Impact of Behavioural Changes in Mosquito Feeding on Malaria Invasion: A Model-Based Approach

Sungchan Kim

Pusan National University

Yongkuk Kim

Kyungpook National University

Byul Nim Kim

Kyungpook National University

M A Masud

Pusan National University

Il Hyo Jung (✉ ilhjung@pusan.ac.kr)

Pusan National University College of Natural Science <https://orcid.org/0000-0002-6086-5124>

Research

Keywords: branching process, individual-based stochastic simulation algorithm, transmission heterogeneity, vector-bias

Posted Date: August 25th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-62181/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

RESEARCH

Impact of Behavioural Changes in Mosquito Feeding on Malaria Invasion: A Model-Based Approach

Sungchan Kim^{1,2}, Yongkuk Kim³, Byul Nim Kim⁴, M A Masud^{2,5,*} and Il Hyo Jung^{1,2,*}

Abstract

Background: Malaria hosts are known to manipulate the feeding behaviour of mosquitoes to protect them from external threats and control. In particular, the phenomenon in which a mosquito's feeding target is biased toward an infectious host is called a vector-bias, and it can be a threat to malaria eradication if not considered. Aim of the study is to understand the problems that may arise when vector-bias is not considered in early invasion scenarios.

Methods: Stochastic formulations of malaria transmission, including the vector-bias effect, were constructed. Invasive dynamics were investigated using an individual-based continuous time Markov chain model and the offspring distributions of secondary infections. In addition, the extinction probability was derived using the negative binomial count model.

Results: Invasions will occur quickly, and once the disease spreads, extinction will become difficult compared to when the vector-bias effect is not considered. In a highly heterogeneous environment, vector-bias has rare effect on decreasing the extinction probability.

Conclusion: The early detection of a malaria invasion and the early control beginning are more important due to vector-bias for the malaria eradication in early invasion scenarios. In addition, some possible mosquito-biased behaviours were discussed in terms of adaptive dynamics.

Keywords: branching process; individual-based stochastic simulation algorithm; transmission heterogeneity; vector-bias

Introduction

The *adaptive host manipulation hypothesis* [1] states that parasites evolve themselves to control specific aspects of their host's behaviour and thereby enhance

the frequency of their encounters with suitable hosts and thus, the rate of transmissibility of a parasite as well [2]. Such manipulation by parasites has also been found in several cases of malaria outbreaks. For example, a mosquito finding a host to feed on is influenced by the host odour and olfactory cues [3, 4]

Full list of author information is available at the end of the article

*Corresponding authors: M A Masud (ma.masud@northsouth.edu), and Il

Hyo Jung (ilhjung@pusan.ac.kr)

attributes that are exploited by parasites to attract mosquitoes [3, 4, 5, 6, 7]. During the 1980s, an experiment was conducted using mice [8, 9], hens [10], and lambs [11], in which mosquitoes were found to feed preferentially on infected hosts. A decade earlier, a similar result was found in the case of malaria in a human host [12], in which it was determined that malaria-infected humans have a greater attractiveness to mosquitoes, a phenomenon that was later called *vector-bias* [13], and more evidences of mosquito's feeding bias toward *Plasmodium*-infected vertebrates were found [14, 15, 16, 17, 18, 19]. Such studies encouraged thinking over whether the parasites manipulate their hosts to increase their probability of survival or not.

Such manipulation of mosquitoes by malaria parasites cause significant difficulties in predicting or controlling malaria [20, 21]. Therefore, the mosquito feeding behaviour is important in epidemiological studies of malaria transmission. Numerous modelling attempts have been made to analyse or quantify the effects of mosquitoes on the changes in feeding behaviour [13, 22, 23, 24]. The first mathematical model, which dealt with mosquito behaviour increasing the total biting rate (the total biting rate of susceptible and infected mosquitoes), proved to increase the equilibrium infection level during endemic equilibrium, whereas infected host preference was found to exert both increasing and decreasing effects [22]. Discussions regarding impact of the manipulation of mosquitoes by malaria parasites to the transmission probability of malaria diseases was presented by Cator et al. [25, 26]. In [13], the authors presented a vector-bias model and concluded that mosquitoes are most preferred by a high prevalence of the parasites. Although both positive and negative effects were reported quantitatively, no argument for this dual role has been presented, but was recently clarified in [27]. It was shown that mosquito encounters with susceptible hosts are as likely as mosquito

encounters with infected hosts, but that bites occur in infected hosts with a higher probability. Thereafter, numerous studies on vector-bias were conducted, with a focus on the periodicity of mosquito abundance [28], time-delay [29], fractional-order [30], spatial structure [31], and real-world application [32]. It can be seen that the aforementioned studies dealing with the modelling of vector-bias focused on the impacts of the long-term behavioural dynamics.

However, there have been few studies on how vector-bias provides momentum for the spread of the disease during the initial stages of malaria transmission. Motivated by this, in this paper, we investigated the impact of vector-bias at the initial stages of *Plasmodium falciparum* malaria transmission using a stochastic method, by comparing the dynamics when considering vector-bias and when not considering it. Mainly, malaria invasion and extinction were studied. Since early dynamics such as disease invasion are known to be better understood in stochastic models than in deterministic models [33, 34], and are also sensitive to changes in the behaviour of each individual, an individual-based continuous time Markov chain model of the underlying approach introduced in this study was constructed. The suggested formulation allows applying Gillespie's stochastic simulation when considering the biased behaviour of each mosquito [35, 36, 37]. To consider the transmission heterogeneity and consequent extinction probabilities, the offspring distribution along the negative binomial count model was calculated. Finally, the impact of vector-bias on malaria control was discussed.

