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Abstract

We present an improved mathematical model of population dynamics of mosquito-borne disease transmission. Our model considers the effect of mosquito repellent use and the mosquito's behavior or attraction to the infected human, which cause mosquitoes' biased distribution around the human population. Our analysis of the model clearly shows the existence of thresholds for mosquito repellent efficacy and its utilization rate in the human population with respect to the elimination of mosquito-borne diseases. Further, the results imply that the suppression of mosquito-borne diseases becomes more difficult when the mosquitoes' distribution is biased to a greater extent around the human population.

Keywords (separated by '-')	Mosquito-borne disease - Mosquito repellent - Mosquitoes' biased distribution
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ORIGINAL ARTICLE

A Population Dynamics Model of Mosquito-Borne Disease Transmission, Focusing on Mosquitoes' Biased Distribution and Mosquito Repellent Use

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Abstract

We present an improved mathematical model of population dynamics of mosquito-borne disease transmission. Our model considers the effect of mosquito repellent use and the mosquito's behavior or attraction to the infected human, which cause mosquitoes' biased distribution around the human population. Our analysis of the model clearly shows the existence of thresholds for mosquito repellent efficacy and its utilization rate in the human population with respect to the elimination of mosquito-borne diseases. Further, the results imply that the suppression of mosquito-borne diseases becomes more difficult when the mosquitoes' distribution is biased to a greater extent around the human population.

Keywords Mosquito-borne disease · Mosquito repellent · Mosquitoes' biased distribution

1 Introduction

Mosquito-borne diseases are spread by several types of mosquitoes, for example *Aedes aegypti* and *Aedes albopictus* for dengue, zika, yellow fever, and chikungunya, *anopheles* for malaria, and *culex* for Japanese encephalitis and West Nile fever (Calvo et al. 2016; Yang et al. 2018). These diseases are mainly caused by viruses, bacteria, or parasites. In many cases, infections in mosquitoes do not affect the mosquito itself.

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These diseases have posed serious public health problems in many countries (WHO 2017; ECDC 2018) not only because of the unavailability of medicines to cure infected humans but also in pro and contra with regard to vaccines, and controversies on the best vector control strategies.

Different mosquito control strategies, such as insecticides (larvicides or adulticides), insecticide-treated nets, mechanical reduction in mosquito habitats, screens, and mosquito repellents, are used as primary prevention strategies for mosquito-borne diseases. These strategies reduce the contact rate between mosquito and human, by decreasing the population density of mosquitoes or the chance of contact itself. Although the use of mosquito repellents is the easiest and cheapest way to reduce contact between humans and mosquitoes, numerous implementation challenges remain, such as the difficulties of testing and quantifying the repellency and the fact that many different repellent phenomena are not well-defined (Deletre et al. 2016). Despite these aspects, many studies since 2015 have proven how mosquito repellents potentially prevent infections in humans due to mosquito bites (Alpern et al. 2016; Diaz 2016).

Besides the problems mentioned above, the characteristics of each disease also affect the complexity in understanding the spread of the disease. These include the extrinsic incubation period, effect of multiple strains of viruses, antibody-dependent enhancement (ADE), and temporary cross-immunity phenomena pertaining to dengue (Ferguson et al. 1999; Kooi et al. 2013), effect of multiple species of malarial parasites (Anderson et al. 1992), and the vector-bias effect in malaria and chikungunya (Tsetsarkin et al. 2007). Vector bias in malaria is defined as a situation where mosquitoes are more attracted to malaria-infected individuals (Lacroix et al. 2005). These phenomena arise as the anopheles mosquito searches for its meal (human blood) by using the sweat, breath, and odors of its human victims (Costantini et al. 1996; Mukabana et al. 2004).

A wide variety of mathematical models have been constructed and used to discuss and understand different aspects of the epidemic dynamics of mosquito-borne diseases [for modern reviews, see Mandal et al. (2011), Wiratsudakul et al. (2018)]. A mathematical model that discusses a vector-bias effect on the spread of malaria can be found in Xu and Zhao (2012), Xu and Zhang (2015), Kim et al. (2017), and Li et al. (2018). The model was constructed as a system of ordinary/partial differential equations, and then the routine exercise was conducted (e.g., analyses of equilibrium states with regard to existence and stability, and basic reproduction number) to arrive at the results. The optimal control problem was applied to the malaria model by Buonomo and Vargas-De-León (2014), and the results showed that the intervention costs would increase whenever the vector-bias effect increases.

A mathematical model discussing how mosquito repellent potentially reduces the spread of dengue can be found in Aldila et al. (2012a, b). By applying the optimal control problem to their model, they found that mosquito repellent could successfully and optimally suppress the spread of dengue. However in these models, mosquito repellent only reduces the human–mosquito contact. The fact that mosquito repellent can also reduce the ability of mosquitos to find their meal (blood) for reproduction has not been discussed yet in these models. Such an effect on the mosquito reproduction could affect the mosquito population dynamics, and subsequently on the dynamics of mosquito-borne disease spread.

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In this paper, we shall show a reasonable mathematical modeling introducing such effects of a mosquito repellent use, taking into account the relationship between its use and the mosquito population dynamics. Following the modeling, our mathematical model includes not only the effect of mosquito repellent use but also the mosquito's attraction to the infected human, which causes mosquitoes' biased distribution around the human population. Since we believe that our model is open to developments in the future to other aspects of mosquito-borne diseases, and since the modeling includes some non-trivial parts for its reasonable design, we carefully describe it in the first part of this paper. Then, we analyze our model to show the existence of thresholds for mosquito repellent efficacy and its utilization rate in the human population with respect to the containment of mosquito-borne disease. Further, we show that the containment of mosquito-borne disease becomes harder when the mosquitoes' distribution is biased more around the human population. We expect that this paper could contribute to the more advanced study on some vector-borne disease dynamics and to reconsider on the problem discussed in the previous literatures making use of the mathematical model.

2 Generic Model System

Let the human population (N) be divided into three classes, that is, susceptible (S), infected (I), and recovered (R) humans, while the adult mosquito population (M) is divided into two classes, namely non-carrier (susceptible) (U) and carrier (infected) (V) mosquitoes. Moreover, we consider the mosquito larva population (L) to ensure correct modeling, as described in later sections. We assume that there is no migration both in the human and mosquito populations, and that *no additional death rate is attributed to mosquito-borne diseases*.

In this paper, we consider the population dynamics governed by the following system of ordinary differential equations:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = B(N) - \Lambda_h S - \mu_h S + \nu R \tag{1a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \Lambda_h(S, I, R, V)S - \rho I - \mu_h I \tag{1b}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \rho I - \mu_h R - \nu R \tag{1c}$$

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \chi(L)\, r_m(U, V) - \gamma L \tag{1d}$$

$$\frac{\mathrm{d}U}{\mathrm{d}t} = \gamma L - \Lambda_m U - \mu_m U \tag{1e}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \Lambda_m(S, I, R)U - \mu_m V, \tag{1f}$$

where $S = S(t)$, $I = I(t)$, $R = R(t)$, $L = L(t)$, $U = U(t)$, and $V = V(t)$ are the population sizes (e.g., density) for the corresponding classes at time t. The functions Λ_h, Λ_m, and r_m are, respectively, the infection rate per susceptible human,

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the infection rate per non-carrier adult mosquito, and the net reproduction rate of the mosquito population, which are generally as functions of related population sizes (see the later sections for details on their modeling). Specifically, Λ_h and Λ_m are sometimes called the "force of infection" from the mosquito to the human, and that from the human to the mosquito. The term $B(N)$ is the net reproduction rate of the human population, which is now assumed to be independent of the epidemic structure, and to depend only on the total human population size $N = S + I + R$.

Positive parameters μ_h and μ_m are the natural death rates, respectively, for the human and the adult mosquito, which are assumed to be independent of the state in terms of the disease. Positive parameter ρ is the recovery rate of the infected human. Thus, the expected duration for the infected to retain infectivity is given by $1/\rho$. We assume now that the recovered human has gained immunity against the mosquito-borne disease. Positive parameter ν is the rate of the waning of the immunity. The expected duration to maintain the immunity is now given by $1/\nu$.

The positive parameter γ is the coefficient of the transition of a larva to an adult. Hence, the expected duration of the larva period is now given by $1/\gamma$. The function $\chi(L)$ of L introduces a density effect with regard to the survival and growth of larvae. The larvae need an appropriate microhabitat, such as a puddle with water, for their survival, growth, and maturation. Thus, the larva population size is limited by environmental conditions, which restrict the availability of appropriate habitats within the region inhabited by the mosquito population. Moreover, there is intraspecific competition between larvae within each microhabitat. In fact, Lord (1998) provided evidence suggesting the density effect due to such habitat limitations and intraspecific competition pertaining to larvae population dynamics. [The overview and discussion about the density effect on the mosquito larvae population can be found in Legros et al. (2009), and related classical arguments can be seen in Gurney et al. (1980) and Dye (1984).] Thus, we introduce the density effect with a function $\chi(L)$ of L. The function χ is assumed to not exceed 1 and be a continuous function that monotonically decreases in terms of $L > 0$: $\chi(0) = 1$, $\chi(L) < 1$, and $\chi'(L) < 0$ for any $L > 0$.

3 Modeling to Introduce the Effect of Mosquito Repellent Use

3.1 Biting Rate and Mosquito Repellent Use

Lacroix et al. (2005) found that malaria-infected human individuals were more attractive to mosquitoes. Their study suggested that mosquitoes are more attracted to human individuals infected with the transmissible gametocyte stage of malaria parasites than to uninfected ones or ones infected with asexual, non-transmissible stages. A similar preference has been found for Chikungunya fever (Tsetsarkin et al. 2007).

Since such a vector-bias effect exists between the human and mosquito, resulting in differences in the likeliness of encounters between them, we introduce the "biting rate" via a positive constant parameter b. Then, we assume that the expected number of bites by the mosquito in the sufficiently short period Δt is given by $b\Delta t$ between a mosquito and a human individual without the mosquito repellent. Note that in this

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paper, we consider the simplest case, assuming that *the biting rate is independent of the states of the mosquito and human in terms of disease*.

Further, we assume that *mosquito repellent use reduces the number of bites*. The biting rates for a human who has applied mosquito repellent are now given by $(1-\xi)b$, with a positive parameter ξ $(0 < \xi < 1)$, which refers to the efficacy of the mosquito repellent to reduce the number of bites. The more effective the mosquito repellent, the larger the value of ξ. In reality, the efficacy of mosquito repellent depends on how manufacturers/pharmaceutical companies develop and choose the best chemicals to make the mosquito repellent. In a variety of mosquito repellent materials, for example, some are based on plants that emit mosquito-repelling scents, such as lavender, lemon eucalyptus oil, and thyme extract oil.

It should be noted that we ignore the intraspecific competition in the adult mosquito population with respect to the encounters with and bites to human individuals, which can be regarded as the resource for the energy required for the mosquito's reproduction. Further, we do not take into account any density-dependent interaction between adult mosquitoes in our modeling. This type of modeling assuming a constant biting rate without density dependence may be called "reservoir frequency-dependent transmission" (Wonham et al. 2006), which follows Anderson and May (1991).

3.2 Biased Distribution of Mosquitoes Among Human Individuals

We use the parameter α to introduce *the bias of a mosquito's to be attracted to the infected human*. When $\alpha = 0$, the mosquito randomly comes into contact with human individuals, without any bias depending on the encountered human's state in terms of the disease. For the case of malaria, we could consider $\alpha > 0$ because the mosquito is attracted to infected individuals rather than uninfected ones (Lacroix et al. 2005; Tsetsarkin et al. 2007).

Using the parameter α, we introduce the biased distribution of adult mosquitoes among human individuals in the following way. The expected total number of adult mosquitoes around the susceptible human individuals $\mathcal{M}_{\mathrm{S}}$ is assumed to be given by

$$\mathcal{M}_{\mathrm{S}} = \theta \frac{S}{S + (1+\alpha)I + R} M, \tag{2}$$

while those around the infected human individuals $\mathcal{M}_{\mathrm{I}}$ and the recovered human individuals $\mathcal{M}_{\mathrm{R}}$ are, respectively, given by

$$\mathcal{M}_{\mathrm{I}} = \theta \frac{(1+\alpha)I}{S + (1+\alpha)I + R} M \quad \text{and} \quad \mathcal{M}_{\mathrm{R}} = \theta \frac{R}{S + (1+\alpha)I + R} M \tag{3}$$

with the positive parameter $\theta < 1$. The ratio θ of the adult mosquito population $M = U + V$, that is, $\theta M = \mathcal{M}_{\mathrm{S}} + \mathcal{M}_{\mathrm{I}} + \mathcal{M}_{\mathrm{R}}$ is assumed to lie in the zone they encounter human individuals in. The parameter θ refers to the *encounterability* between the

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adult mosquito and the human, which could reflect the sanitary conditions, cultural and social factors, etc., related to the encounter between them. In other words, the ratio $1-\theta$ of the adult mosquito population, $(1-\theta)M$, is assumed to be outside the zone in which the human hardly encounters them.

