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Research Article

Determining Effective Spraying Periods to Control Malaria via Indoor Residual Spraying in Sub-Saharan Africa

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Indoor residual spraying—spraying insecticide inside houses to kill mosquitoes—is an important method for controlling malaria vectors in sub-Saharan Africa. We propose a mathematical model for both regular and non-fixed spraying, using impulsive differential equations. First, we determine the stability properties of the nonimpulsive system. Next, we derive minimal effective spraying intervals and the degree of spraying effectiveness required to control mosquitoes when spraying occurs at regular intervals. If spraying is not fixed, then we determine the "next best" spraying times. We also consider the effects of climate change on the prevalence of mosquitoes. We show that both regular and nonfixed spraying will result in a significant reduction in the overall number of mosquitoes, as well as the number of malaria cases in humans. We thus recommend that the use of indoor spraying be re-examined for widespread application in malaria-endemic areas.

1. Introduction

Malaria causes more than 300 million acute illnesses and at least one million deaths annually, and remains one of the most important human diseases throughout the tropical and subtropical regions of the world [1]. It is a leading cause of death and disease in many developing countries, where young children and pregnant women are the groups most affected. 40% of the world's population live in malaria-endemic areas [2]; 90% of deaths due to malaria occur in sub-Saharan Africa [3], 75% of whom are African children [4].

Control of malaria is largely through vector control and chemoprophylaxis. Vector control is an intervention targeted to reducing vector population density and survival, which

aims as an end product to reduce malaria transmission. Indoor residual spraying (IRS) is one of the primary vector control interventions for reducing and interrupting malaria transmission. In recent years, however, it has received relatively little attention. Recent data reconfirm the efficacy and effectiveness of IRS in malaria control in countries where it was implemented well [5]. Since many malaria vectors are endophilic, resting inside houses after taking a blood meal, they are particularly susceptible to be controlled through IRS. This method kills the mosquitoes after they have fed, thereby stopping transmission of the disease. IRS resulted in the suppression of *An. funestus*, which is no longer an important vector for transmission of malaria, in some areas of the subregion [6]. *An. gambiae s.s.* was also well controlled [5]. The user is able to spray the whole house or dwelling on the inside, and under the eaves on the outside. The duration of effective action ranges from two to greater than six months [7].

Malaria eradication projects in the 1950's through 1970's in Benin, Brukina Faso, Burundi, Cameroon, Kenya, Liberia, Madagascar, Nigeria, Rwanda, Senegal, Uganda, and the United Republic of Tanzania demonstrated that malaria was highly responsive to control by IRS, with a significant reduction of anopheline vector mosquitoes and malaria. The application of IRS consistently over time in large areas has altered the vector distribution and subsequently the epidemiological pattern of malaria in Botswana, Namibia, South Africa, Swaziland, and Zimbabwe [8–11]. IRS has commonly been the intervention of choice in areas of particular economic interest (e.g., tourism, mining, oil extraction, and agricultural schemes) that require a rapid and effective prevention, where financial and logistic constraints do not prevail [5].

We have developed a mathematical model to account for IRS using impulsive differential equations, in order to determine the minimal effective spraying period, as well as the amount by which mosquitoes should be reduced at each spraying event. However, the spraying may not happen at fixed intervals, due to limitations in resources and unforeseen events. If the spraying times are not fixed, then the optimal solution for the next spraying event can be calculated, but it depends on the entire history of spraying events, which may not be known. However, a suboptimal solution can be found, using partial information: the spraying effectiveness and the time of the last two spraying events.

This paper is organised as follows. In Section 2, we introduce the mathematical model. In Section 3, we analyse the nonimpulsive version of the model and determine the basic reproductive ratio. In Section 4, we analyse the model with impulses and determine minimal effective spraying times and spraying effectiveness, for both regular and nonfixed spraying. In Section 5, we examine the effects of climate change on the results. In Section 6, we illustrate the results with numerical simulations. Finally, in Section 7, we discuss the implications of the results.