Materials and Methods

Underlying model

The host-vector model developed by Kim et al. [27] deals with the effects of behavioural changes of mosquitoes on the epidemic of *Plasmodium falciparum* malaria, where the host population is divided into susceptible (S_h), infectious (I_h) and recovered (R_h)

classes; and the mosquito population is divided into susceptible (S_v), and infectious (I_v) classes:

$$\begin{aligned}
 \frac{dS_h(t)}{dt} &= \mu_h N - bp_h \frac{S_h(t)}{\lambda I_h(t) + (N - I_h(t))} I_v(t) \\
 &\quad + \xi R_h(t) - \mu_h S_h(t), \\
 \frac{dI_h(t)}{dt} &= bp_h \frac{S_h(t)}{\lambda I_h(t) + (N - I_h(t))} I_v(t) - \gamma I_h(t) \\
 &\quad - \mu_h I_h(t), \\
 \frac{dR_h(t)}{dt} &= \gamma I_h(t) - \xi R_h(t) - \mu_h R_h(t), \\
 \frac{dS_v(t)}{dt} &= \mu_v M - bp_v \frac{\lambda I_h(t)}{\lambda I_h(t) + (N - I_h(t))} S_v(t) \\
 &\quad - \mu_v S_v(t), \\
 \frac{dI_v(t)}{dt} &= bp_v \frac{\lambda I_h(t)}{\lambda I_h(t) + (N - I_h(t))} S_v(t) - \mu_v I_v(t).
 \end{aligned} \tag{1}$$

Here, $1/\gamma$ is the average infectious period of the host.

We consider the birth and death rates to be the same for both the host and the mosquito, as symbolized by μ_h for the host and μ_v for the mosquito. In addition, ξ is the per capita rate of the loss of immunity of the recovered host, and p_h and p_v are the probability of mosquito-to-human and human-to-mosquito transmission of a disease, respectively, for each bite. λ is called a bias parameter. Notably, $\lambda = 1$ means that there is no vector-bias and the vector-bias increases as the value of $\lambda > 1$ increases. The total human population $N = S_h(t) + I_h(t) + R_h(t)$ and mosquito population $M = S_v(t) + I_v(t)$ are constants.

The basic reproduction number, which is the average number of secondary infected hosts generated by a single infected host introduced under a wholly susceptible state [38], is given by the following:

$$R_0 = \sqrt{\frac{bp_h}{\mu_v}} \sqrt{\frac{\lambda M bp_v}{N(\mu_h + \gamma)}} \equiv \sqrt{\lambda} \times c,$$

where $c = \sqrt{b^2 p_h p_v M / N(\mu_h + \gamma)}$ is a constant. It should be noted that λ increases the basic reproduction number and enforces a breakout.

Distribution of a bias parameter

The estimated parameter λ were fitted to a Weibull distribution with the probability density function

$$f_\lambda(\varphi) = \left(\frac{\beta}{\alpha}\right) \times \left(\frac{\varphi}{\alpha}\right)^{\beta-1} \exp\left(-\left(\frac{\varphi}{\alpha}\right)^\beta\right). \tag{2}$$

where the scale parameter $\alpha = 4.34$ and the shape parameter $\beta = 0.83$ (i.e., the expected value of λ , $\bar{\lambda}$, is 4.78 and the coefficient of variation is 0.58) in [27] based on the assay conducted in [12]. In Figure 1, the suitability of a Weibull distribution fitting of the bias parameter was demonstrated (see Figure 1 in [27]).

Figure 1 Weibull probability plot of bias parameter: the probability density function of Weibull distribution is given by (2) with $\alpha = 4.34$ and $\beta = 0.83$.

Continuous time Markov chain model formulation and individual-based stochastic simulation algorithm

Based on the underlying model (1), we formulated a continuous time Markov chain (CTMC) model. We define the discrete random variables S_h , I_h , R_h , S_v and I_v satisfying

$$\begin{aligned}
 S_h(t), I_h(t), R_h(t) &\in \{0, 1, \dots, N\}, \\
 S_v(t), I_v(t) &\in \{0, 1, \dots, M\},
 \end{aligned}$$

and denote $X(t) = (S_h(t), I_h(t), R_h(t), S_v(t), I_v(t))$ where $t \in [0, \infty)$. We denote

$$p_{(s_h, i_h, r_h, s_v, i_v) \rightarrow (s_h + \Delta s_h, i_h + \Delta i_h, r_h + \Delta r_h, s_v + \Delta s_v, i_v + \Delta i_v)}(\Delta t) \tag{3}$$

as the transition probability associated with the stochastic process for $\Delta t > 0$, not fixed but the duration at which something happens next, which is defined as follows:

Figure 2 Description of the individual-based CTMC model and its simulation algorithm.