3.3 Infection Rate Per Susceptible Human Individual Λ_h

Using the above-mentioned expected number of mosquitoes around the susceptible human individuals, the expected number of mosquitoes per susceptible human individual is now given by $\mathcal{M}_S/S$. Within this number of mosquitoes, the ratio of carrier mosquitoes is expected to be given by V/M. Here, we are making use of the *mean-field approximation* in contact dynamics. Then, the expected *total* number of bites by the carrier mosquitoes in the period Δt for the susceptible human individual *without* the mosquito repellent use is given by

$$b\Delta t\,\frac{V}{M}\,\frac{\mathcal{M}_S}{S}, \tag{4}$$

while that for the susceptible human individual *with* the mosquito repellent use is given by

$$(1-\xi)b\Delta t\,\frac{V}{M}\,\frac{\mathcal{M}_S}{S}. \tag{5}$$

Let us assume that the probability of infection for a susceptible human individual in the sufficiently short period Δt is proportional to the expected total number of bites by the carrier mosquitoes in this period. Hence, from (4) and (5),

$$\beta_h b\Delta t\,\frac{V}{M}\,\frac{\mathcal{M}_S}{S} \tag{6}$$

for the human individual *without* the mosquito repellent use, and

$$\beta_h(1-\xi)b\Delta t\,\frac{V}{M}\,\frac{\mathcal{M}_S}{S} \tag{7}$$

for the human individual *with* the mosquito repellent use. The positive coefficient β_h denotes the probability of successful infection *per bite* by the carrier mosquito ($0 < \beta_h \leq 1$). Thus, its value would reflect the detail of disease transmission to determine the possibility of the susceptible human contracting a successful infection from the carrier mosquito. The larger β_h refers to the easier transmission of the disease from the carrier mosquito to the susceptible human.

From (6) and (7) with (2), the infection rate Λ_h per susceptible human individual is now given by

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$$\Lambda_h = (1-\omega)\,\beta_h b\,\frac{V}{M}\,\frac{\mathcal{M}_S}{S} + \omega\beta_h(1-\xi)b\,\frac{V}{M}\,\frac{\mathcal{M}_S}{S}$$
$$= (1-\xi\omega)\,\beta_h b\,\theta\,\frac{V}{S+(1+\alpha)I+R} \tag{8}$$

as the function of S, I, R, and V, where ω is the ratio of human individuals who use the mosquito repellent, say *the utilization rate* of the mosquito repellent. We now assume that *the utilization rate is independent of the state of the human with respect to the disease*. That is, the ratio of susceptible human individuals who use the mosquito repellent is assumed to be equal to that of infected human individuals and to that of removed human individuals. The utilization rate of the mosquito repellent ω is related to the human behavior determined also by the cultural and social background of the considered population. It could be controlled and changed by an intensive social campaign, and be affected by the policy on the public health by the government.

Hereafter, we call the parameter value $\xi\omega$ ($0 \le \xi\omega \le 1$) *the effective utilization rate*. Indeed, if $\xi = 0$ when the mosquito repellent is useless, the utilization rate ω has no meaning with regard to controlling the epidemic dynamics. In contrast, if $\xi = 1$ when the mosquito repellent can always repel the mosquito from the human, then the utilization rate ω itself denotes the frequency of disease-free human individuals. The larger the effective utilization rate $\xi\omega$, the stronger the effect of mosquito repellent use on epidemic dynamics, as shown in the later sections.

Strictly speaking, the infection rate Λ_h of (8) refers to the expected infection rate for a susceptible randomly chosen human individual, independent of whether the individual uses the mosquito repellent or not. At the same time, it can be regarded as the infection rate averaged over all susceptible human individuals when the ratio ω of the human population uses the mosquito repellent.

3.4 Infection Rate of Non-carrier Mosquitoes Λ_m

Similarly, for the case of disease transmission from a carrier mosquito to a susceptible human, we assume that the probability of the successful disease transmission from the infected human to the non-carrier mosquito within a sufficiently short period Δt is proportional to the total number of bites. Thus, we refer $\beta_m b\Delta t$ for a non-carrier mosquito around an infected human who does not use mosquito repellent, and $\beta_m(1-\xi)b\Delta t$ for a non-carrier mosquito around an infected human who uses mosquito repellent, with the positive parameter β_m, a proportional coefficient closely related to the infectivity of the disease from the infected human to the non-carrier mosquito via biting. That is, the positive coefficient β_m refers to the probability of the successful transmission of the pathogen from the infected human to the non-carrier mosquito *per bite* ($0 < \beta_m \le 1$).

Since the probability that a randomly chosen non-carrier mosquito stays around an infected human is given by $\mathcal{M}_I/M$, the infection rate Λ_m per non-carrier mosquito is now given by

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$$\Lambda_m = \beta_m b\,(1-\omega)\,\frac{\mathcal{M}_\mathrm{I}}{M} + \beta_m (1-\xi) b\,\omega\,\frac{\mathcal{M}_\mathrm{I}}{M}$$
$$= (1-\xi\omega)\,\beta_m b\,\theta\,\frac{(1+\alpha)I}{S+(1+\alpha)I+R}, \tag{9}$$

where we use (3). The infection rate of mosquito Λ_m is the function of S, I, and R.

Such modeling for the coefficients Λ_h and Λ_m described in the previous and the present section follows that of Ngwa and Shu (2000) and Brauer et al. (2016) pertaining to malaria dynamics, or of Bowman et al. (2005), Cruz-Pacheco et al. (2005), and Wonham et al. (2006) for the West Nile virus transmission. In their modelings, these coefficients were simply proportional to V/N and I/N, respectively, since their models did not consider biased distribution of adult mosquitoes among host individuals, which is the case when $\alpha = 0$ in our model It should be noted that modeling to include the disease transmission term(s) is crucial for an appropriate conclusion to be derived from the analysis of the model, as reviewed and discussed by Wonham et al. (2006).

3.5 Mosquito Net Reproduction Rate r_m

In this section, we first consider the energy gain of the mosquito from biting humans. It is well-known that the reproduction of the mosquito population depends on the extent of access of the mosquito to the blood of other living creatures, primarily humans. Some species of mosquitoes show a preference for the blood source used for their metabolism, energy, and reproduction of eggs (Takken and Verhulst 2013). Phasomkusolsil et al. (2013) experimentally found that the durability rate, fecundity rate, and hatching rate decreased when sheep provided the blood source for the mosquito compared to when it was human. Other than the above facts, here in this paper, we shall try to capture the nature of a mosquito-borne disease especially in urban areas where the population density is relatively high and the other blood sources for the mosquito reproduction would be hardly available, so that we could regard the humans as the principal resource and ignore the other blood sources for the mosquito reproduction.

Let us assume that the energy gain of a mosquito individual in the sufficiently short period Δt is proportional to the number of human individuals bitten in the same period. Further, the reproduction of mosquito offsprings in the period Δt is assumed to be proportional to the energy gain in the period, and is independent of the state of the mosquito with respect to disease. *Every offspring is assumed to be non-carrier, that is, no vertical transmission is introduced.*

In the case without mosquito repellent use, each mosquito around the human produces the expected number of non-carrier offsprings, given by $cb\Delta t$ in the period Δt, where c is the coefficient used to convert the energy gain to the reproduction rate. Since the biting rate becomes $(1-\xi)b$ $(0 < \xi < 1)$ for the human with mosquito repellent use, as introduced in the previous section, so does the reproduction rate.

As a result, we obtain the following equation as the total number of produced mosquito offsprings $r_m \Delta t$ in the sufficiently short period Δt:

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$$
\begin{aligned}
r_m \Delta t = {} & cb\Delta t\,(1-\omega)\,\frac{U}{M}\,\mathcal{M}_{\mathrm{S}} + c(1-\xi)b\Delta t\,\omega\,\frac{U}{M}\,\mathcal{M}_{\mathrm{S}} \\
& + cb\Delta t\,(1-\omega)\,\frac{U}{M}\,\mathcal{M}_{\mathrm{I}} + c(1-\xi)b\Delta t\,\omega\,\frac{U}{M}\,\mathcal{M}_{\mathrm{I}} \\
& + cb\Delta t\,(1-\omega)\,\frac{U}{M}\,\mathcal{M}_{\mathrm{R}} + c(1-\xi)b\Delta t\,\omega\,\frac{U}{M}\,\mathcal{M}_{\mathrm{R}} \\
& + cb\Delta t\,(1-\omega)\,\frac{V}{M}\,\mathcal{M}_{\mathrm{S}} + c(1-\xi)b\Delta t\,\omega\,\frac{V}{M}\,\mathcal{M}_{\mathrm{S}} \\
& + cb\Delta t\,(1-\omega)\,\frac{V}{M}\,\mathcal{M}_{\mathrm{I}} + c(1-\xi)b\Delta t\,\omega\,\frac{V}{M}\,\mathcal{M}_{\mathrm{I}} \\
& + cb\Delta t\,(1-\omega)\,\frac{V}{M}\,\mathcal{M}_{\mathrm{R}} + c(1-\xi)b\Delta t\,\omega\,\frac{V}{M}\,\mathcal{M}_{\mathrm{R}} \\
= {} & (1-\xi\omega)c\theta bM\Delta t. \qquad (10)
\end{aligned}
$$

The reproduction rate r_m is now given by the function of the total adult mosquito population size $M = U + V$: $r_m = r_m(M)$.

4 Dynamics of Total Population Sizes

From (1), we obtain the following equations, which govern the dynamics of total population sizes, $N = S + I + R$ and $M = U + V$:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = B(N) - \mu_h N \qquad (11a)$$

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \chi(L)\, r_m(M) - \gamma L \qquad (11b)$$

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \gamma L - \mu_m M, \qquad (11c)$$

where Eq. (11b) is the same as Eq. (1d).

Note that the system (11) does not include any epidemic variable (of S, I, R, U, and V) but is composed of only variables in terms of total population sizes N, L, and M. This means that the dynamics of total population sizes is not affected by the epidemic dynamics within it, and those sizes temporally change independently of how the epidemic variables do at the same time.

4.1 Assumption for Total Population Size in Epidemic Dynamics

In this paper, we consider a mathematical model under the condition that *the total population sizes of humans and mosquitoes have become constant independently of time*. This assumption may be called the "stationary state approximation" (SSA). This means that we consider the equilibrium state for the dynamics of total population size. Then, we discuss the efficiency of mosquito repellent use to suppress the outbreak of

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mosquito-borne disease under the condition that the total population sizes of humans and mosquitoes are constant independently of time.

This assumption would be reasonable in most real cases because the life cycle of mosquito is sufficiently faster than that of human. For this reason, we regard the time scale of epidemic dynamics as sufficiently fast compared to that of a significant change in the human population size.

Alternatively, our approach described in the following sections with the above assumption of constant population sizes to derive the model system given in the later Sect. 5 may be regarded as considering the *asymptotically autonomous system* for (1), as seen in the arguments by Castillo-Chavez and Thieme (1995). This means that the asymptotic behavior of (1) as $t \to \infty$ can be regarded as mathematically equivalent to that of the *limiting system* given in Sect. 5 for the asymptotically autonomous system rewritten from (1). We shall not step further in the mathematical arguments with the theory of asymptotically autonomous system, because our model system given in Sect. 5 can be indeed regarded as a model per se based on the reasonable modeling described in the following sections. [For an example of the mathematical detail treatment about the asymptotically autonomous system, see Bai et al. (2019) and references therein.]

