)–(l) decaying ITN efficacy and periodic ITN replacement time (R_c^T) as functions of ITN coverage (b_0) for different values of (a), (e), and (i): ITN efficacy (ε_{s0}), (b), (f), and (j): ITN efficacy (ε_{s0}), (c), (g), and (k): rates at which adult mosquitoes lose resistance to insecticides (σ_r), and (d), (h), and (l): the proportion of exposed humans who are symptomatic at the end of the incubation period (m). The values of the other parameters used for the simulations are presented in Table 1.

below one (red curve in Fig. 13(c)), while reducing $\bar{R}_c$ or R_c^T below one is impossible even if everybody sleeps under an ITN (red curves in Fig. 13(g) and (k)). The proportion of humans required to sleep under ITNs reduces with increases in the rate at which adult mosquitoes lose resistance to insecticides. Specifically, if $\sigma_r = 0.75$ *per day*, then at least 53% (70%) of the population must use ITN protection to reduce R_c ($\bar{R}_c$) below one (magenta curves in Fig. 13(c) and Fig. 13(g), respectively), while 92% of the population must adopt ITN protection to reduce R_c^T below one (magenta curve in Fig. 13(k)). The reduction in the required ITN coverage is more significant if the rate at which resistant mosquitoes lose resistance is higher. Results for the model (2.1) with constant and decaying ITN efficacy are presented in Fig. S10 of the SI.

The impact of incorporating a separate asymptomatic infectious human class on malaria dynamics is highlighted in Fig. 13(d), (h), and (l). This result reveals that disease burden is higher in models in which asymptomatic infectious humans are not accounted for through a separate asymptomatic infectious human class. In particular, if the efficacy of ITNs against sensitive mosquitoes is 96% and $m = 1.0$ (i.e., if every exposed human becomes symptomatic), then at least 76% of the population is required to use ITNs in order to reduce R_c below one (red curve in Fig. 13(d)), while reducing $\bar{R}_c$ or R_c^T below unity is impossible (red curves in Fig. 13(h) and (l)). But if only 10% of exposed humans become symptomatic at the end of the incubation period (i.e., if $m = 0.1$), then only about 25% (34%) of the human population is required to use ITNs to reduce R_c ($\bar{R}_c$) below one (green curves in Fig. 13(d) and (h), respectively), and 48% ITN coverage is required to reduce R_c^T below one (green curve in Fig. 13(l)).

6. Discussion and conclusion

Insecticide-treated nets are the most inexpensive and widely used control measures against malaria in many malaria-endemic countries (Lengeler, 2004a; Phillips-Howard et al., 2003; Trape et al., 2011; Bhatt et al., 2015; Lindsay et al., 2021). Since even untreated bed-nets still protect humans from mosquito bites, introducing insecticides in bed-nets, as is the case with ITNs, provides an additional layer of protection (by repelling mosquitoes from humans or killing mosquitoes that get into contact with the ITNs). Insecticide-treated nets have contributed significantly in decreasing malaria morbidity and mortality among children and pregnant women in Africa (D'Alessandro et al., 1995; Nevill et al., 1996; Habluetzel et al., 1997; Ter Kuile et al., 2003; Trape et al., 2011). Unfortunately, these, and other benefits of using ITNs in the fight against malaria are threatened by factors such as net attrition, natural and human-induced decay in ITN efficacy (Minakawa et al., 2008; Briët et al., 2012; McLean et al., 2014; Bush et al., 2017; Diema et al., 2017; Short et al., 2018; Sherrard-Smith et al., 2019; Solomon et al., 2019)), and resistance exhibited by mosquitoes to insecticides (e.g. pyrethroids) used in ITNs (World Health Organization, 2013; Brogdon and McAllister, 1998.; Mawejje et al., 2013; Churcher et al., 2016; Ranson and Lissenden, 2016; Namias et al., 2021).