$$\begin{aligned}
 & p(s_h, i_h, r_h, s_v, i_v) \rightarrow (s_h + \Delta s_h, i_h + \Delta i_h, r_h + \Delta r_h, s_v + \Delta s_v, i_v + \Delta i_v)(\Delta t) \\
 & = \mathbb{P}(X(t + \Delta t) = (s_h + \Delta s_h, i_h + \Delta i_h, r_h + \Delta r_h, s_v + \Delta s_v, i_v + \Delta i_v) \mid X(t) = (s_h, i_h, r_h, s_v, i_v)) \\
 & = \begin{cases} \mu_h N \Delta t + o(\Delta t), & \Delta x = (+1, 0, 0, 0, 0) \\ \mu_v M \Delta t + o(\Delta t), & \Delta x = (0, 0, 0, +1, 0) \\ bp_h \frac{s_h}{\lambda i_h + (N - i_h)} i_v \Delta t + o(\Delta t), & \Delta x = (-1, +1, 0, 0, 0) \\ bp_v \frac{\lambda i_h}{\lambda i_h + (N - i_h)} s_v \Delta t + o(\Delta t), & \Delta x = (0, 0, 0, -1, +1) \\ \xi r_h \Delta t + o(\Delta t), & \Delta x = (+1, 0, -1, 0, 0) \\ \gamma i_h \Delta t + o(\Delta t), & \Delta x = (0, -1, +1, 0, 0) \\ \mu_h s_h \Delta t + o(\Delta t), & \Delta x = (-1, 0, 0, 0, 0) \\ \mu_h i_h \Delta t + o(\Delta t), & \Delta x = (0, -1, 0, 0, 0) \\ \mu_h r_h \Delta t + o(\Delta t), & \Delta x = (0, 0, -1, 0, 0) \\ \mu_v s_v \Delta t + o(\Delta t), & \Delta x = (0, 0, 0, -1, 0) \\ \mu_v i_v \Delta t + o(\Delta t), & \Delta x = (0, 0, 0, 0, -1) \\ 1 - [\mu_h N + \mu_v M + bp_h \frac{s_h}{\lambda i_h + (N - i_h)} i_v + bp_v \frac{\lambda i_h}{\lambda i_h + (N - i_h)} s_v \\ \quad + \xi r_h + \gamma i_h + \mu_h (s_h + i_h + r_h) + \mu_v (s_v + i_v)] \Delta t + o(\Delta t), & \Delta x = (0, 0, 0, 0, 0) \\ o(\Delta t), & \text{otherwise,} \end{cases} \quad (3)
 \end{aligned}$$

where $\Delta x = (\Delta s_h, \Delta i_h, \Delta r_h, \Delta s_v, \Delta i_v)$. The transition probabilities are dependent upon the time between events Δt , not on the time t . The time $t + \Delta t$ at which something happens next follows an exponential distribution with a parameter equal to the sum of all process rates.

The CTMC model (3) can be simulated using Gillespie's stochastic simulation algorithm. This algorithm is one of the most practical stochastic numerical simulation algorithms [35, 36, 37]. The idea behind Gillespie's algorithm is that it first determines when

the next event will happen. Suppose that the current time is t . Second, it determines the event that is next to occur by randomly applying the probability following the processing rates. As we showed in the previous section, the experimental results indicate that the biased behaviours of each mosquito differ significantly. Following this, we consider a refined model (3) which assumes that the bias parameter of each mosquito is different. Motivated by [39], we extract and simulate sets of random bias parameters, s , for each mosquito using the Monte-Carlo procedure, to allow different

¹bias parameter values to be assigned to each mosquito.
²From these procedures, we can divide the two events
³of human infection and mosquito infection, into i_v in-
⁴dependent sub-events of human infection and s_v inde-
⁵pendent sub-events of mosquito infection. This model
⁶is called as individual-based CTMC model. Table 1
⁷shows a summary of the events of the individual-based
⁸CTMC model. A detailed description of the simulation
⁹procedure of the model is shown in Figure 2.

¹⁰Because λ is fitted with a Weibull distribution, the
¹¹randomly selected bias parameter is given as
¹²
$$\lambda_{r_3} = \alpha (\ln(1/r_3))^\beta$$

¹³for the random number r_3 , following a uniform distri-
¹⁴bution, $\text{Unif}(0, 1)$. This iteration is repeated until the
¹⁵final limit is reached or there is no reaction in the sys-
¹⁶tem.
¹⁷

¹⁸
¹⁹Branching process formulation of the underlying model
²⁰Gillespie's stochastic simulation algorithm is suitable
²¹for depicting the profile or distribution of a popula-
²²tion over time, although it is not possible to show the
²³extinction probability and offspring distribution. We
²⁴therefore consider the branching process model [40],
²⁵known as the Galton–Watson process. Instead of a dis-
²⁶crete branching process, a continuous branching pro-
²⁷cess is suitable to deal with an infectious disease model.
²⁸A general branching process with a finite individual
²⁹life span dies out if and only if the embedded Galton–
³⁰Watson process of the generations dies out. Thus,
³¹the extinction probability for the Galton–Watson pro-
³²cesses is established in the same way for any branching
³³process, in spite of the different time-to-extinction val-
³⁴ues, because generations tend to spread out in chrono-
³⁵logical time, unless reproduction and survival are sea-
³⁶sonal [41]. Thus, we use the Galton–Watson process to
³⁷estimate the extinction probability.