4.2 The Human Population Size *N*

For the human total population size N governed by (11a), the assumption of the constant size leads to the following equality:

$$B(N) = \mu_h N. \tag{12}$$

Hence, we hereafter consider the population dynamics (1) with the human total population size N of a constant satisfying the equality (12), assuming a priori that it is asymptotically stable for the population dynamics given by (11a). Although a concrete formula of the function B of N is necessary to determine the size N, we do not need to determine it while we just use N as a constant size of the human population. Thus, we hereafter replace $B(N)$ by $\mu_h N$ with a given constant N.

4.3 The Mosquito Population Sizes *L* and *M*

Since the reproduction rate r_m is given by (10) which is the function of M only, the system of (11b, c) is closed in terms of L and M as follows:

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \chi(L)\,(1-\xi\omega)c\theta b M - \gamma L \tag{13a}$$

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \gamma L - \mu_m M. \tag{13b}$$

To apply the assumption of constant population sizes L and M, we need the following arguments to make sense the assumption as a reasonable modeling, and to make

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clear the relation of the mosquito population sizes L and M to the repellent use (i.e., ξ and ω) and the other factors involved in the population dynamics.

Let us consider the equilibrium $(L, M) = (L^*_\omega, M^*_\omega)$, which satisfies the following equations:

$$\chi(L^*_\omega)\,(1-\xi\omega)c\theta b M^*_\omega - \gamma L^*_\omega = 0; \quad \gamma L^*_\omega - \mu_m M^*_\omega = 0. \tag{14}$$

As a result, if the equilibrium $(L, M) = (L^*_\omega, M^*_\omega)$ exists, it is given by the positive root of the equation

$$\chi(L^*_\omega) = \frac{\mu_m}{(1-\xi\omega)c\theta b} \tag{15}$$

and $M^*_\omega = (\gamma/\mu_m)L^*_\omega$. Note that the values of L^*_ω and M^*_ω necessarily depend on those of ω and ξ. In other words, the equilibrium state depends on the mosquito repellent use. Notably, when nobody uses the mosquito repellent, let us denote the non-trivial equilibrium of (L, M) by (L^*_0, M^*_0), if it exists. By the monotonically decreasing nature of function χ, it is clear from (15) that L^*_ω is monotonically decreasing in terms of ω. Therefore, $L^*_\omega < L^*_0$ and subsequently $M^*_\omega < M^*_0$ for any positive ω, whenever they exist. This is a consistent nature of L^*_ω and M^*_ω because mosquito repellent use is now assumed to have a negative effect on mosquito reproduction.

Since $\chi(L)$ is less than 1 and monotonically decreasing in terms of $L > 0$, as mentioned in Sect. 2, the following condition should be necessarily satisfied for the existence of $L^*_\omega > 0$ satisfying (15):

$$\inf_{L\geq 0}\chi(L) < \frac{\mu_m}{(1-\xi\omega)c\theta b} < \chi(0) = 1,$$

that is,

$$\frac{c\theta b}{\mu_m}\inf_{L\geq 0}\chi(L) < \frac{1}{1-\xi\omega} < \frac{c\theta b}{\mu_m}, \tag{16}$$

where $\chi(L) < \chi(0) = 1$ for any $L > 0$ as assumed in Sect. 2. Generally, we allow that $\inf_{L\geq 0}\chi(L) = -\infty$. Further since $\chi(L)$ is monotonically decreasing in terms of $L > 0$, the non-trivial equilibrium is unique if it exists. Consequently, we obtain the following theorem about the existence of non-trivial equilibrium (L^*_ω, M^*_ω):

Theorem 1 *The non-trivial equilibrium (L^*_ω, M^*_ω) for the total mosquito population size exists only if condition (16) is satisfied. If it exists, it is uniquely given by*

$$L^*_\omega = \chi^{-1}\Big(\frac{\mu_m}{(1-\xi\omega)c\theta b}\Big); \quad M^*_\omega = \frac{\gamma}{\mu_m}L^*_\omega. \tag{17}$$

Then, we have the following corollary:

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Corollary 1 *The non-trivial equilibrium* $(L, M) = (L^*_\omega, M^*_\omega)$ *for the total mosquito population size exists only if*

$$\mathscr{R}_m := \frac{c\theta b}{\mu_m} > 1. \tag{18}$$

We define $\mathscr{R}_m$ as the *intrinsic net reproduction rate* of the mosquito population. This is because $\mathscr{R}_m$ refers to the upper bound for the net reproduction rate in terms of mosquito repellent use. The *net reproduction rate* is generally defined as the expected number of surviving (i.e., successfully mature) offsprings produced by a mosquito during its life span, which may be called *reproductive success*. In the context of our modeling, $\mathscr{R}_m$ can be regarded as the net reproduction rate of the mosquito population when nobody uses mosquito repellent. Indeed, from (10), the production rate of offsprings per adult mosquito in a unit time is given by $c\theta b$, while the expected life span of an adult mosquito is now given by $1/\mu_m$ from (11c).

Condition (16) means that the intrinsic net reproduction rate of the mosquito population $\mathscr{R}_m$ should necessarily be larger than a critical value $1/(1-\xi\omega)$ for the existence of $L^*_\omega > 0$ satisfying (15). Note that the value of $1/(1-\xi\omega)$ is necessarily not below 1 and not over $1/(1-\xi)$, because $0 \le \omega \le 1$ and $0 < \xi < 1$. Specifically, when nobody uses mosquito repellent, condition (16) results in the condition $\mathscr{R}_m > 1$. Hence, we note that under condition (16) with $\omega \ge 0$, the condition $\mathscr{R}_m > 1$ is necessarily satisfied.

These arguments are only about the existence of the equilibrium $(L, M) = (L^*_\omega, M^*_\omega)$, and it is still unclear whether an equilibrium such as the stable state is reachable. To reasonably apply the assumption of constant population sizes L and M, it is necessary to have a stable equilibrium for (13). Unstable equilibrium is not reasonable for our modeling with the assumption. Therefore, *we need to find the condition to make the equilibrium stable*. We discuss this aspect in the following sections.

4.4 Case of Unbounded Mosquito Population Growth

Equation (15) does not have any positive root if the following condition is satisfied:

$$\inf_{L\ge 0} \chi(L) > \frac{\mu_m}{(1-\xi\omega)c\theta b} = \frac{1}{(1-\xi\omega)\mathscr{R}_m}, \tag{19}$$

because $\chi(L)$ is monotonically decreasing in terms of $L > 0$. This is a case when condition (16) is unsatisfied. In this case, we obtain the following inequality from Eq. (13a):

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \chi(L)\,(1-\xi\omega)c\theta bM - \gamma L > \mu_m M - \gamma L = -\frac{\mathrm{d}M}{\mathrm{d}t}$$

for any $t \ge 0$. Then, we have

$$\frac{\mathrm{d}(L+M)}{\mathrm{d}t} > 0$$

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for any $t \geq 0$. Hence, if equation (15) does not have any positive root under condition (19), the mosquito population has no equilibrium and keeps temporally increasing in size toward infinity, that is, *unbounded mosquito population growth* occurs. This case of unbounded mosquito population growth can be easily proven by the phase plane analysis for system (13):

Theorem 2 *If the continuous function $\chi(L)$ satisfies condition (19), the mosquito population size temporally increases toward infinity, that is, the mosquito population size tends to grow unboundedly.*

As a special case, if

$$\inf_{L \geq 0} \chi(L) > \frac{1}{\mathscr{R}_m}, \tag{20}$$

the mosquito population grows unboundedly when nobody uses mosquito repellent. Thus, if condition (16) is satisfied for some $\omega > 0$ under condition (20), there could be a case where the unbounded mosquito population growth could be suppressed by the use of mosquito repellent but the growth would continue without its use.

If the condition of the inverse inequality to (19) is satisfied for a chosen function $\chi(L)$, the unbounded mosquito population growth never occurs, since it is easily shown in such a case that $d(L + M)/dt < 0$ for a sufficiently large value of $L + M$. As a specific variant of this result, we obtain the following corollary:

Corollary 2 *If the continuous function $\chi(L)$ satisfies the condition that $\lim_{L \to \infty} \chi(L) \leq 0$, the mosquito population approaches a positive equilibrium or goes extinct.*

4.5 Case of Mosquito Extinction

The non-trivial equilibrium cannot exist if

$$\mathscr{R}_m < \frac{1}{1 - \xi\omega}, \tag{21}$$

because this is the case when condition (16) is unsatisfied. In this case, we can easily find that the mosquito population eventually goes extinct:

Theorem 3 *If condition (21) is satisfied, the mosquito population goes extinct.*

From (13) and the decreasing nature of $\chi(L)$, we have

$$\begin{aligned} \frac{\mathrm{d}(L+M)}{\mathrm{d}t} &= \chi(L)\,(1-\xi\omega)c\theta bM - \mu_m M \\ &\leq \chi(0)\,(1-\xi\omega)c\theta bM - \mu_m M \\ &= (1-\xi\omega)\mu_m M\left(\mathscr{R}_m - \frac{1}{1-\xi\omega}\right) < 0 \end{aligned} \tag{22}$$

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for any $M > 0$ when condition (21) is satisfied. Thus, $L + M$ monotonically decreases in time as long as $M > 0$. This means that when condition (21) is satisfied, the mosquito population goes extinct.

Further, we find that condition (21) is necessarily satisfied if $\mathscr{R}_m < 1$, because the right-hand side of (21) is not less than 1 for any ω and $(1 - \xi)$. Thus, we have the following corollary:

Corollary 3 *If $\mathscr{R}_m < 1$, the mosquito population eventually goes extinct, independently of mosquito repellent use.*

This result is consistent with the meaning of the intrinsic net reproduction rate $\mathscr{R}_m$. When $\mathscr{R}_m < 1$, the expected number of surviving offsprings produced by a mosquito during its life span is less than 1, so that the expected number of adults in the subsequent generation must be less than the present value. This results in the eventual decrease in the population toward its extinction. In contrast, the mosquito extinction as per Theorem 3 when $\mathscr{R}_m > 1$ and condition (21) is satisfied can be regarded as the *repellent-induced* mosquito extinction. This repellent-induced mosquito extinction can occur in our model because only humans are assumed to be the resource for the mosquito's reproduction. However, even when other resources (besides humans) exist, such extinction could occur, for instance with a demographic fluctuation, if the other resources could not supply satisfactory reproductive energy for the mosquito population.

The behavior of the population dynamics given by (13) significantly depends on the detailed nature of function $\chi(L)$. However, we can carry out the local stability analysis on the trivial equilibrium $(L, M) = (0, 0)$ for any function $\chi(L)$ of class C^1. The Jacobian matrix about the equilibrium $(L, M) = (0, 0)$ is easily obtained as

$$\begin{bmatrix} -\gamma & (1-\xi\omega)c\theta b \\ \gamma & -\mu_m \end{bmatrix}. \tag{23}$$

From the characteristic equation for matrix (23), it can be easily proved that the equilibrium $(L, M) = (0, 0)$ is locally asymptotically stable if condition (21) is satisfied. This result is consistent with Theorem 3.

The results of this section and the previous allow us to draw the following conclusion:

Theorem 4 *Whenever the non-trivial equilibrium for the total population sizes exists, the mosquito population never goes extinct. In contrast, whenever the trivial equilibrium is asymptotically stable, the mosquito population necessarily goes extinct and no non-trivial equilibrium exists.*

4.6 Effect of Mosquito Repellent Use on the Persistence of the Mosquito Population

From the result, given as Corollary 3, it is not worthwhile to consider the case that $\mathscr{R}_m < 1$, because the mosquito population goes extinct independently of mosquito repellent use. Thus, let us consider only the case of $\mathscr{R}_m > 1$ in this section.

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Condition (21) can be rewritten as

$$\omega > \omega_c := \frac{1}{\xi}\left(1 - \frac{1}{\mathscr{R}_m}\right). \tag{24}$$

When condition (24) is satisfied, the mosquito population eventually becomes extinct. In contrast, when $\omega < \omega_c$, the mosquito population persists, so that mosquito repellent use cannot exterminate the mosquito population. This result means that a possibility exists such that a sufficiently large utilization rate of mosquito repellent causes the extinction of the mosquito population.

Even when condition (24) is not satisfied (so that the mosquito population is persistent), the improvement in the utilization rate of mosquito repellent is likely to not only suppress but also exterminate the mosquito population if

$$\xi > \xi_c := 1 - \frac{1}{\mathscr{R}_m}. \tag{25}$$

This is because ω_c is less than 1 when $\xi > \xi_c$.