In this study, mathematical models for the dynamics of malaria that account for the decay in ITN efficacy over time and mosquito resistance to insecticides are formulated and analyzed both analytically and numerically. One version of the models accounts for partially immune humans who contribute in disease transmission, while the other factors in an asymptomatic infectious human class, with a partially immune class that does not contribute to disease transmission. Both versions are considered for the case in which ITN efficacy is constant and the case in which ITN efficacy decays over time. Analytical results of versions of both models in which the efficacy of ITNs is constant show that both models exhibit a forward bifurcation when the control reproduction number (R_c) is greater than one and that a backward bifurcation is possible for some parameter regimes for which $R_c < 1$. These results are confirmed using numerical simulations. The existence of a forward bifurcation depicts a situation in which the disease can invade or establish itself within a community, while the existence of a backward bifurcation in a disease model renders control or elimination difficult since the model's reproduction number must be lowered substantially below unity (i.e., below another threshold, R_c^{bb}) for the unique disease-free equilibrium to be globally asymptotically stable. Thus, disease control measures must be implemented and sustained until $R_c < R_c^{bb}$. Furthermore, the study suggests the possibility of disease elimination in the autonomous models due to the assumption of constant ITN efficacy over time. However, this is not the case with the non-autonomous models, due to the additional realism of decaying ITN efficacy built in. Specifically, due to replacement of ITNs after their useful life, the dynamics of the non-autonomous models are oscillatory with period corresponding to the replacement time of ITNs. This finding is in line with results from other studies that have shown that ITNs as the only control and mitigation measure against malaria are insufficient for containing the disease (Ngufor et al., 2011; West et al., 2014; Protopopoff et al., 2015; Killeen and Smith, 2007; Govella et al., 2010; Bugoro et al., 2011; Govella and Ferguson, 2012).

A global uncertainty and sensitivity analysis of each of the models considered in this study suggests that uncertainty or variability in the maximum biting rate of resistant mosquitoes (β_{r1}), the ITN coverage (b_0), the probability of an infectious mosquito (human) infecting a susceptible human (mosquito), p_{vh} (p_{hv}), the initial ITN efficacy (ε_{s0}), and the rate at which resistant (sensitive) mosquitoes lose (develop) resistance to insecticides, σ_r (σ_s) will introduce the greatest uncertainty and variability in the control reproduction number for the models with constant ITN efficacy and in the cumulative disease prevalence for both the model with constant and decaying ITN-efficacy. In particular, increases in $\beta_{r1}, p_{vh}, p_{hv}$, and σ_s will lead to significant inccreases in the control reproduction number and disease prevalence, while increases in b_0, ε_{s0}, and σ_r will lead to significant reductions in the control reproduction number and disease prevalence. Other parameters that have a significant impact on the control reproduction number and malaria prevalence are the natural mortality rates of sensitive and resistant mosquitoes (μ_{s0} and μ_{r0}, respectively), the modification factor for the efficacy of ITNs against resistant mosquitoes, the recovery rate of symptomatically infectious humans (γ_{sh}), the mosquito recruitment rate (Λ_v), and the maximum biting rate of sensitive mosquitoes (β_{s1}). Some of these parameters can be associated with malaria control measures. Specifically, mosquito-biting rates can be lowered by increasing the use of personal protective measures such as ITNs or making home changes to limit exposure to mosquitoes. The high impact of b_0, ε_{s0}, and p implies that replacing ITNs regularly or when the efficacy has waned to a certain level, and ensuring that as many humans as possible sleep under ITNs is important for controlling malaria. Bio-control measures involving the use of transmission-blocking Wolbachia bacteria can reduce the likelihood of mosquito-to-human transmission (Kambris et al., 2010; Hughes et al., 2011; Walker and Moreira, 2011). Furthermore, the mosquito reproduction rate (Λ_v) can be lowered by removing vector breeding grounds near human dwellings and through the use of larvicides, while the adult mosquito death rate can be increased through indoor residual spraying and the use of ITNs and adulticides. The recovery rate (γ_{sh}) can be boosted via anti-malaria drug therapy (e.g., artemether-lumefantrine, artesunate–amodiaquine, artesunate–pyronaridine, and dihydroartemisinin–piperaquine against *Plasmodium falciparum* in the WHO African region World Health Organization, 2021). Also, since the rate at which adult mosquitoes develop resistance (σ_s) or lose resistance (σ_r) to insecticides has a significant impact on the control reproduction number and malaria prevalence albeit a lesser extent compared to β_{r1}, b_0, and ε_{s0}, designing new methods for managing insecticide resistance is critical for malaria control. For example, resistance to insecticides can be reduced through the use of new chemicals to which mosquitoes are not resistant or chemicals that can suppress or reverse insecticide resistance in mosquitoes.