2. The model

It can be assumed that mosquitoes are either susceptible (M) or infected (N), have birth rate Λ, and their death rate (μ) does not vary significantly if they are infected. Thus, we assume that the infective period of the vector ends with its death, and therefore the vector does not recover from being infective [12]. Individuals who have experienced infection may recover (without substantial gain in immunity) at recovery rate h or may become temporarily immune at acquired immunity rate α. See [13–17] for further details. Temporarily immune individuals will become susceptible again at rate δ. The rate of infection of a susceptible individual is β_H, and the rate of infecting a mosquito is β_M. The birth rate for humans is π,

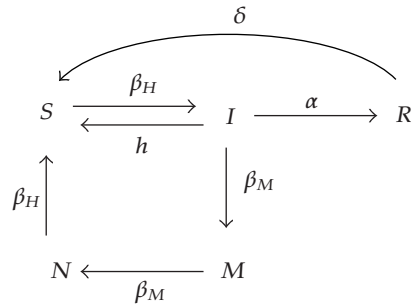

Figure 1: The model consists of susceptible (S), infected (I), and recovered (R) humans, as well as susceptible (M) and infected (N) mosquitoes. Humans may recover without immunity at rate h, or may become temporarily immune at rate α. Such individuals will later become susceptible again at rate δ. The rate of infection of a susceptible individual is β_H, and the rate of infecting a mosquito is β_M. The birth and death rates are not drawn in, for conciseness.

the background death rate is μ_H, and γ is the death rate due to malaria. Humans may be susceptible (S), infected (I), or temporarily immune (R). See Figure 1.

We assume that spraying reduces both susceptible and infected mosquitoes by the same proportion r (satisfying $0 \leq r \leq 1$), and that it occurs at distinct times t_k ($k = 0, 1, 2, \ldots$). These times may be fixed or variable. We model the effect of spraying by a system of impulsive differential equations. Impulsive differential equations consist of a system of ordinary differential equations (ODEs), together with difference equations. Between "impulses" t_k, the system is continuous, behaving as a system of ODEs. At the impulse points, there is an instantaneous change in state in some or all of the variables. This instantaneous change can occur when certain spatial, temporal, or spatiotemporal conditions are met. This has the advantage of capturing the dynamics between spraying events, while ignoring the short-term transient behaviour during the spraying itself. We refer the interested reader to [18–21] for more details on the theory of impulsive differential equations.

Thus, the model is

$$\begin{aligned}
\frac{dS}{dt} &= \pi - \beta_H SN + hI + \delta R - \mu_H S,\\
\frac{dI}{dt} &= \beta_H SN - hI - \alpha I - (\mu_H + \gamma) I,\\
\frac{dR}{dt} &= \alpha I - \delta R - \mu_H R,\\
\frac{dM}{dt} &= \Lambda - \mu M - \beta_M MI,\\
\frac{dN}{dt} &= \beta_M MI - \mu N
\end{aligned} \tag{2.1}$$

for $t \neq t_k$, with impulsive conditions given by

$$\begin{aligned}
\Delta M &= -rM^-,\\
\Delta N &= -rN^-
\end{aligned} \tag{2.2}$$

for $t = t_k$, where $\Delta M = M^+ - M^-$, $M^- \equiv M(t_k^-)$, and, equivalently, $M^+ \equiv M(t_k^+)$.

Hence, we are modelling the situation where IRS occurs simultaneously in multiple households, as occurs in areas in several countries [5]. Our model assumes that both humans and mosquitoes are well mixed in these areas. However, our results do not depend upon the form of the model for humans and only rely on certain aspects of the equations for mosquitoes. Further implications are taken up in Section 7.

3. Analysis of the nonimpulsive system

First, we will analyse the system without impulses; that is, without spraying. The disease-free equilibrium for the nonimpulsive model is given by

$$E_0 = (\overline{S}, \overline{I}, \overline{R}, \overline{M}, \overline{N}) = \left(\frac{\pi}{\mu_H}, 0, 0, \frac{\Lambda}{\mu}, 0\right). \tag{3.1}$$