If $\xi < \xi_c$, condition (24) cannot be satisfied for any ω such that $0 \le \omega \le 1$, because ω_c is then greater than 1. This means that when the efficacy of mosquito repellent ξ is poor and thus smaller than the critical value ξ_c, the mosquito population cannot be exterminated only with the improvement in the mosquito repellent utilization rate. In such a case, when and only when the efficacy of mosquito repellent ξ is improved, becoming high enough to exceed ξ_c, it becomes possible to exterminate the mosquito population with a sufficiently high mosquito repellent utilization rate. Hence, in this case, it becomes possible to exterminate the mosquito population with mosquito repellent use only after a new mosquito repellent with a sufficiently high efficacy could be developed and circulated in the human population.

4.7 Local Stability of the Non-trivial Equilibrium for the Mosquito Population

Let us consider the case that the non-trivial equilibrium $(L, M) = (L^*_\omega, M^*_\omega)$ exists under condition (16). The Jacobian matrix for the non-trivial equilibrium $(L, M) = (L^*_\omega, M^*_\omega)$ for system (13) can be obtained as follows:

$$\begin{aligned} J(L^*_\omega, M^*_\omega) &= \begin{bmatrix} \chi'(L^*_\omega)\,(1-\xi\omega)c\theta b M^*_\omega - \gamma & \chi(L^*_\omega)\,(1-\xi\omega)c\theta b \\ \gamma & -\mu_m \end{bmatrix} \\ &= \begin{bmatrix} \gamma\left\{\frac{\chi'(L^*_\omega)L^*_\omega}{\chi(L^*_\omega)} - 1\right\} & \mu_m \\ \gamma & -\mu_m \end{bmatrix}, \end{aligned} \tag{26}$$

where we use (14) and (15). Since $\chi'(L^*_\omega) < 0$ from the assumption for function χ, we immediately obtain $\mathrm{tr}\, J(L^*_\omega, M^*_\omega) < 0$ and $\det J(L^*_\omega, M^*_\omega) > 0$. Therefore, the real part of every eigenvalue for $J(L^*_\omega, M^*_\omega)$ is negative for any $L^*_\omega > 0$. As a result, we find that the non-trivial equilibrium is necessarily locally stable whenever it exists.

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From Theorems 1 and 4, and using the (L, M)-phase plane analysis, we can get the following conclusion:

Theorem 5 *The non-trivial equilibrium for the total population sizes is necessarily globally asymptotically stable whenever it exists.*

Since the aim of this paper is to theoretically discuss the effect of mosquito repellent use on the epidemic dynamics of mosquito-borne disease, we must primarily start our argument with the situation in which the disease exists for the considered human population. This means that we need to discuss our problem with regard to the persistent mosquito population. Therefore, in the following part, *we consider our model under condition* (16), *when the non-trivial equilibrium* $(L, M) = (L^*_\omega, M^*_\omega)$ *is globally stable.*

5 Epidemic Dynamics Model with the Constant Total Population Sizes

Using the results obtained in Sect. 4 for model (1), we apply the assumption of constant total population sizes of humans and mosquitoes. Then, we have the following system as our epidemic dynamics model with (8) and (9):

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \mu_h N - (1-\xi\omega)\beta_h b\theta \frac{V}{S+(1+\alpha)I+R} S - \mu_h S + \nu R \tag{27a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = (1-\xi\omega)\beta_h b\theta \frac{V}{S+(1+\alpha)I+R} S - \rho I - \mu_h I \tag{27b}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \rho I - \mu_h R - \nu R \tag{27c}$$

$$\frac{\mathrm{d}U}{\mathrm{d}t} = \mu_m M^*_\omega - (1-\xi\omega)\beta_m b\theta \frac{(1+\alpha)I}{S+(1+\alpha)I+R} U - \mu_m U \tag{27d}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = (1-\xi\omega)\beta_m b\theta \frac{(1+\alpha)I}{S+(1+\alpha)I+R} U - \mu_m V, \tag{27e}$$

where $N = S + I + R$ and $M^*_\omega = U + V$ are constant independently of time, and M^*_ω is given by (17) under condition (16). This system (27) may be regarded as the limiting system for the asymptotically autonomous system (1) with (11) (Castillo-Chavez and Thieme 1995; Bai et al. 2019).

This model (27) is similar to that for malaria dynamics in Bustamam et al. (2018), whereas their model did not take into account either the biased distribution of mosquitoes or the effect of mosquito repellent use; rather, it specifically involved the effect of vaccination in the vaccinated class of the human population.

Note that the total population size of mosquitoes M^*_ω depends on the efficacy (ξ) and the utilization rate of mosquito repellent (ω). As mentioned in the previous section, we discuss the epidemic dynamics when the mosquito population keeps a certain positive size, that is, when it persists, under condition (16).

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Making use of the following transformations of variables and parameters,

$$f_S = \frac{S}{N}; \quad f_I = \frac{I}{N}; \quad f_R = \frac{R}{N}; \quad f_U = \frac{U}{M_\omega^*}; \quad f_V = \frac{V}{M_\omega^*};$$
$$\eta_\omega = \frac{M_\omega^*}{N}; \quad \sigma_h = \beta_h b\,\theta; \quad \sigma_m = \beta_m b\,\theta, \tag{28}$$

we obtain the system in terms of population frequencies, f_S, f_I, f_R, f_U, and f_V with $f_S + f_I + f_R = 1$ and $f_U + f_V = 1$, which is mathematically equivalent to (27):

$$\frac{\mathrm{d}f_S}{\mathrm{d}t} = \mu_h - (1-\xi\omega)\sigma_h \frac{f_V}{f_S + (1+\alpha)f_I + f_R}\eta_\omega f_S - \mu_h f_S + \nu f_R \tag{29a}$$
$$\frac{\mathrm{d}f_I}{\mathrm{d}t} = (1-\xi\omega)\sigma_h \frac{f_V}{f_S + (1+\alpha)f_I + f_R}\eta_\omega f_S - \rho f_I - \mu_h f_I \tag{29b}$$
$$\frac{\mathrm{d}f_R}{\mathrm{d}t} = \rho f_I - \mu_h f_R - \nu f_R \tag{29c}$$
$$\frac{\mathrm{d}f_U}{\mathrm{d}t} = \mu_m - (1-\xi\omega)\sigma_m \frac{(1+\alpha)f_I}{f_S + (1+\alpha)f_I + f_R} f_U - \mu_m f_U \tag{29d}$$
$$\frac{\mathrm{d}f_V}{\mathrm{d}t} = (1-\xi\omega)\sigma_m \frac{(1+\alpha)f_I}{f_S + (1+\alpha)f_I + f_R} f_U - \mu_m f_V. \tag{29e}$$

Then, we can draw the following three-dimensional closed system from the above five-dimensional system (29):

$$\frac{\mathrm{d}f_S}{\mathrm{d}t} = -(1-\xi\omega)\sigma_h \frac{f_V f_S}{1+\alpha f_I}\eta_\omega + (\mu_h + \nu)(1 - f_S) - \nu f_I \tag{30a}$$
$$\frac{\mathrm{d}f_I}{\mathrm{d}t} = (1-\xi\omega)\sigma_h \frac{f_V f_S}{1+\alpha f_I}\eta_\omega - (\mu_h + \rho) f_I \tag{30b}$$
$$\frac{\mathrm{d}f_V}{\mathrm{d}t} = (1-\xi\omega)\sigma_m \frac{(1+\alpha)f_I(1-f_V)}{1+\alpha f_I} - \mu_m f_V. \tag{30c}$$

6 Basic Reproduction Number

In the biological context, the basic reproduction number is defined as the expected number of new cases of an infection caused by an infected individual in a population consisting of susceptible contacts only. Following this biological definition, a mathematical theory is used to derive the basic reproduction number as the spectrum radius of a specific matrix called the "next-generation matrix" for the system of ordinary differential equations governing epidemic dynamics [see Diekmann et al. (2013) for a complete reference, or see van den Driessche (2017) for the recent review]. As shown in "Appendix A," making use of the next-generation matrix with the theory given by van den Driessche and Watmough (2002, 2008), we can derive the following basic reproduction number $\mathscr{R}_0$ for model (30):

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$$\mathscr{R}_0 := \frac{(1-\xi\omega)^2\sigma_m\sigma_h\eta_\omega(1+\alpha)}{\mu_m(\mu_h+\rho)}$$
$$= \underbrace{\left\{(1-\xi\omega)\beta_m b\theta(1+\alpha)\cdot\frac{1}{\rho+\mu_h}\right\}}_{\text{production of carrier mosquitoes}}\cdot\underbrace{\left\{(1-\xi\omega)\beta_h b\theta\eta_\omega\cdot\frac{1}{\mu_h}\right\}}_{\text{human infection with the carrier mosquitoes}}. \quad (31)$$

Note that this formula of the basic reproduction number $\mathscr{R}_0$ may be specifically called "type reproduction number," similar to the terminology of Roberts and Heesterbeek (2003) and Heesterbeek and Roberts (2007), because we are interested only in the total number of expected secondary infections in human individuals originating from an infected human individual (also see Smith et al. 2007; Yakob and Clements 2013; van den Driessche 2017). Although a different formula ($\mathscr{R}_0$) could be mathematically derived for our model (30), we consider only the above $\mathscr{R}_0$ of (31) in this paper. [For such possibly different expressions of the basic reproduction number, see the arguments in Brauer et al. (2016), Cushing and Diekmann (2016), van den Driessche (2017), and Lewis et al. (2019).]

The basic reproduction number $\mathscr{R}_0$, given by (31), can be rewritten as follows:

$$\mathscr{R}_0 = (1-\xi\omega)^2\frac{M_\omega^*}{M_0^*}\overline{\mathscr{R}}_0, \quad (32)$$

where $\overline{\mathscr{R}}_0$ is the basic reproduction number when nobody uses mosquito repellent, that is, when $\omega = 0$:

$$\overline{\mathscr{R}}_0 := \frac{\sigma_m}{\mu_m}(1+\alpha)\frac{\sigma_h}{\mu_h+\rho}\frac{M_0^*}{N}. \quad (33)$$

It is clear that $\mathscr{R}_0 \le \overline{\mathscr{R}}_0$ always, because $M_\omega^* \le M_0^*$ always and $1-\xi\omega \le 1$.

7 Equilibrium States

7.1 Disease-Free Equilibrium E_0

The disease-free equilibrium (DFE) E_0 of system (30) is given by $(f_S, f_I, f_V) = (1, 0, 0)$. The local stability of E_0 can be analyzed with the Jacobian matrix approach. The Jacobian matrix of system (30), evaluated at E_0 gave us three eigenvalues, that is, $-\mu_h - \nu$ and the other two derived from the roots of the following quadratic equation in terms of λ:

$$\lambda^2 + (\mu_h+\mu_m+\rho)\lambda + \mu_m(\mu_h+\rho)(1-\mathscr{R}_0) = 0.$$

Hence, we can easily find that the real part of every eigenvalue is negative if and only if $\mathscr{R}_0 < 1$:

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Lemma 1 *The disease-free equilibrium E_0 of system (30) always exists and is locally asymptotically stable if $\mathscr{R}_0 < 1$, while it is unstable if $\mathscr{R}_0 > 1$.*

7.2 Endemic Equilibrium E_+

At the endemic equilibrium E_+, all classes in both the human and mosquito populations have positive equilibrium values. The endemic equilibrium E_+ given by $(f_S, f_I, f_V) = (f_S^*, f_I^*, f_V^*)$ is uniquely determined by

$$f_S^* = 1 - \frac{\rho + \mu_h + \nu}{\mu_h + \nu} f_I^*, \quad \frac{f_V^*}{1 - f_V^*} = \frac{\sigma_m}{\mu_m}(1 - \xi\omega)\frac{(1+\alpha) f_I^*}{1 + \alpha f_I^*}, \tag{34}$$

and f_I^* is obtained as follows: when $\alpha = 0$,

$$f_I^* = \left(\mathscr{R}_0\big|_{\alpha=0} - 1\right)\left\{\frac{\rho + \mu_h + \nu}{\mu_h + \nu}\mathscr{R}_0\big|_{\alpha=0} + \frac{\sigma_m}{\mu_m}(1 - \xi\omega)\right\}^{-1}, \tag{35}$$

and when $\alpha > 0$, $f_I^* = \frac{\zeta^* - 1}{\alpha}$ with

$$\zeta^* = \frac{a_1 + \sqrt{a_1^2 + 4a_0a_2}}{2a_2} \tag{36}$$

which is the larger root of the following quadratic equation in terms of ζ such that $1 < \zeta^* < 1 + \frac{\mu_h + \nu}{\rho + \mu_h + \nu}\alpha$ in order to make both f_I^* and f_S^* positive and their sum less than 1:

$$F(\zeta) := a_2\zeta^2 - a_1\zeta - a_0 = 0, \tag{37}$$

where

$$\begin{aligned} a_2 &= \alpha + \frac{\sigma_m}{\mu_m}(1+\alpha)(1 - \xi\omega); \\ a_1 &= \frac{\sigma_m}{\mu_m}(1+\alpha)(1 - \xi\omega) - \frac{\rho + \mu_h + \nu}{\mu_h + \nu}\mathscr{R}_0; \\ a_0 &= \left(\alpha + \frac{\rho + \mu_h + \nu}{\mu_h + \nu}\right)\mathscr{R}_0. \end{aligned}$$