Untreated nets (i.e., nets with no insecticides) serve as physical shields between humans and mosquitoes, while ITNs constitute both physical and chemical shields for humans sleeping beneath them from

mosquitoes. Hence, both untreated nets and ITNs have a positive impact on reducing the transmission of malaria. However, ITNs contribute more significantly in preventing the spread of malaria (Clarke et al., 2001; Lengeler, 2004b,a; Pryce et al., 2018; Yang et al., 2018). In particular, the efficacy of untreated nets is about half the original efficacy of ITNs (Clarke et al., 2001). The effectiveness of ITNs in combating malaria is threatened by mosquito resistance to insecticides used in ITNs such as pyrethroids. Since mosquito resistance to insecticides reduces the efficacy of ITNs and hence constitute a serious challenge to the sustained management of many mosquito-borne infections (Machani et al., 2020), boosting the effectiveness of ITNs with synergists such as PBOs that improve the ability of ITNs to kill resistant mosquitoes, as well as restrict their human biting capability is critical (Bingham et al., 2011; Dadzie et al., 2017). It has been reported in some countries that the use of PBO can completely restore mosquito susceptibility to insecticides (World Health Organization, 2021). This study assesses the impact of traditional ITNs and PBO ITNs on malaria prevalence and control through two different ITN efficacies — the efficacy of ITNs against sensitive mosquitoes and the efficacy of ITNs against resistant mosquitoes. These efficacies are different for traditional ITNs and both sensitive and resistant mosquitoes retain the same efficacy for PBO ITNs. Results of this study show that PBO ITNs can be more effective than traditional ITNs in malaria control, especially in areas with high mosquito resistance to insecticides and especially when the efficacies of the PBO ITNs are high. This is consistent with results in Staedke et al. (2020), Gleave et al. (2018) and Martin et al. (2021).

The study highlights the importance of factoring in asymptomatic infectious humans and the decay in ITN efficacy over time with periodic ITN replacement. Specifically, the results show that the control reproduction number (and hence disease burden) is underestimated in a model in which asymptomatic infectious humans are accounted for through a separate asymptomatic infectious compartment, compared to a model with no separate asymptomatic infectious human class in which asymptomatic infectious humans are accounted for through a partially immune class. This result is consistent with that in Aguilar and Gutierrez (2020). Furthermore, the study indicates that the model (2.1) with constant ITN efficacy underestimates the control reproduction number (and hence disease burden) compared to the model (2.1) with decaying ITN efficacy, while the model (3.1) with constant ITN efficacy underestimates the control reproduction number compared to the model (3.1) with decaying ITN efficacy. In particular, the ITN coverage level required to reduce the control reproduction number below one is lowest for the versions of the models with constant ITN efficacy followed by the versions of the models with time-averaged ITN efficacy, and then the versions of the models with decaying ITN efficacy. Depending on the initial ITN efficacy, it might or might not be possible to reduce the control reproduction number below one. For example, for ITNs with high initial efficacy against susceptible and resistant mosquitoes of 96%, it is possible to reduce the control reproduction number of the model (3.1) with decaying ITN efficacy below one through a 71% ITN coverage, whereas for the model (2.1), 83% of the population is required to use ITNs to reduce the control reproduction number below one. The study also shows that eliminating malaria is unattainable if ITN efficacy or use is low and ITNs are not supplemented with other control measures. This is in line with results in Lengeler et al. (1998) and Ngonghala et al. (2020).

Additionally, the study shows that ITNs that can retain their efficacy and integrity longer perform better in malaria control than ITNs with shorter lifespans and that replacing ITNs before their useful lifespans is better for malaria control than replacing them after the lifespan. This outcome is consistent with results in Ngonghala et al. (2014) and a study in Gnanguenon et al. (2014) that recommended a serviceable lifespan of two years for ITNs. The integrity of ITNs deteriorates over time due to several factors including net attrition, frequent washing, especially for light colored ITNs (Gnanguenon et al., 2014; Mutuku et al., 2013; Githinji et al., 2010), etc. Hence, to maximize the protective and killing efficacy of ITNs, they should be replaced in a timely manner.

The models in this study are based on some assumptions. These include the fact that all ITNs are replaced at the same time. Accounting for variable ITN replacement times might lead to slightly different outcomes. The study also fails to account for the impact of human decision to use ITNs properly or improperly, which can lead to useful public health information. This aspect is under study and will be reported in a separate paper. Nonetheless, the study shows that introducing a separate class (from the partially immune class) to account for asymptomatic infectious humans, or failing to account for the decay in ITN efficacy, underestimates the control reproduction number and hence the burden of the disease and the effort required to contain the disease. Furthermore, the study shows that it is critically important for malaria control to replace ITNs before their prescribed useful lifespans, design ITNs with longer lifespans, and to use PBO ITNs (which are more effective in inhibiting or reversing insecticide resistance and in preventing malaria transmission than regular ITNs). Consequently, by using highly effective ITNs widely, chances of effectively controlling malaria are improved, particularly if the ITNs have long useful lives and are replaced before their useful lifespans expire.

CRediT authorship contribution statement

Calistus N. Ngonghala: Conceptualization, Formal analysis, Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.jtbi.2022.111281.

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