³⁸ Z_n is a random variable that denotes the number
³⁹of individuals for each generation n . Here, a genera-

tion indicates the mean infection period for one person.¹
 When the outbreak is limited, it is assumed that one²
 infection occurs in a wholly susceptible human popu-³
 lation, $Z_0 = 1$, and that the offspring distribution of⁴
 each person in each generation is an independent and⁵
 identically distributed random variable, Z_1 . Applying⁶
 $q_k = \mathbb{P}(Z_1 = k)$, the extinction probability is then de-⁷
 fined as the smallest fixed point of G_{Z_1} , that is, the⁸
 extinction probability is the smallest solution within⁹
 $[0, 1]$ for

$$G_{Z_1}(x) = x, \quad (4)$$

where G_{Z_1} is the probability generating function of q_k .

Next, we define the offspring distribution q_k . In gen-
 eral, the Poisson distribution is used extensively for
 counting, although the Poisson model cannot repre-
 sent an overdispersion of the data. Hence, we use the
 negative binomial counting model [42, 43] for consider-
 ing the heterogeneity of the population. The model is
 derived as follows: let $Z_1 | \nu \sim \text{Poisson}(\nu)$ and assume
 $\nu \sim \text{Gamma}(R_0/s, s)$, i.e., ν is Gamma distributed
 with dispersion parameter s with the dispersion pa-
 rameter s with a mean R_0 . Then, a simple calculation
 yields

$$q_k = \frac{\Gamma(s+k)}{k! \Gamma(s)} \left(\frac{R_0}{s+R_0} \right)^k \left(\frac{s}{s+R_0} \right)^s, \quad (5)$$

and when considering the distribution of the bias pa-
 rameter, f_λ ,

$$q_k = \int_0^\infty \frac{\Gamma(s+k)}{k! \Gamma(s)} \left(\frac{R_0}{s+R_0} \right)^k \left(\frac{s}{s+R_0} \right)^s f_\lambda(\varphi) d\varphi, \quad (6)$$

is obtained, where Γ is the Gamma function [44]. Note
 that the offspring distribution Z_1 is distributed as a
 negative binomial, i.e., $Z_1 \sim \text{NegBin}\left(\frac{s}{s+R_0}, s\right)$ with
 variance $R_0(1 + R_0/s)$. The dispersion parameter s
 determines the level of variation in the number of

Table 1 Definition of events in the individual-based CTMC model, where $\Delta X(t)$ denotes $\Delta X(t) = X(t + \Delta t) - X(t)$.

Event No.	Event description	Changes, $\Delta X(t)^T$	Probability
(E1)	Birth of human	$(+1, 0, 0, 0, 0)$	$\mu_h N \Delta t + o(\Delta t)$
(E2)	Birth of mosquito	$(0, 0, 0, +1, 0)$	$\mu_v M \Delta t + o(\Delta t)$
(E3 - k)	Human infection	$(-1, +1, 0, 0, 0)$	$bp_h \frac{s_h}{N + (\lambda_k - 1)i_h} \Delta t + o(\Delta t), \text{ for } k = 1, 2, \dots, i_v$
(E4 - k)	Mosquito infection	$(0, 0, 0, -1, +1)$	$bp_v \frac{\lambda_k i_h}{N + (\lambda_k - 1)i_h} \Delta t + o(\Delta t), \text{ for } k = 1, 2, \dots, s_v$
(E5)	Loss of immunity of human	$(+1, 0, -1, 0, 0)$	$\xi r_h \Delta t + o(\Delta t)$
(E6)	Recovery of human	$(0, -1, +1, 0, 0)$	$\gamma i_h \Delta t + o(\Delta t)$
(E7)	Death of susceptible human	$(-1, 0, 0, 0, 0)$	$\mu_h s_h + o(\Delta t)$
(E8)	Death of infectious human	$(0, -1, 0, 0, 0)$	$\mu_h i_h + o(\Delta t)$
(E9)	Death of recovered human	$(0, 0, -1, 0, 0)$	$\mu_h r_h + o(\Delta t)$
(E10)	Death of susceptible mosquito	$(0, 0, 0, -1, 0)$	$\mu_v s_v + o(\Delta t)$
(E11)	Death of infectious mosquito	$(0, 0, 0, 0, -1)$	$\mu_v i_v + o(\Delta t)$

secondary infections. The heterogeneity increases as $s \ll 1$ [42, 45]. Note that this model includes the Poisson model ($s \rightarrow \infty$). That is, the smaller the dispersion parameter, the more clustered the group is. The offspring distribution (5) yields the following:

$$G_{Z_1}(x) = \left(\frac{s}{s + (1 - x)c\sqrt{\lambda}} \right)^s. \quad (7)$$

when $|x| < 1 + s/c\sqrt{\lambda}$; otherwise, the value is zero.