It can be easily proved that equation $F(\zeta) = 0$ given by (37) has a unique root greater than 1 and less than $1 + \frac{\mu_h + \nu}{\rho + \mu_h + \nu}\alpha$ if and only if $F(1) < 0$ and $F(1 + \frac{\mu_h + \nu}{\rho + \mu_h + \nu}\alpha) > 0$. In conclusion, we can obtain the following result about the existence of the endemic equilibrium E_+:

Lemma 2 *The endemic equilibrium E_+ of system (30) exists if and only if $\mathscr{R}_0 > 1$.*

Further, when the endemic equilibrium E_+ exists, we can prove that it is locally asymptotically stable, as shown in "Appendix B," making use of a local Lyapunov function:

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Lemma 3 *The endemic equilibrium E_+ of system (30) is locally asymptotically stable whenever it exists.*

As a result, we obtain the following theorem from Lemmas 1, 2, and 3:

Theorem 6 *If $\mathscr{R}_0 < 1$, only the disease-free equilibrium exists to be locally asymptotically stable. If $\mathscr{R}_0 > 1$, the disease-free equilibrium is unstable, while the endemic equilibrium exists, and is unique and locally asymptotically stable.*

Numerical calculations about our model imply that the endemic equilibrium E_+ would be not only locally but also globally asymptotically stable whenever it exists, though we could not give the mathematical proof.

8 Dependence of Endemics on Each Factor

In this section, we analyze the dependence of the basic reproduction number $\mathscr{R}_0$ on the parameters α, ω, and ξ, and discuss the relation of the endemics of disease to mosquito repellent use. To simplify the argument, we carry out the following arguments under the condition that the total adult mosquito population size M_0^* given by (17) with $\omega = 0$ exists. Thus, from Corollary 3, we hereafter consider the case when the intrinsic net reproduction rate of the mosquito population $\mathscr{R}_m$ necessarily satisfies the condition $\mathscr{R}_m > 1$.

Now, let us consider a case with $\omega > 0$ such that M_ω^* given by (17) exists when condition (16) is satisfied. Since $\mathscr{R}_0 \leq \overline{\mathscr{R}}_0$ (the basic reproduction number when nobody uses mosquito repellent), if $\overline{\mathscr{R}}_0 < 1$, as shown in Theorem 6, the disease eventually disappears even when nobody uses mosquito repellent. Such a case is not of our interest because it can be regarded as a situation where mosquito-borne diseases would not pose a serious public health problem. Thus, let us hereafter consider the case that the disease is endemic without mosquito repellent use, so that $\overline{\mathscr{R}}_0 > 1$.

8.1 Mosquito Repellent Use

As M_ω^* and $1 - \xi\omega$ are decreasing in terms of ω, the higher the mosquito repellent use, the smaller the value of $\mathscr{R}_0$. This is a consistent result because mosquito repellent use is now assumed to have a negative effect on mosquito reproduction, possibly reducing the endemicity of mosquito-borne disease.

8.2 Mosquito's Preference to an Infected Human

A larger α denotes that the mosquito's preference (attraction) to the infected human is stronger, which causes a biased distribution of mosquitoes with respect to the human state of disease infection. Since the mosquito's stronger preference makes $\overline{\mathscr{R}}_0$ and subsequently $\mathscr{R}_0$ greater, the mosquito's preference contributes positively to the endemics.

In the next section, we discuss the contribution of the biased distribution of mosquitoes to the endemics in more detail, making use of a specific linear function χ.

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8.3 Case of Specific Linear Function χ

Now, let us consider a specific function $\chi(L)$ given by

$$\chi(L) = 1 - \frac{L}{K} \tag{38}$$

with a positive parameter K. The introduction of this linear function for χ may be regarded as that of a density-dependent competition in the larvae population. In the mathematical modeling of intraspecific competition, it is frequently introduced by a quadratic-like term of the population density, like the logistic equation for the single species population dynamics. This could be regarded as the case also in our model with the above linear function (38).

r_m means the mosquito net reproduction rate given by (10), which provides the renewal of mosquito offspring density as explained in Sect. 3.5. As explained in Sect. 2, the function χ can be translated as the per capita survival and growth probability of mosquito larva, including the density effect on the survival and growth. Since the density effect in (38) is given by the term proportional to the larva density L, the net reduction in the larva population size under the density effect results in a proportional term to Lr_m. The product Lr_m is not the square of L but is proportional to the product of L and M, which can be regarded as a second-order term of larva population density. Indeed in our modeling, the renewal of larva population r_m is introduced by (10), proportional to the adult mosquito population density M, so that the term by the product of L and M does not mean the interaction between the larva and the adult but does that among the larvae.

In this case, from Corollary 2, the mosquito population dynamics necessarily has an asymptotically stable nonnegative equilibrium. Since M^*_ω is given by (17) under condition (16):

$$M^*_\omega = \frac{\gamma}{\mu_m} K\left\{1 - \frac{1}{(1-\xi\omega)\mathscr{R}_m}\right\} \tag{39}$$

with $(1-\xi\omega)\mathscr{R}_m > 1$, the basic reproduction number (32) becomes

$$\mathscr{R}_0 = \frac{(1-\xi\omega)\{(1-\xi\omega) - 1/\mathscr{R}_m\}}{1 - 1/\mathscr{R}_m}\,\overline{\mathscr{R}}_0 \tag{40}$$

with

$$\overline{\mathscr{R}}_0 = \frac{\sigma_m}{\mu_m}(1+\alpha)\,\mathscr{B}\Big(1 - \frac{1}{\mathscr{R}_m}\Big), \tag{41}$$

where

$$\mathscr{B} := \frac{\sigma_h}{\mu_h + \rho}\,\frac{\gamma}{\mu_m}\,\frac{K}{N}.$$

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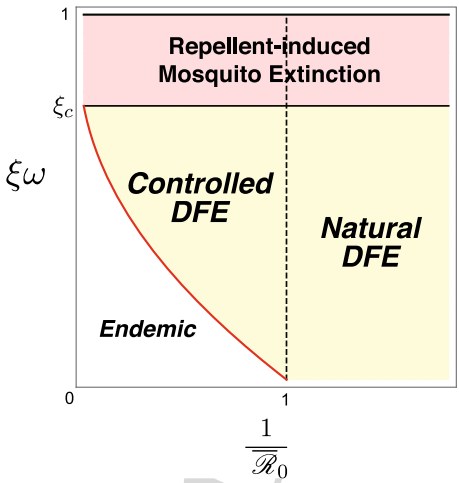

Fig. 1 Classification of the parameter region $(1/\overline{\mathscr{R}}_0, \xi\omega)$ with $\mathscr{R}_m > 1$ in case of the specific function $\chi(L)$ given by (38). For the region where $1/\overline{\mathscr{R}}_0 > 1$, the disease is naturally eliminated even without mosquito repellent use. For the region where $1/\overline{\mathscr{R}}_0 < 1$, mosquito repellent use can make the resultant reproduction number $\mathscr{R}_0$ less than 1 and eliminate the disease. The boundary between the regions of *Controlled DFE* and *Endemic* is given by (42). For details, see the main text

Then, we can obtain the following necessary and sufficient condition for $\mathscr{R}_0 < 1$:

$$\xi\omega > 1 - \frac{1}{2}\left\{\frac{1}{\mathscr{R}_m} + \sqrt{\left(\frac{1}{\mathscr{R}_m}\right)^2 + \frac{4}{\overline{\mathscr{R}}_0}\left(1 - \frac{1}{\mathscr{R}_m}\right)}\right\}, \tag{42}$$

where the right-hand side is necessarily positive and less than $\xi_c = 1 - 1/\mathscr{R}_m$ because the intrinsic net reproduction rate $\mathscr{R}_m$ is now assumed to be larger than 1 in order to ensure the persistence of the mosquito population when nobody uses mosquito repellent, while the upper bound of the basic reproduction number $\overline{\mathscr{R}}_0$ is similarly assumed to be larger than 1 in order to assure the endemic state of the disease when nobody uses mosquito repellent.

From condition (42) with Theorems 4 and 6, we get the result seen in Fig. 1, which shows the effect of mosquito repellent use. It is easily seen that if the efficacy of mosquito repellent is too poor so as to be

$$\xi < \xi_c^* := 1 - \frac{1}{2}\left\{\frac{1}{\mathscr{R}_m} + \sqrt{\left(\frac{1}{\mathscr{R}_m}\right)^2 + \frac{4}{\overline{\mathscr{R}}_0}\left(1 - \frac{1}{\mathscr{R}_m}\right)}\right\}, \tag{43}$$

then mosquito repellent use cannot eliminate the disease from the human population. This is because $\xi\omega \le \xi$. Thus, if condition (43) is satisfied, condition (42) cannot be satisfied for any utilization rate ω of mosquito repellent. In other words, *use of mosquito repellent can help eliminate the disease only if its efficacy is high enough to satisfy* $\xi > \xi_c^*$.

If $\xi > \xi_c^*$, a utilization rate ω, which satisfies condition (42), may exist when mosquito repellent successfully eliminates the disease from the human population. In such a case, the critical value ω_c^* for the utilization rate ω is given by

$$\omega_c^* := \frac{\xi_c^*}{\xi}. \tag{44}$$

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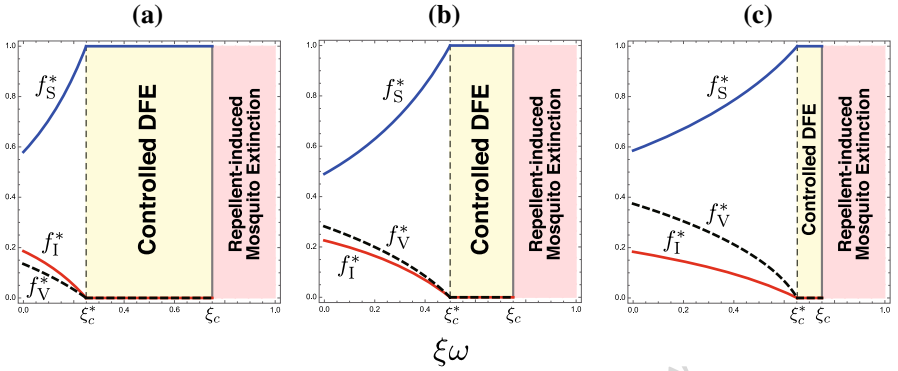

Fig. 2 Dependence of equilibrium values in the endemic state on mosquito repellent use. The figure was drawn for the linear function $\chi(L)$ given by (38), making use of (34)–37, (40), and (41) with $\sigma_h = 0.0084$; $\sigma_m = 0.084$; $\mu_h = 3.9 \times 10^{-5}$; $\mu_m = 0.1$; $\nu = 2.74 \times 10^{-3}$; $\rho = 3.5 \times 10^{-3}$; $\mathscr{R}_m = 4.0$ ($\xi_c = 0.75$); $\eta_0 = M_0^*/N = 1.0$; **a** $\alpha = 0.0$, $\overline{\mathscr{R}}_0 = 1.99$, $\xi_c^* = 0.249$; **b** $\alpha = 2.0$, $\overline{\mathscr{R}}_0 = 5.98$, $\xi_c^* = 0.499$; **c** $\alpha = 10.0$, $\overline{\mathscr{R}}_0 = 21.9$, $\xi_c^* = 0.652$. Parameters value are taken from Chitnis et al. (2008) and CDC (2015) (same in every other numerical calculations of this paper)