The endemic equilibrium is given by

$$E_1 = (S^*, I^*, R^*, M^*, N^*), \tag{3.2}$$

where

$$\begin{aligned}
S^* &= \frac{\pi}{\mu_H} + \frac{\delta\alpha I^*}{\mu_H(\delta + mu_H)} - \frac{\alpha + \mu_H + \gamma}{\mu_H} I^*, \\
R^* &= \frac{\alpha I^*}{\delta + \mu_H}, \\
M^* &= \frac{\Lambda}{\mu + \beta_M I^*}, \\
N^* &= \frac{\beta_M \Lambda I^*}{\mu(\mu + \beta_M I^*)}, \\
I^* &= \frac{\left[\beta_H \beta_M \Lambda\pi - (h + \alpha + \mu_H + \gamma)\mu^2\mu_H\right](\delta + \mu_H)}{\beta_M\left[(\mu_H + \gamma)(\beta_H\Lambda + \mu)(\delta + \mu_H) + (\beta_M\Lambda + \mu)\alpha\mu_H + \mu h(\delta + \mu_H) + \mu\alpha\delta\right]}.
\end{aligned} \tag{3.3}$$

It can be seen that E_0 attracts the region

$$\Omega_0 = \{(S, I, R, M, N) : I = R = N = 0\}. \tag{3.4}$$

Theorem 3.1. *The basic reproductive ratio [22] for model* (2.1) *is given by*

$$R_0 = \frac{\beta_H \beta_M \Lambda\pi}{\mu^2\mu_H(\mu_H + \alpha + \gamma + h)}. \tag{3.5}$$

The disease-free equilibrium is stable if and only if $R_0 < 1$. *Furthermore, the endemic equilibrium is positive if and only if* $R_0 > 1$.

Proof. The Jacobian matrix for model (2.1) is

$$J = \begin{bmatrix} -\beta_H N - \mu_H & h & \delta & 0 & -\beta_H S \\ \beta_H N & -(h+\alpha+\mu_H+\gamma) & 0 & 0 & \beta_H S \\ 0 & \alpha & -(\delta+\mu_H) & 0 & 0 \\ 0 & -\beta_M M & 0 & -\mu-\beta_M I & 0 \\ 0 & \beta_M M & 0 & \beta_M I & -\mu \end{bmatrix}. \tag{3.6}$$

At the disease-free equilibrium,

$$J|_{I=N=0} = \begin{bmatrix} -\mu_H & h & \delta & 0 & -\beta_H \overline{S} \\ 0 & -(h+\alpha+\mu_H+\gamma) & 0 & 0 & \beta_H \overline{S} \\ 0 & \alpha & -(\delta+\mu_H) & 0 & 0 \\ 0 & -\beta_M \overline{M} & 0 & -\mu & 0 \\ 0 & \beta_M \overline{M} & 0 & 0 & -\mu \end{bmatrix}. \tag{3.7}$$

The eigenvalues of this matrix satisfy the characteristic equation

$$(-\mu_H-\lambda)(-\delta-\mu_H-\lambda)(-\mu-\lambda)\det\begin{bmatrix} -(h+\alpha+\mu_H+\gamma)-\lambda & \beta_H\overline{S} \\ \beta_M\overline{M} & -\mu-\lambda \end{bmatrix} = 0. \tag{3.8}$$

The only change in sign from the eigenvalues can occur from this last determinant, which satisfies

$$\lambda^2 + \lambda(\mu + h + \alpha + \mu_H + \gamma) + \mu(h + \alpha + \mu_H + \gamma) - \beta_H\beta_M\overline{S}\,\overline{M} = 0. \tag{3.9}$$

This equation will have negative roots if $\mu(h+\alpha+\mu_H+\gamma) - \beta_H\beta_M\overline{S}\,\overline{M} > 0$, or, equivalently, if and only if

$$R_0 \equiv \frac{\beta_H\beta_M\Lambda\pi}{\mu^2\mu_H(\mu_H+\alpha+\gamma+h)} < 1. \tag{3.10}$$

Finally, I^* is clearly positive if and only if $R_0 > 1$. □

Remark 3.2. It follows that there is a transcritical bifurcation at $R_0 = 1$. Thus, R_0 is the average number of mosquitoes infected by a single human ($\beta_M\pi/\mu^2$) multiplied by the average number of humans infected by a single mosquito ($\beta_H\Lambda/\mu_H(\mu_H+\alpha+\gamma+h)$).

4. Analysis of the impulsive system

When spraying events are included, the system will undergo an instantaneous jump when IRS is applied. We thus analyse model (2.1) when impulses are included. However, the mosquito dynamics will prove to be far more important in the model than those of humans.