To show the effect of the vector-bias in the extinction of malaria, we calculated the extinction probability using the varying bias parameter λ and dispersion parameter s . In many cases, it is difficult to find the solution of (4) analytically. Hence, we used a numerical method known as cobwebbing for finding the fixed point of G_{Z_1} in (7). We performed iterations using the initial assumption $x_1 = 0.1$, until the difference of the prior and posterior term, $|x_{\text{prior}} - x_{\text{posterior}}| < 10^{-10}$ was reached. Because negative binomial distributions with $s = 1000$ and $s \rightarrow \infty$ are indistinguishable in

practice [43], it is sufficient to simulate the model using $s \in (0.001, 1000)$.

Results

In this section, we investigated the impact of vector-bias on malaria invasion and extinction under a low-transmission setting. The parameter values adopted in the simulation are listed in Table 2.

The probability of mosquito infection from infectious human

We showed the effect of vector-bias on the mosquito infections. If we let X be an event in which a human is infectious and is chosen by a mosquito, then the probability that a human is infectious when chosen by a mosquito, $\mathbb{P}(X)$ was given by $\frac{\lambda \mathcal{I}_h}{1 + (\lambda - 1)\mathcal{I}_h}$ from the underlying model (1), where $\mathcal{I}_h = \frac{I_h}{N}$. In this way, if we set a fixed condition $\mathcal{I}_h = k$ and use the probability density of bias parameter λ , i.e., Equation (2), we can obtain the probability that a human is infectious when chosen by a mosquito under a fixed infectious condition

Table 2 Parameter descriptions and values.

Description, Notation (Unit)	Value	Source
Human birth rate and death rate, μ_h (day^{-1})	3.90×10^{-5}	Estimated
Mosquito birth rate and death rate, μ_v (day^{-1})	0.10	[27]
Biting rate of a mosquito, b (day^{-1})	0.35	[27]
Per capita recovery rate, γ (day^{-1})	3.50×10^{-3}	[27]
Per capita rate of loss of immunity, ξ (day^{-1})	2.74×10^{-3}	[27]
Transmission probability of infection from an infectious mosquito to a non-malaria infected human when a contact between the two occurs, p_h (1)	0.024	[27]
Transmission probability of infection from an infectious human to a susceptible mosquito when a contact between the two occurs, p_v (1)	0.24	[27]

$\mathcal{I}_h = k$ as

$$\mathbb{P}(X|\mathcal{I}_h = x) = \int_0^\infty \mathbb{P}(X|\lambda = \varphi, \mathcal{I}_h = x) f_\lambda(\varphi) d\varphi.$$

Figure 3 shows the probability of the rate of infectious humans $\mathcal{I}_h$. The solid line indicates the probability $\mathbb{P}(X|\mathcal{I}_h = x)$ without considering the vector-bias, and the dashed line shows the probability when considering the vector-bias for a fixed x . In the figure, the probability that a human is infectious when chosen by a mosquito is always higher when the vector-bias is considered than when it is not. For example, a mosquito might bite an infectious human once after two attempts, despite infectious humans in the community being approximately 25%. Thus, mosquitoes, particularly susceptible mosquitoes, have a greater chance of being infected with malaria owing to a vector-bias in the invading situation.

Figure 3 The probability that the human is infectious when chosen by a mosquito under the fixed condition $\mathcal{I}_h = x$ when not considering (solid line) and considering (dashed line) a vector-bias effect.

These results indicate that the vector-bias first increases the probability of a mosquito being infected from the first infectious human infection from the first infectious human during an invasion, leading to a rapid increase in infectious mosquitoes, which finally results in an easy invasion of human populations by infectious mosquitoes, as compared to an invasion in the absence of such bias. By contrast, after an invasion of malaria, the probability of an infectious mosquito biting into a susceptible human decreases as the fraction of infectious humans x increases. Thus, we may say that, in a highly endemic area, we might under-estimate the risk of infection unless the vector-bias is considered. This supports previous the results in [27], which show that the effect lessens the endemicity in a high transmission area and increases it in a low transmission area.

Invasion of malaria

We simulated an individual-based CTMC model to show the effect of vector-bias in the early invasive phase after a first outbreak. All simulations are repeated 10^4 times under the same qualifications. We assume that the populations of humans and mosquitoes are same, at 1000, i.e., $N = M = 10^3$. The results were compared with the simulations wherein the vector-bias was not considered. In addition, we compared the two invasion scenarios:

(Scenario A) invasion from a mosquito, i.e.,

$$(I_h(0), I_v(0)) = (0, 1); \text{ and}$$

(Scenario B) invasion from a human, i.e.,

$$(I_h(0), I_v(0)) = (1, 0).$$

In addition, $R_h(0) = 0$ was assumed.

Table 3 shows the probability that an infection will occur, and the probability of a secondary infection of

Table 3 Probabilities of the secondary infection and time to the secondary infection against two initial invasion scenarios.

Initial invasion scenario	Description	NOT considering vector-bias effect	Considering vector-bias effect
Scenario A	Probability that infection of human occurs due to a primary infectious mosquito invader	49.2%	90.5%
	Probability that infection of mosquito occurs due to a primary infectious human invader	50.0%	91.8%
Scenario B	Probability that the secondary infection of human occurs	73.6%	99.1%
	Time to the secondary infection of human	117.0days	44days

Table 4 Time-to-extinction of infectious human.