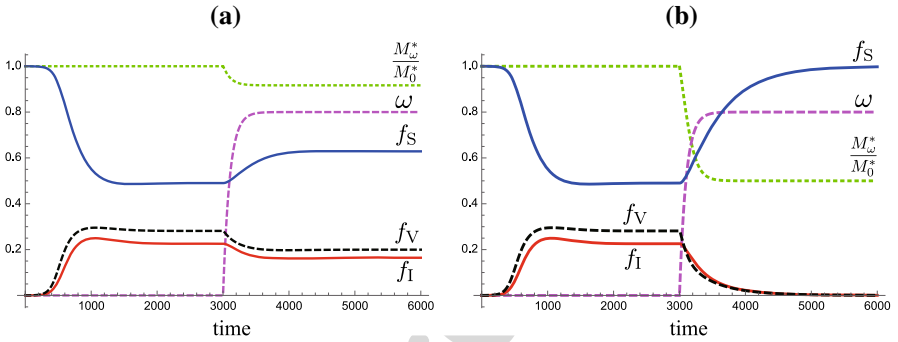

Fig. 3 Numerical calculation of the temporal variation for system (30) with the linear function $\chi(L)$ given by (38) and a temporally variable utilization rate of mosquito repellent ω: $\omega = 0.0$ for $t \le 3000$ and $\omega = 0.8(1-\exp[-0.01(t-3000)])$ for $t > 3000$. $\sigma_h = 0.0084$; $\sigma_m = 0.084$; $\mu_h = 3.9 \times 10^{-5}$; $\mu_m = 0.1$; $\nu = 2.74 \times 10^{-3}$; $\rho = 3.5 \times 10^{-3}$; $\alpha = 2.0$; $\mathscr{R}_m = 4.0$ ($\xi_c = 0.75$); $\eta_0 = M_0^*/N = 1.0$; $\overline{\mathscr{R}}_0 = 5.98$; $\xi_c^* = 0.499$; $(f_S(0),\ f_I(0),\ f_V(0)) = (1.0, 0.0, 0.001)$; $\left(f_S^*,\ f_I^*,\ f_V^*\right) = (0.490, 0.226, 0.282)$ for $t \le 3000$. **a** $\xi = 0.25$, $\left(f_S^*,\ f_I^*,\ f_V^*\right) = (0.629, 0.164, 0.200)$ for $t > 3000$; **b** $\xi = 0.75$, $\left(f_S^*,\ f_I^*,\ f_V^*\right) = (0.0, 1.0, 0.0)$ for $t > 3000$. In (**b**), mosquito repellent use induces the elimination of disease, that is, the epidemic dynamics are controlled by mosquito repellent use toward the DFE

When $\xi > \xi_c^*$, mosquito repellent use successfully eliminates the disease from the human population if $\omega > \omega_c^*$.

These results are also shown in Fig. 2 by numerical calculations. It is clear that even if $\xi < \xi_c^*$, mosquito repellent use can serve to decrease the frequency of infection in humans, since the basic reproduction number is reduced by it, as indicated in Sect. 8.1. As an example, the numerical result in Fig. 3a, which concerns the temporal variation in $(f_S(t),\ f_I(t),\ f_V(t))$ and the relative size of the adult mosquito population M_ω^*/M_0^* demonstrates a case where mosquito repellent use can work toward reducing

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the frequency of infected human individuals when $\xi < \xi_c^*$. In Fig. 3b, we demonstrate a case of the controlled DFE with highly efficient mosquito repellent use when $\xi > \xi_c^*$.

Note that in the numerical calculation seen in Fig. 3, we use the quasi-stationary state approximation (QSSA) such that the temporal change in the mosquito population size is relatively very fast compared to the epidemic dynamics, and it can be approximated with the value M_ω^* determined by the value of the utilization rate ω at each moment while ω is temporally varying [in the application of QSSA for mathematical modeling of biological population dynamics. For example, see Segel and Slemrod (1989), De Boer and Perelson (1995), Borghans et al. (1996), Huisman and De Boer (1997), Schneider and Wilhelm (2000), Tzafriri and Edelman (2004), Schnell et al. (2006), Pedersen et al. (2007) and Seno (2016)].

On the other hand, Fig. 2 clearly indicates that the controllability of endemics significantly depends on the strength of the mosquito's preference to the infected human. The controllability becomes more difficult as the mosquito's preference gets stronger, being consistent with the result indicated in Sect. 8.2.

As seen from Fig. 2, however, the dependence of the frequencies at the endemic state on the mosquito's preference to the infected human, indexed by the parameter α, is not simple. Actually, our numerical calculation of the equilibrium frequency $f_{\rm I}^*$ as the function of α, determined by (35)–(37), indicates the existence of a specific positive value α, say α_c that maximizes the value $f_{\rm I}^*$, as shown in Fig. 4. For the range of α larger than the specific α_c, the equilibrium frequency $f_{\rm I}^*$ gets smaller for larger α. This feature is supported by the more detailed numerical investigation shown in Fig. 5 about the parameter dependence of the equilibrium frequency of infected human individuals $f_{\rm I}^*$ at the endemic state. The higher mosquito density makes the feature more noticeable, while it appears less noticeable for sufficiently low mosquito density. Further, more effective mosquito repellent use with larger $\xi\omega$ makes it less noticeable. As a consequence, we find that *the mosquito's stronger preference to the infected human does not necessarily mean a higher frequency of infected human individuals.*

From the evolutionary viewpoint with regard to the benefit of mosquito-borne disease, it would be optimal to maximize the infected human population for the pathogen's reproduction. In this sense, the mosquito with the preference indexed by α nearer to the value α_c would be evolutionarily favored if a beneficial relation exists between

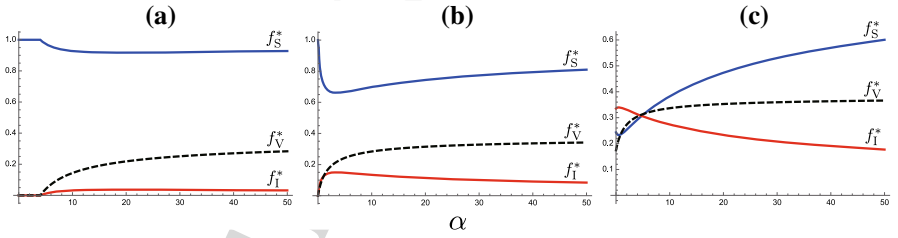

Fig. 4 Dependence of frequencies at the endemic state on the mosquito's preference to the infected human, indexed by the parameter α. Numerically drawn for the linear function $\chi(L)$ given by (38), making use of (34)–(37), (40), and (41) with $\sigma_h = 0.0084$; $\sigma_m = 0.084$; $\mu_h = 3.9 \times 10^{-5}$; $\mu_m = 0.1$; $\nu = 2.74 \times 10^{-3}$; $\rho = 3.5 \times 10^{-3}$; $\mathscr{R}_m = 4.0$ ($\xi_c = 0.75$); $\xi\omega = 0.25$; **a** $\eta_0 = M_0^*/N = 0.2$; **b** $\eta_0 = 1.0$; **c** $\eta_0 = 5.0$. In each case, the value $f_{\rm I}^*$ (resp. $f_{\rm S}^*$) takes its maximum (resp. minimum) for a specific value of α, say α_c

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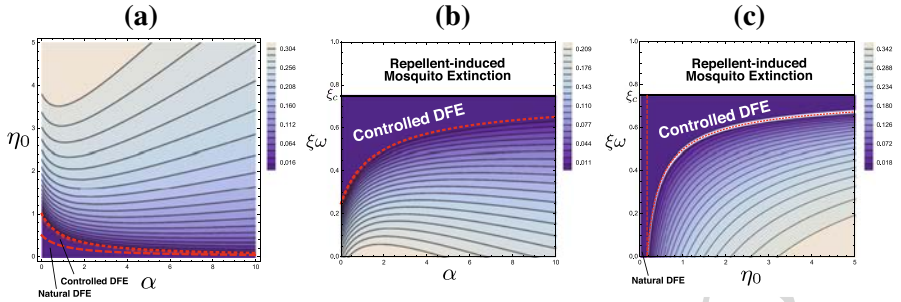

Fig. 5 Contour maps showing parameter dependence of the equilibrium frequency of infected human individuals f_{I}^* at the endemic state. Numerically drawn for the linear function $\chi(L)$ given by (38), making use of (34)–(37), (40), and (41) with $\sigma_h = 0.0084$; $\sigma_m = 0.084$; $\mu_h = 3.9 \times 10^{-5}$; $\mu_m = 0.1$; $\nu = 2.74 \times 10^{-3}$; $\rho = 3.5 \times 10^{-3}$; $\mathscr{R}_m = 4.0$ ($\xi_c = 0.75$); **a** $\xi\omega = 0.25$; **b** $\eta_0 = M_0^*/N = 1.0$; (c) $\alpha = 2.0$. For the region of "Natural DFE", $\overline{\mathscr{R}}_0 < 1$, while for the region of "Controlled DFE", $\overline{\mathscr{R}}_0 > 1$ and $\mathscr{R}_0 < 1$

the mosquito and the pathogen with respect to their fitnesses, whereas the preference indexed by α is the behavioral nature of the mosquito even for the non-infected mosquito individual. We do not argue about this issue in more detail here because such evolutionary discussion is out of the scope of our modeling study. Nonetheless, it is an interesting problem in terms of the mosquito's preference according to its evolutionary meaning.

9 Concluding Remarks

In this paper, we presented a mathematical model of the population dynamics of mosquito-borne disease transmission, carefully describing its modeling for future development, since the modeling includes some non-trivial parts for its reasonable design. Our model takes into account of the effect of mosquito repellent use and the mosquito's behavior (i.e., attraction to the infected human), which causes the mosquitoes' biased distribution. Our analysis of the model clearly shows that thresholds exist with regard to the efficacy of mosquito repellent use and its utilization rate in the human population with respect to the elimination of mosquito-borne disease. Further, the results imply that the suppression of mosquito-borne disease becomes more difficult as the mosquitoes' distribution in the human population grows more biased.

Three types of interventions in epidemic dynamics are considered for the purpose of protection or control of mosquito-borne (or more generally, vector-borne) disease: vaccination, reduction in contact rate with mosquitoes, and reduction in mosquito population size. Use of mosquito repellent or prevention screens is interventions that reduce the contact rate with mosquitoes. The first type of intervention, vaccination, itself is, in principle, independent of the others. Vaccinations can be regarded as playing a role in suppressing the number of *infected* individuals. Such a vaccinated individual may be regarded as being identical to a *recovered* one, as in many previous mathematical models. Alternatively, from the viewpoint of mean-field approximation applied to

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population dynamics, the effect of vaccination could be introduced as the reduction in the likelihood of successful infection of disease in the human by the carrier mosquito. In such a modeling, the effect of vaccination could be expressed as a reduction in the value of the parameter β_h introduced in Sect. 3.3, which denotes the probability of successful infection of disease per bite by the carrier mosquito. Then, its reduction corresponds to the smaller value of σ_h in (29), so that the basic reproduction number (31) becomes smaller, proportional to the value of σ_h (i.e., β_h).

The third type of intervention to reduce the mosquito population size includes the use of insecticides (larvicides or adulticides), insecticide-treated nets, or mechanical reduction in mosquito habitats. The effect of insecticide is to increase the death rate of mosquitoes. Thus, it could be considered in the death rate as an increase in μ_m or in the reproduction rate as a decrease in r_m. The effect of adulticides would typically entail an increase in the death rate, though some types of adulticides may affect and disturb the reproduction cycle of mosquitoes. The reduction in the reproduction rate by such an effect could be introduced in the parameter c defined in Sect. 3.5. This effect (to reduce the value of c) is reflected to the decrease in the intrinsic net reproduction rate $\mathscr{R}_m$ defined in (18) of our model. The inverse value of the rate $\mathscr{R}_m$ contributes to the basic reproduction number $\mathscr{R}_0$, as shown by (40) and (41), and related arguments in Sect. 8. Therefore, the intervention of insecticide use would contribute to the epidemic dynamics in a nonlinear manner. In contrast, the effect of the mechanical reduction in mosquito habitats to suppress their population size could be introduced as the smaller value of K in (38) in our model. Since the contribution of K is proportional to the basic reproduction number $\mathscr{R}_0$ of (40) and (41), the effect of such an intervention would appear in an easy, tractable manner.