If we define the total mosquito population by

$$\Psi = M + N, \tag{4.1}$$

then we have the decoupled impulsive differential equation

$$\begin{aligned} \frac{d\Psi}{dt} &= \Lambda - \mu\Psi, \quad t \neq t_k, \\ \Delta\Psi &= -r\Psi, \quad t = t_k. \end{aligned} \tag{4.2}$$

Thus,

$$\begin{aligned} \Psi^+ - \Psi^- &= -r\Psi^-, \\ \Psi^+ &= (1-r)\Psi^-. \end{aligned} \tag{4.3}$$

Hence, for $t_k \leq t < t_{k+1}$,

$$\begin{aligned} \Psi'(t) + \mu\Psi(t) &= \Lambda, \\ \frac{d}{dt}\left(e^{\mu t}\Psi\right) &= \Lambda e^{\mu t}, \\ e^{\mu t}\Psi(t) - e^{\mu t_k}\Psi\left(t_k^+\right) &= \frac{\Lambda}{\mu}e^{\mu t} - \frac{\Lambda}{\mu}e^{\mu t_k}, \\ \Psi(t) &= \frac{\Lambda}{\mu}\left(1 - e^{\mu(t_k - t)}\right) + \Psi\left(t_k^+\right)e^{\mu(t_k - t)}. \end{aligned} \tag{4.4}$$

It follows that

$$\begin{aligned} \Psi_{k+1}^- &= \frac{\Lambda}{\mu}\left(1 - e^{-\mu(t_{k+1} - t_k)}\right) + \Psi_k^+ e^{-\mu(t_{k+1} - t_k)} \\ &= \frac{\Lambda}{\mu}\left(1 - e^{-\mu(t_{k+1} - t_k)}\right) + (1-r)\Psi_k^- e^{-\mu(t_{k+1} - t_k)}, \end{aligned} \tag{4.5}$$

using (4.3).

We thus have a recurrence relation for the total number of mosquitoes immediately before spraying. This relation depends on the birth and death rates of mosquitoes, the spraying times, and the spraying effectiveness.

Theorem 4.1. *If spraying occurs at fixed times, satisfying $t_{k+1} - t_k = \tau$, then*

$$\widetilde{\Psi}^-(r) = \frac{\Lambda}{\mu} \cdot \frac{1 - e^{-\mu\tau}}{1 + (r-1)e^{-\mu\tau}} \tag{4.6}$$

is a globally asymptotically stable fixed point of the recurrence relation

$$\Psi_{k+1}^- = \frac{\Lambda}{\mu}\left(1 - e^{-\mu(t_{k+1} - t_k)}\right) + (1-r)\Psi_k^- e^{-\mu(t_{k+1} - t_k)}. \tag{4.7}$$

Proof. For completeness, define Ψ_0 to be the preimage of $\Psi(0)$ under the impulsive condition. That is, $\Psi_0 = (1/(1-r))\Psi(0)$. Then, we have

$$\begin{aligned}
\Psi_1^- &= \frac{\Lambda}{\mu}\left(1-e^{-\mu(t_1-t_0)}\right) + (1-r)\Psi_0 e^{-\mu(t_1-t_0)},\\
\Psi_2^- &= \frac{\Lambda}{\mu}\left(1-e^{-\mu(t_2-t_1)}\right) + (1-r)\Psi_1^- e^{-\mu(t_2-t_1)}\\
&= \frac{\Lambda}{\mu}\left(1-e^{-\mu(t_2-t_1)}\right) + (1-r)\frac{\Lambda}{\mu}\left(1-e^{-\mu(t_1-t_0)}\right)e^{-\mu(t_2-t_1)} + (1-r)^2\Psi_0 e^{-\mu(t_1-t_0)}e^{-\mu(t_2-t_1)}\\
&= \frac{\Lambda}{\mu}\left(1-re^{-\mu(t_2-t_1)} - (1-r)e^{-\mu(t_2-t_0)}\right) + (1-r)^2\Psi_0 e^{-\mu(t_2-t_0)},\\
\Psi_3^- &= \frac{\Lambda}{\mu}\left(1-e^{-\mu(t_3-t_2)}\right) + (1-r)\Psi_2^- e^{-\mu(t_3-t_2)}\\
&= \frac{\Lambda}{\mu}\left(1-e^{-\mu(t_3-t_2)}\right) + (1-r)\frac{\Lambda}{\mu}\left(1-re^{-\mu(t_2-t_1)} - (1-r)e^{-\mu(t_2-t_0)}\right)e^{-\mu(t_3-t_2)} + (1-r)^3\Psi_0 e^{-\mu(t_2-t_0)}e^{-\mu(t_3-t_2)}\\
&= \frac{\Lambda}{\mu}\left(1-re^{-\mu(t_3-t_2)} - r(1-r)e^{-\mu(t_3-t_1)} - (1-r)^2e^{-\mu(t_3-t_0)}\right) + (1-r)^3\Psi_0 e^{-\mu(t_3-t_0)},\\
\Psi_4^- &= \frac{\Lambda}{\mu}\left(1-re^{-\mu(t_4-t_3)} - r(1-r)e^{-\mu(t_4-t_2)} - r(1-r)^2e^{-\mu(t_4-t_1)} - (1-r)^3e^{-\mu(t_4-t_0)}\right) + (1-r)^4\Psi_0 e^{-\mu(t_4-t_0)}\\
&\vdots\\
\Psi_n^- &= \frac{\Lambda}{\mu}\left(1-\sum_{i=1}^{n-1} r(1-r)^{n-i-1}e^{-\mu(t_n-t_i)} - (1-r)^{n-1}e^{-\mu(t_n-t_0)}\right) + (1-r)^n\Psi_0 e^{-\mu(t_n-t_0)}.
\end{aligned} \tag{4.8}$$