Initial invasion scenario	NOT considering vector-bias effect	Considering vector-bias effect
Scenario A	239days	63days
Scenario B	210days	40days

mosquitos and humans, as two invasion scenarios [46] and the time taken for the secondary infection of a human to occur, under the human invasion scenario. In both cases, the probability of infection is doubled when considering the vector-bias. When an infection occurs, the probability that malaria will persist increases due to the vector-bias. This is because the number of infected people increases after the first invader arrives, whether a mosquito or human. When there is an invasion by one person, vector-bias has a three-fold impact on the results. Therefore, it is important to apply treatment prior to the invasion because the probability of persistence increases rapidly, once the initial invasion occurs.

Figure 4 shows the endemic state distribution when eliminating the states equal to zero and the invasion probabilities, defined as the probability of an endemic by a primary invader, under both scenarios. The endemic prevalence of humans and mosquitos is high for both, when considering vector-bias. In addition, the probability of an endemic is twice as high as when not considering vector-bias under both scenarios.

Extinction of malaria

Figure 5 and Figure 6 show the offspring distribution of secondary infection and corresponding extinction probabilities under various dispersion scenarios respectively. The left panel of Figure 6 indicates the extinction probabilities against the dispersion parameter. The extinction probability decreases as the dispersion parameter increases, because the heterogeneity increases the uncertainty of infection and consequently increases the extinction probability. In addition, for a fixed dispersion parameter s , the extinction probability decreases when considering the vector-bias as based on the expression for R_0 , we know that an increasing λ increases R_0 . Therefore, an increase in λ will also reduce the disease extinction probability. Thus, it can be seen that the vector-bias reduces the chance of malaria extinction in some endemic or invasive communities. Although vector-bias lessens the endemic level in a high transmission area [27], it provides a positive potential to maintain the malaria endemic.

The right panel of Figure 6 shows that the vector-bias has no effect on reducing the malaria extinction probability in a highly heterogeneous environment. Although the bias towards infectious humans is 20-times higher, the extinction probability is only reduced to 0.23% (0.9993 to 0.9970). However, as heterogeneity decreases, the decreasing rate of extinction probability owing to vector-bias increases. It can be seen that

Figure 4 Multivariate distribution of endemic states (states at 10 years) when removing states hitting zero in Scenario A (left) and Scenario B (right). The invasion probability is abbreviated as IP. Northern and southern curves of each panels are histograms of endemic states against infectious humans and infectious mosquitoes, respectively.

Figure 5 Offspring distribution (6) of secondary infections through negative binomial counting model

Figure 6 Extinction probability against dispersion parameter s (left) and bias parameter λ (right).

the extinction probability decreases rapidly as the bias parameter increases but remains above a certain level. In terms of the adaptive host manipulation hypothesis in biology, these results suggest two possibilities: first, an extreme-biased behaviour of mosquitos can occur in areas having a high heterogeneity to increase the viability of a malaria parasite, and second, a low level of biased behaviour is sufficient to increase the viability of the parasite in areas with a low heterogeneity. Table 4 shows the time-to-extinction through the individual-based CTMC model. The time is short when considering a vector-bias, which means that if it does not occur during an early phase, and does not become extinct, it becomes an invasion with a high probability. This is because the vector-bias accelerates the initial invasion speed owing to an increase in R_0 , which makes the extinction more difficult, by rapidly making the endemicity exceed the extinction threshold and increasing the extinction probability.

Conclusion

The biased behaviour of mosquitos toward infectious humans accelerates an invasion of malaria into humans to endemic levels within a short time span, and during an endemic state, it makes the eradication of malaria difficult by lowering the extinction probability. Therefore, in areas without malaria, it is most important not to let the first patient enter a community, without a thorough examination, and even if an outbreak starts from the first patient, it is strongly necessary to stop

the malaria endemic by introducing control measures in the earliest possible time. The results of this study also indicate that an extremely biased behaviour may occur in a highly heterogeneous environment, whereas a biased behaviour may not be necessary for the survival of parasites in a low heterogeneous environment from an evolution perspective. In the future, malaria will evolve into more diverse areas owing to the rapid climate change. Therefore, studies on observing the behaviour of mosquitoes and identifying the causes of such behavioural changes are needed for the prediction and control of malaria. In addition, studies on malaria transmission dynamics by considering the manipulated behaviours and evolution of parasites should be actively carried out for the eradication of malaria.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in published articles [12] and [27].

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP) NRF-2017R1A5A1015722 to Il Hyo Jung; NRF-2017R1E1A1A03069992 to Byul Nim Kim; NRF-2019R1A2C2007249 to Il Hyo Jung.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65

Author's contributions

2YK and IHJ conceptualized the roles of the group. MAM and IHJ designed the studies. SK and BNK applied the modelling, and SK developed the numerical simulation. SK, MAM, and YK verified the results. All the members discussed the results and wrote the manuscript.

Acknowledgements

Not applicable.