As mentioned above, the model presented in this paper would be adaptable with extended development to other problems related to mosquito-borne diseases. As an example of the future direction of this work, we may additionally introduce a specific characteristic of human behavior with regard to the use of mosquito repellent, as suggested in Brauer (2017). Humans tend to use mosquito repellent more readily when the mosquito density per human rises. This is because a human would be more likely to use repellent when the individual is aware of the danger posed by mosquitoes around him/her, while a human would be more likely to stop using it when the individual is less aware of the danger. This remark introduces a functional relation between the utilization rate ω and the mosquito density around each human individual. Then, one choice would be to model the relation between them such that the utilization rate of mosquito repellent ω has a functional relation to the mosquito density around the human individual. Such a function indicates that the mosquito density per human determines the utilization rate ω of mosquito repellent. In other words, the mosquitoes total population size is determined by the natural and social environment and has a feedback relation to the utilization rate ω, or alternatively to the frequency of human individuals who use mosquito repellent. Another interesting issue about the epidemic dynamics of mosquito-borne disease is the contribution of such a response of human behavior to it.

As for our density dependence modeling, we chose the simplest mathematical structure to construct the model. From the characteristics of the density effect for the mosquito population, which are mentioned in Sect. 2 about the function χ, we simply

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introduced it in the juvenile population dynamics, because the density effect for the mosquito population would be significant especially for the juvenile, whereas only the adult mosquito contributes to the disease transmission. It would seem possible to use a logistic equation for the adult mosquito population without taking account of the juvenile population dynamics. However, as mentioned in Sect. 2, the density effect for the mosquito population would be significant especially for the juvenile. For this reason, we introduced the juvenile population in our modeling for the mosquito population dynamics. One of the easiest human interventions to suppress the mosquito-borne disease is to reduce the microhabitats for the mosquito juvenile, though we did not discuss the effect in this paper. We expect that our modeling would be useful to develop a model to consider the effect of such a kind of intervention, since it could be easily introduced with an appropriate modification of our modeling.

As Rock et al. (2014) described, mathematical modeling for infectious diseases has developed significantly, and the theoretical/mathematical considerations of the mathematical model provide some useful ideas for practical discussions on public health even if the model is simple. Further, although such practical use and discussion regarding public health frequently require a complex modeling above and beyond mathematical analysis, the mathematical understanding of the skeleton model is essential to discuss the results obtained from such a model. It would be usually analyzed numerically with a certain set of parameter values estimated from the real data. As many public health professionals recognize, many problems in epidemic dynamics await detailed mathematical/theoretical studies. We expect that the work presented in this paper will contribute to this area of study.

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A Derivation of the Basic Reproduction Number $\mathscr{R}_0$

At first we rearrange the system (30) as follows in the order according to the relation to the disease transmission:

$$\begin{aligned}
\frac{\mathrm{d}f_{\mathrm{I}}}{\mathrm{d}t} &= (1-\xi\omega)\sigma_h \frac{f_{\mathrm{V}} f_{\mathrm{S}}}{1+\alpha f_{\mathrm{I}}}\eta_\omega - (\rho+\mu_h) f_{\mathrm{I}} \\
\frac{\mathrm{d}f_{\mathrm{V}}}{\mathrm{d}t} &= (1-\xi\omega)\sigma_m \frac{(1+\alpha) f_{\mathrm{I}}(1-f_{\mathrm{V}})}{1+\alpha f_{\mathrm{I}}} - \mu_m f_{\mathrm{V}} \\
\frac{\mathrm{d}f_{\mathrm{S}}}{\mathrm{d}t} &= \mu_h - (1-\xi\omega)\sigma_h \frac{f_{\mathrm{V}} f_{\mathrm{S}}}{1+\alpha f_{\mathrm{I}}}\eta_\omega - \mu_h f_{\mathrm{S}} + \nu(1-f_{\mathrm{S}}-f_{\mathrm{I}}).
\end{aligned} \tag{45}$$

Next, we decompose the dynamical terms into two classes in which one shows the new infection process, and the other does show the other processes of the population dynamics:

$$\frac{\mathrm{d}\boldsymbol{\varphi}}{\mathrm{d}t} = \mathscr{F}(f_{\mathrm{I}}, f_{\mathrm{V}}, f_{\mathrm{S}}) - \mathscr{V}(f_{\mathrm{I}}, f_{\mathrm{V}}, f_{\mathrm{S}}), \tag{46}$$

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where $\boldsymbol{\varphi} := {}^{\mathsf{T}}\left[f_{\mathrm{I}}\ f_{\mathrm{V}}\ f_{\mathrm{S}}\right]$;

$$\mathscr{F}(f_{\mathrm{I}}, f_{\mathrm{V}}, f_{\mathrm{S}}) := \begin{bmatrix} (1-\xi\omega)\sigma_h \frac{f_{\mathrm{V}} f_{\mathrm{S}}}{1+\alpha f_{\mathrm{I}}}\, \eta_\omega \\ 0 \\ 0 \end{bmatrix};$$

$$-\mathscr{V}(f_{\mathrm{I}}, f_{\mathrm{V}}, f_{\mathrm{S}}) := \begin{bmatrix} -(\rho+\mu_h) f_{\mathrm{I}} \\ (1-\xi\omega)\sigma_m \frac{(1+\alpha) f_{\mathrm{I}}(1-f_{\mathrm{V}})}{1+\alpha f_{\mathrm{I}}} - \mu_m f_{\mathrm{V}} \\ \mu_h - (1-\xi\omega)\sigma_h \frac{f_{\mathrm{V}} f_{\mathrm{S}}}{1+\alpha f_{\mathrm{I}}}\, \eta_\omega - \mu_h f_{\mathrm{S}} + \nu(1-f_{\mathrm{S}}-f_{\mathrm{I}}) \end{bmatrix}.$$

The vector $\mathscr{F}$ is for the terms of new infection process, while $-\mathscr{V}$ is for the other. The Jacobian matrices of $\mathscr{F}$ and $\mathscr{V}$ about the disease-free equilibrium $\boldsymbol{\varphi}_0 := {}^{\mathsf{T}}[0\ 0\ 1]$ are given by

$$D\mathscr{F}(\boldsymbol{\varphi}_0) = \begin{bmatrix} 0 & (1-\xi\omega)\sigma_h\eta_\omega & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix};$$

$$D\mathscr{V}(\boldsymbol{\varphi}_0) = \begin{bmatrix} \rho+\mu_h & 0 & 0 \\ -(1-\xi\omega)\sigma_m(1+\alpha) & \mu_m & 0 \\ \nu & (1-\xi\omega)\sigma_h\eta_\omega & \mu_h+\nu \end{bmatrix}.$$

Then, with the 2×2 matrices

$$\mathcal{F} := \begin{bmatrix} 0 & (1-\xi\omega)\sigma_h\eta_\omega \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad \mathcal{V} := \begin{bmatrix} \rho+\mu_h & 0 \\ -(1-\xi\omega)\sigma_m(1+\alpha) & \mu_m \end{bmatrix},$$

the next-generation matrix $\mathcal{K}$ is given by $\mathcal{F}\mathcal{V}^{-1}$, that is,

$$\mathcal{K} = \mathcal{F}\mathcal{V}^{-1} = \begin{bmatrix} \dfrac{(1-\xi\omega)^2\sigma_m\sigma_h\eta_\omega(1+\alpha)}{\mu_m(\mu_h+\rho)} & \dfrac{(1-\xi\omega)\sigma_h\eta_\omega}{\mu_m} \\ 0 & 0 \end{bmatrix}. \tag{47}$$

The theory by van den Driessche and Watmough (2002), van den Driessche and Watmough (2008) says that the spectrum radius, that is, the maximum absolute value of the eigenvalue of $\mathcal{K}$ gives the basic reproduction number $\mathscr{R}_0$. Therefore, from (47), we can derive the basic reproduction number (31).

B Local Stability of the Endemic Equilibrium E_+

In this appendix, we consider the local stability of the endemic equilibrium E_+, $(f_{\mathrm{S}}, f_{\mathrm{I}}, f_{\mathrm{V}}) = \left(f_{\mathrm{S}}^*, f_{\mathrm{I}}^*, f_{\mathrm{V}}^*\right)$ uniquely determined by (34)–(37) when it exists, that is, when $\mathscr{R}_0 > 1$ as shown in Lemma 2. Setting $(f_{\mathrm{S}}, f_{\mathrm{I}}, f_{\mathrm{V}}) = \left(f_{\mathrm{S}}^* + x, f_{\mathrm{I}}^* + y, f_{\mathrm{V}}^* + z\right)$, we can get the following system of linear ordinary differential equations in terms of the perturbation ${}^{\mathsf{T}}[x\ y\ z]$ around the endemic equilibrium E_+ for (30):

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$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} x \\ y \\ z \end{bmatrix} = \begin{Bmatrix} -(\mu_h+\rho)\,\frac{f_{\mathrm{I}}^*}{f_{\mathrm{S}}^*} - (\mu_h+\nu) & (\mu_h+\rho)\,\frac{\alpha f_{\mathrm{I}}^*}{1+\alpha f_{\mathrm{I}}^*} - \nu & -(\mu_h+\rho)\,\frac{f_{\mathrm{I}}^*}{f_{\mathrm{V}}^*} \\ (\mu_h+\rho)\,\frac{f_{\mathrm{I}}^*}{f_{\mathrm{S}}^*} & -(\mu_h+\rho)\,\frac{1+2\alpha f_{\mathrm{I}}^*}{1+\alpha f_{\mathrm{I}}^*} & (\mu_h+\rho)\,\frac{f_{\mathrm{I}}^*}{f_{\mathrm{V}}^*} \\ 0 & \mu_m\,\frac{f_{\mathrm{V}}^*/f_{\mathrm{I}}^*}{1+\alpha f_{\mathrm{I}}^*} & -\frac{\mu_m}{1-f_{\mathrm{V}}^*} \end{Bmatrix} \begin{bmatrix} x \\ y \\ z \end{bmatrix}, \tag{48}$$

where we used the relations (34) about E_+.

Next, let us consider the following function $\mathscr{L} = \mathscr{L}(x, y, z)$ constructed by the solution ${}^{\mathsf{T}}[x\ y\ z]$ of the ordinary differential equations given by (48):

$$\mathscr{L}(x, y, z) := \frac{1}{2}(x+y)^2 + \frac{\rho + 2(\mu_h+\nu)}{2(\mu_h+\rho)}\,\frac{f_{\mathrm{S}}^*}{f_{\mathrm{I}}^*}\,y^2 + \frac{Q}{2}z^2, \tag{49}$$

where we will determine a positive constant Q appropriately in the following arguments. With a positive constant Q, the function $\mathscr{L}$ takes only nonnegative value, and becomes zero when and only when $x = y = z = 0$, which corresponds to the endemic state E_+.

Time derivative of $\mathscr{L}$ along the solution ${}^{\mathsf{T}}[x\ y\ z]$ of (48) gives the following equation:

$$\begin{aligned} \left.\frac{\mathrm{d}\mathscr{L}}{\mathrm{d}t}\right|_{(48)} &= -(\mu_h+\nu)x^2 - (A_0y^2 - A_1yz + A_2z^2) \\ &= -(\mu_h+\nu)x^2 - A_0\Big(y - \frac{A_1}{2A_0}z\Big)^2 + \frac{A_1^2 - 4A_0A_2}{4A_0}z^2 \end{aligned} \tag{50}$$

with positive constants given by

$$\begin{aligned} A_0 &= \rho + \mu_h + \nu + \big\{\rho + 2(\mu_h+\nu)\big\}\,\frac{f_{\mathrm{S}}^*/f_{\mathrm{I}}^*}{1+\alpha f_{\mathrm{I}}^*}; \\ A_1 &= \big\{\rho + 2(\mu_h+\nu)\big\}\,\frac{f_{\mathrm{S}}^*}{f_{\mathrm{V}}^*} + \mu_m\,\frac{f_{\mathrm{V}}^*/f_{\mathrm{I}}^*}{1+\alpha f_{\mathrm{I}}^*}\,Q; \\ A_2 &= \frac{\mu_m}{1-f_{\mathrm{V}}^*}\,Q. \end{aligned}$$

Hence, if we can choose a positive value of Q such that $A_1^2 - 4A_0A_2 < 0$, then we have the time derivative (50) which is always non-positive for any ${}^{\mathsf{T}}[x\ y\ z]$ and becomes zero for ${}^{\mathsf{T}}[0\,0\,0]$. The formula $A_1^2 - 4A_0A_2$ can be expressed as the quadratic function of Q, $G(Q) := B_2Q^2 - 2B_1Q + B_0$ with positive constants

$$B_2 = \mu_m^2\left(\frac{f_{\mathrm{V}}^*/f_{\mathrm{I}}^*}{1+\alpha f_{\mathrm{I}}^*}\right)^2;$$

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$$B_1 = \mu_m\left\{\rho + 2(\mu_h + \nu)\right\}\frac{f_S^*/f_I^*}{1+\alpha f_I^*}\frac{1+f_V^*}{1-f_V^*} + \frac{2\mu_m(\rho+\mu_h+\nu)}{1-f_V^*};$$

$$B_0 = \left\{\rho + 2(\mu_h + \nu)\right\}^2\left(\frac{f_S^*}{f_V^*}\right)^2.$$

Since $B_1 > 0$ and $B_1^2 - B_0B_2 > 0$, we find that the equation $G(Q) < 0$ for a positive finite range of Q. Therefore, if we choose a value of Q from the positive range, then the time derivative (50) is always non-positive for any ${}^{\mathsf{T}}[x\ y\ z]$. Since the largest invariant set where the time derivative (50) becomes zero is the singleton consisting of only ${}^{\mathsf{T}}[0\ 0\ 0]$, the function $\mathscr{L}$ becomes a Lyapunov function for the equilibrium ${}^{\mathsf{T}}[0\ 0\ 0]$ of the dynamical system (48). Thus, by LaSalle's invariance principle (LaSalle 1976), the equilibrium ${}^{\mathsf{T}}[0\ 0\ 0]$ is asymptotically stable with respect to the dynamical system (48). Consequently, the endemic equilibrium E_+ is locally asymptotically stable whenever it exists.

References

Aldila D, Götz T, Soewono E (2012a) An optimal control problem arising from dengue disease transmission model. Math Biosci 242(1):9–16

Aldila D, Nuraini N, Soewono E (2012b) On the analysis of effectiveness in mass application of mosquito repellent for dengue prevention. AIP Conf Proc 1450:103–109

Anderson RM, May RM (1991) Infectious diseases of humans. Oxford University Press, Oxford

Anderson RM, May RM, Anderson B (1992) Infectious diseases of humans: dynamics and control, Revised edn. Oxford University Press, New York

Alpern JD, Dunlop SJ, Dolan BJ, Stauffer WM, Boulware DR (2016) Personal protection measures against mosquitoes, ticks, and other arthropods. Med Clin North Am 100:303–316

Bai J, Ju X, Li D, Wang X (2019) On the eventual stability of asymptotically autonomous systems with constraints. Discrete Contin Dyn Syst B 24(8):4457–4473

Borghans JAM, De Boer RJ, Segel L (1996) Extending the quasi-steady state approximation by changing variables. Bull Math Biol 58:43–63

Bowman C, Gumel AB, van den Driessche P, Wu J, Zhu H (2005) A mathematical model for assessing control strategies against West Nile virus. Bull Math Biol 67:1107–1133

Brauer F (2017) Mathematical epidemiology: past, present, and future. Infect Dis Model 2:113–127

Brauer F, Castillo-Chavez C, Mubayi A, Towers S (2016) Some models for epidemics of vector-transmitted diseases. Infect Dis Model 1:79–87

Buonomo B, Vargas-De-León C (2014) Effects of mosquitoes host choice on optimal intervention strategies for malaria control. Acta Appl Math 132(1):127–138

Bustamam A, Aldila D, Yuwanda A (2018) Understanding dengue control for short- and long-term intervention with a mathematical model approach. J Appl Math 9674138(1–9674138):13

Calvo EP, Sanchez-Quete F, Duran S, Sandoval I, Casrellanos JE (2016) Easy and inexpensive molecular detection of dengue, chikungunya and zika viruses in febrile patients. Acta Trop 163:32–37

Castillo-Chavez C, Thieme H (1995) Asymptotically autonomous epidemic models. In: Arino O, Axelrod DE, Kimmel M, Langlais M (eds) Mathematical population dynamics: analysis of heterogeneity: theory of epidemics, vol 1. Wuerz Publishing Ltd., Winnipeg, pp 33–50

Center for Disease Control and Prevention (CDC) (2015) Anopheles mosquitoes. https://www.cdc.gov/malaria/about/biology/mosquitoes/

Chitnis N, Hyman JM, Cushing JM (2008) Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model. Bull Math Biol 70(5):1272–1296

Costantini C, Gibson G, Sagnon N, Torre AD, Brady J, Coluzzi M (1996) Mosquito responses to carbon dioxide in a West African Sudan savanna. Med Vet Entomol 10:220–227

Cruz-Pacheco G, Esteva L, Montano-Hirose JA, Vargas C (2005) Modelling the dynamics of West Nile virus. Bull Math Biol 67:1157–1172

Cushing JM, Diekmann O (2016) The many guises of R_0 (a didactic note). J Theor Biol 404:295–302

De Boer RJ, Perelson AS (1995) Towards a general function describing T cell proliferation. J Theor Biol 175:567–576

Deletre E, Schatz B, Bourguet D, Chandre F, Williams L, Ratnadass A, Martin T (2016) Prospects for repellent in pest control: current developments and future challenges. Chemoecology 26:127–142

Diaz JH (2016) Chemical and plant-based insect repellents: efficacy, safety, and toxicity. Wilderness Environ Med 27:153–163

Diekmann O, Heesterbeek JAP, Britton T (2013) Mathematical tools for understanding infectious disease dynamics. Princeton University Press, Princeton

Dye C (1984) Models for the population dynamics of the yellow fever mosquito, *Aedes aegypti*. J Anim Ecol 53:247–268

European Centre for Disease Prevention and Control (ECDC) An agency of the European Union (2018) Vector-borne diseases. https://ecdc.europa.eu/en/climate-change/climate-change-europe/vector-borne-diseases

Ferguson N, Anderson R, Gupta S (1999) The effect of antibody-dependent enhancement on the transmission dynamics and persistence of multiple-strain pathogens. Proc Natl Acad Sci USA 96(2):790–794

Gurney WSC, Blythe SP, Nisbet RM (1980) Nicholson's blowflies revisited. Nature 287:17–21

Heesterbeek JAP, Roberts MG (2007) The type-reproduction number T in models for infectious disease control. Math Biosci 206:3–10

Huisman G, De Boer RJ (1997) A formal derivation of the "Beddington" functional response. J Theor Biol 185:389–400

Kim S, Masud MA, Cho G, Jung IH (2017) Analysis of a vector-bias effect in the spread of malaria between two different incidence areas. J Theor Biol 419:66–76

Kooi BW, Aguiar M, Stollenwerk N (2013) Bifurcation analysis of a family of multi-strain epidemiology models. J Comput Appl Math 252:148–158

Lacroix R, Mukabana WR, Gouagna LC, Koella JC (2005) Malaria infection increases attractiveness of humans to mosquitoes. PLoS Biol 3(9):1590–1593 (e298)

LaSalle JP (1976) The stability of dynamical systems. Regional conference series in applied mathematics. SIAM, Philadelphia

Legros M, Lloyd AL, Huang Y, Gould F (2009) Density-dependent intraspecific competition in the larval stage of *Aedes aegypti* (Diptera: Culicidae): revisiting the current paradigm. J Med Entomol 46(3):409–419

Lewis MA, Shuai Z, van den Driessche P (2019) A general theory for target reproduction numbers with applications to ecology and epidemiology. J Math Biol 78:2317–2339

Li J, Teng Z, Zhang L (2018) Stability and bifurcation in a vector-bias model of malaria transmission with delay. Math Comput Simul 152:15–34

Lord C (1998) Density dependence in larval *Aedes albopictus* (Diptera: Culicidae). J Med Entomol 35(5):825–829

Mandal S, Sarkar RR, Sinha S (2011) Mathematical models of malaria—a review. Malar J 10:202

Mukabana WR, Takken W, Killeen GI, Knols BGJ (2004) Allomonal effect of breath contributes to differential attractiveness of humans to the African malaria vector Anopheles gambiae. Malar J 3(1):1

Ngwa GA, Shu WS (2000) A mathematical model for endemic malaria with variable human and mosquito populations. Math Comput Model 32:747–763

Pedersen MG, Bersani AM, Bersani E (2007) The total quasi-steady-state approximation for fully competitive enzyme reactions. Bull Math Biol 69:433–457

Phasomkusolsil S, Tawong J, Monkanna N, Pantuwatana K, Damdangdee N, Khongtak W, Kertmanee Y, Evans BP, Schuster AL (2013) Maintenance of mosquito vectors: effects of blood source on feeding, survival, fecundity, and egg hatching rates. J Vector Ecol 38(1):38–45

Roberts MG, Heesterbeek JAP (2003) A new method for estimating the effort required to control an infectious disease. Proc R Soc Lond B 270:1359–1364

Rock K, Brand S, Moir J, Keeling MJ (2014) Dynamics of infectious diseases. Rep Prog Phys 77:026602

Schneider KR, Wilhelm T (2000) Model reduction by extended quasi-steady-state approximation. J Math Biol 40:443–450

Journal: 11538 Article No.: 0666 TYPESET DISK LE CP Disp.:2019/10/1 Pages: 32 Layout: Small-Ex

Schnell S, Chappell MJ, Evans ND, Roussel MR (2006) The mechanism distinguishability problem in biochemical kinetics: the single-enzyme, single-substrate reaction as a case study. C R Biol 329(1):51–61

Segel LA, Slemrod M (1989) The quasi steady-state assumption: a case study in perturbation. SIAM Rev 31:446–477

Seno H (2016) Mathematical modelling of metapopulation dynamics: revisiting its meaning. Math Model Nat Phenom 11(4):34–46

Smith DL, McKenzie FE, Snow RW, Hay SI (2007) Revisiting the basic reproductive number for malaria and its implications for malaria control. PLoS Biol 5:e42

Takken W, Verhulst NO (2013) Host preferences of blood-feeding mosquitoes. Annu Rev Entomol 58(1):433–453

Tsetsarkin KA, Vanlandingham DL, McGee CE, Higgs S (2007) A single mutation in chikungunya virus affects vector specificity and epidemic potential. PLoS Pathog 3(12):e201 PMID: 18069894

Tzafriri AR, Edelman ER (2004) The total quasi-steady-state approximation is valid for reversible enzyme kinetics. J Theor Biol 226:303–313

van den Driessche P (2017) Reproduction numbers of infectious disease models. Infect Dis Model 2:288–303

van den Driessche P, Watmough J (2002) Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math Biosci 180:29–48

van den Driessche P, Watmough J (2008) Further notes on the basic reproduction number. In: Brauer F, van den Driessche P, Wu J (eds) Mathematical epidemiology lecture notes in mathematics, vol 1945. Springer, Berlin, pp 159–178

Wiratsudakul A, Suparit P, Modchang C (2018) Dynamics of Zika virus outbreaks: an overview of mathematical modeling approaches. Peer J 6:e4526. https://doi.org/10.7717/peerj.4526

Wonham MJ, Lewis MA, Rencławowicz J, van den Driessche P (2006) Transmission assumptions generate conflicting predictions in host-vector disease models: a case study in West Nile virus. Ecol Lett 9:706–725

World Health Organization (WHO) (2017) Vector-borne diseases. http://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases

Xu Z, Zhang Y (2015) Traveling wave phenomena of a diffusive and vector-bias malaria model. Commun Pure Appl Anal 14(3):923–940

Xu Z, Zhao X-Q (2012) A vector-bias malaria model with incubation period and diffusion. Discrete Contin Dyn Syst B 17(7):2615–2634

Yakob L, Clements ACA (2013) A mathematical model of Chikungunya dynamics and control: the major epidemic on Réunion Island. PLoS ONE 8(3):e57448

Yang H, Yang H, Li Z, Liu L, Wang W, He T, Fan F, Sun Y, Liu J, Li Y, Zeng X (2018) Japanese encephalitis virus/yellow fever virus chimera is safe and confers full protection against yellow fever virus in intracerebrally challenged mice. Vaccine 36(18):2450–2455

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