Author details

¹Department of Mathematics, Pusan National University, 2, Busandaehak-ro 63beon-gil, 46241, Busan, Republic of Korea. ²Finance · Fishery · Manufacture Industrial Mathematics Center on Big Data, Pusan National University, 2, Busandaehak-ro 63beon-gil, 46241, Busan, Republic of Korea. ³Department of Mathematics, Kyungpook National University, 80, Daehak-ro, 41566, Daegu, Republic of Korea. ⁴Institute for Mathematical Convergence, Kyungpook National University, 80, Daehak-ro, 41566, Daegu, Republic of Korea. ⁵Department of Mathematics and Physics, North South University, Bashundhara, 1229, Dhaka, Bangladesh.

References

- Holmes JC, Bethel WM, Canning EU, Wright CA. Behavioural aspects of parasite transmission. *Zoological Journal of the Linnean Society*. 1972;51:123–149.
- Thomas F, Adamo S, Moore J. Parasitic manipulation: where are we and where should we go? *Behavioural processes*. 2005;68(3):185–199.
- Braks MAH, Anderson RA, Knols BGJ. Infochemicals in mosquito host selection: Human skin microflora and *Plasmodium* parasites; 1999.
- Zwiebel LJ, Takken W. Olfactory regulation of mosquito–host interactions. *Insect Biochemistry and Molecular Biology*. 2004;34(7):645–652.
- Clements AN. The biology of mosquitoes. Vol. 2. Sensory reception and behaviour; 1999.
- Nacher M. Charming the mosquito: do malaria symptoms increase the attractiveness of the host for the vector? *Medical Hypotheses*. 2005;64(4):788–791.
- Willem T, Bart GJK. Olfaction in vector–host interactions: Ecology and control of vector–borne diseases. pp 351. vol. 2. P.O. Box 220, 6700 AE Wageningen, The Netherlands: Wageningen Academic Publishers; 2010.
- Day JF, Ebert KM, Edman JD. Feeding patterns of mosquitoes simultaneously exposed to malarious and healthy mice, including a method for separating blood meals from conspecific hosts. *Journal of Medical Entomology*. 1983;20:120–127.
- Day JF, Edman JD. Malaria renders mice susceptible to mosquito feeding when gametocytes are most infective. *Journal of Parasitology*. 1983;69:163–170.
- Mahon R, Gibbs A. Arbovirus-infected hens attract more mosquitoes. JD Mackenzie, ed *Viral disease in Southeast Asia and the western Pacific*. Academic Press, Sydney. 1982;p. 502–504.
- Turell MJ, Bailey CL, Rossi CA. Increased mosquito feeding on Rift Valley fever virus-infected lambs. *The American Journal of Tropical Medicine and Hygiene*. 1985;33:1232–1238.

- Lacroix R, Mukabana WR, Gouagna LC, Koella JC. Malaria Infection Increases Attractiveness of Humans to Mosquitoes. *PLoS Biol*. 2005;3(9):e298.
- Chamchod F, Britton NF. Analysis of a vector–bias model on malaria transmission. *Bulletin of mathematical biology*. 2011;73(3):639–657.
- Koella JC, Packer MJ. Malaria parasites enhance blood–feeding of their naturally infected vector *Anopheles punctulatus*. *Parasitology*. 1996;113(02):105–109.
- Scott TW, Takken W. Feeding strategies of anthropophilic mosquitoes result in increased risk of pathogen transmission. *Trends in Parasitology*. 2012;28(3):114–121.
- Cornet S, Nicot A, Rivero A, Gandon S. Malaria infection increases bird attractiveness to uninfected mosquitoes. *Ecology letters*. 2013;16(3):323–329.
- De Moraes CM, Stanczyk NM, Betz HS, Pulido H, Sim DG, Read AF, et al. Malaria-induced changes in host odors enhance mosquito attraction. *Proceedings of the National Academy of Sciences*. 2014;111(30):11079–11084.
- Busula AO, Bousema T, Mweresa CK, Masiga D, Logan JG, Sauerwein RW, et al. Gametocytemia and attractiveness of *Plasmodium falciparum*–infected Kenyan children to *Anopheles gambiae* mosquitoes. *The Journal of Infectious Diseases*. 2017;216(3):291–295.
- Busula AO, Verhulst NO, Bousema T, Takken W, de Boer JG. Mechanisms of *Plasmodium*–enhanced attraction of mosquito vectors. *Trends in parasitology*. 2017;33(12):961–973.
- Sherrard-Smith E, Skarp JE, Beale AD, Fornadel C, Norris LC, Moore SJ, et al. Mosquito feeding behavior and how it influences residual malaria transmission across Africa. *Proceedings of the National Academy of Sciences*. 2019;116(30):15086–15095.
- Suh E, Grossman MK, Waite JL, Dennington NL, Sherrard-Smith E, Churcher TS, et al. The influence of feeding behaviour and temperature on the capacity of mosquitoes to transmit malaria. *Nature Ecology & Evolution*. 2020;p. 1–12.
- Kingsolver JG. Mosquito host choice and the epidemiology of malaria. *The American Naturalist*. 1987;130:811–827.
- Agusto FB, Tchuente JM. Control strategies for the spread of malaria in humans with variable attractiveness. *Mathematical Population Studies*. 2013;20(2):82–100.
- Buonomo B, Vargas-De-León C. Stability and bifurcation analysis of a vector–bias model of malaria transmission. *Mathematical Biosciences*. 2013;242(1):59–67.
- Cator LJ, Lynch PA, Read AF, Thomas MB. Do malaria parasites manipulate mosquitoes? *Trends in parasitology*. 2012;28(11):466–470.
- Cator LJ, Lynch PA, Thomas MB, Read AF. Alterations in mosquito behaviour by malaria parasites: Potential impact on force of infection. *Malaria Journal*. 2014;.
- Kim S, Masud MA, Cho G, Jung IH. Analysis of a vector–bias effect in the spread of malaria between two different incidence areas. *Journal of Theoretical Biology*. 2017;.
- Wang X, Zhao XQ. A periodic vector–bias malaria model with incubation period. *SIAM Journal on Applied Mathematics*.

- 2017;77(1):181–201. probability and endemic prevalence for Markovian SIS dynamics on 1
229. Li J, Teng Z, Zhang L. Stability and bifurcation in a vector-bias model 2
- of malaria transmission with delay. *Mathematics and Computers in* 3
- Simulation*. 2018;152:15–34. 4
30. Pan F, Cui X, Xue D, Lu Z. Stability analysis of a fractional-order 5
- vector-bias model on malaria transmission. In: 2019 Chinese Control 6
- And Decision Conference (CCDC). IEEE; 2019. p. 6363–6367. 7
31. Wang J, Chen Y. Threshold dynamics of a vector-borne disease model 8
- with spatial structure and vector-bias. *Applied Mathematics Letters*. 9
- 2020;100:106052. 10
32. Mojeeb AL, Li J. Analysis of a vector-bias malaria transmission model 11
- with application to Mexico, Sudan and Democratic Republic of the 12
- Congo. *Journal of Theoretical Biology*. 2019;464:72–84. 13
1133. Jacquez JA, O'Neill P. Reproduction numbers and thresholds in 14
- stochastic epidemic models I. Homogeneous populations. 15
- Mathematical Biosciences*. 1991;107(2):161–186. 16
34. Britton T. Stochastic epidemic models: a survey. *Mathematical* 17
- biosciences*. 2010;225(1):24–35. 18
35. Gillespie DT. Exact stochastic simulation of coupled chemical 19
- reactions. *The Journal of Physical Chemistry*. 1977;81(25):2340–2361. 20
36. Gillespie DT. Stochastic simulation of chemical kinetics. *Annu Rev* 21
- Phys Chem*. 2007;58:35–55. 22
37. Higham DJ. Modeling and simulating chemical reactions. *SIAM* 23
- Review*. 2008;. 24
38. Diekmann O, Heesterbeek JAP, Metz JAJ. On the definition and the 25
- computation of the basic reproduction ratio R_0 in models for infectious 26
- diseases in heterogeneous populations. *Journal of Mathematical* 27
- Biology*. 1990;. 28
39. Raphaka K, Sánchez-Molano E, Tsairidou S, Anacleto O, Glass EJ, 29
- Woolliams JA, et al. Impact of genetic selection for increased cattle 30
- resistance to bovine tuberculosis on disease transmission dynamics. 31
- Frontiers in veterinary science*. 2018;5. 32
40. Pemberton-Ross P, Chitnis N, Pothin E, Smith TA. A stochastic 33
- model for the probability of malaria extinction by mass drug 34
- administration. *Malaria journal*. 2017;16(1):376. 35
41. Haccou P, Haccou P, Jagers P, Vatutin VA, Vatutin VA. Branching 36
- processes: variation, growth, and extinction of populations. 5. 37
- Cambridge university press; 2005. 38
42. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading 39
- and the effect of individual variation on disease emergence. *Nature*. 40
- 2005;. 41
3243. Lloyd-Smith JO. Maximum likelihood estimation of the negative 42
- binomial dispersion parameter for highly overdispersed data, with 43
- applications to infectious diseases. *PloS one*. 2007;2(2):e180. 44
44. Hogg RV, McKean J, Craig AT. Introduction to Mathematical 45
- Statistics. 7th ed. Pearson; 2012. 46
45. Meehan MT, Cope RC, McBryde ES. On the probability of strain 47
- invasion in endemic settings: Accounting for individual heterogeneity 48
- and control in multi-strain dynamics. *Journal of theoretical biology*. 49
- 2020;487:110109. 50
46. Wilkinson RR, Sharkey KJ. An exact relationship between invasion 51

Figure 1

Figure 2

Figure 3

Figure 4

Scenario A

Scenario B

Figure 5

Figure 6

Figures

Figure 1

Weibull probability plot of bias parameter: the probability density function of Weibull distribution is given by (2) with $\alpha = 4.34$ and $\beta = 0.83$.

Figure 2

Description of the individual-based CTMC model and its simulation algorithm.

Figure 3

The probability that the human is infectious when chosen by a mosquito under the fixed condition $I_h = x$ when not considering (solid line) and considering (dashed line) a vector-bias effect.

Figure 4

Multivariate distribution of endemic states (states at 10 years) when removing states hitting zero in Scenario A (left) and Scenario B (right). The invasion probability is abbreviated as IP. Northern and southern curves of each panels are histograms of endemic states against infectious humans and infectious mosquitoes, respectively.

Figure 5

Offspring distribution (6) of secondary infections through negative binomial counting model

Figure 6

Extinction probability against dispersion parameter s (left) and bias parameter λ (right).