For regular spraying, $t_n - t_i = (n-i)\tau$, so we have

$$\begin{aligned}
\Psi_n^- &= \frac{\Lambda}{\mu}\left(1-\frac{re^{-\mu\tau} - (1-r)^{n-1}re^{-\mu\tau}}{1-(1-r)e^{-\mu\tau}} - (1-r)^{n-1}e^{-\mu n\tau}\right) + (1-r)^n\Psi_0 e^{-\mu n\tau}\\
&\longrightarrow \frac{\Lambda}{\mu}\left(1-\frac{re^{-\mu\tau}}{1-(1-r)e^{-\mu\tau}}\right)
\end{aligned} \tag{4.9}$$

as $n \to \infty$, since $0 < r < 1$. □

Remarks 4.2. (1) Note that

$$\lim_{\substack{\tau\to 0\\ n\to\infty}} \Psi_n^- = 0. \tag{4.10}$$

Thus, the total mosquito population shrinks to zero as spraying period decreases.

(2) It follows from Theorem 4.1 that the impulsive periodic orbit given by (4.4), with endpoints Ψ^- and $(1-r)\Psi^-$, where Ψ^- satisfies (4.6), is asymptotically stable.

Corollary 4.3. (1) *To reduce the total mosquito population below a desired threshold* $\widetilde{\Psi}$*, the minimum spraying effectiveness satisfies*

$$\widetilde{r} = 1 - \left[1 - \frac{\Lambda}{\mu\widetilde{\Psi}}(1 - e^{-\mu\tau})\right]e^{\mu\tau}. \tag{4.11}$$

(2) *To reduce the mosquito population below a desired threshold* $\widetilde{\Psi}$*, the minimum spraying period satisfies*

$$\widetilde{\tau} = -\frac{1}{\mu}\ln\left[\frac{\Lambda - \mu\widetilde{\Psi}}{\Lambda + \mu\widetilde{\Psi}(r-1)}\right]. \tag{4.12}$$

Proof. (1) Since $\Psi(t) \leq \Psi^{-}$ for $t_k \leq t \leq t_{k+1}$, the maximum within each cycle occurs immediately before spraying is undertaken, so we can set $\widetilde{\Psi} = \Psi^{-}$. By Theorem 4.1, we have

$$\begin{aligned}
\widetilde{\Psi} &= \frac{\Lambda}{\mu}\cdot\frac{1 - e^{-\mu\tau}}{1 + (\widetilde{r} - 1)e^{-\mu\tau}},\\
1 + (\widetilde{r} - 1)e^{-\mu\tau} &= \frac{\Lambda}{\mu\widetilde{\Psi}}(1 - e^{-\mu\tau}),\\
\widetilde{r} &= 1 - \left[1 - \frac{\Lambda}{\mu\widetilde{\Psi}}(1 - e^{-\mu\tau})\right]e^{\mu\tau}.
\end{aligned} \tag{4.13}$$

(2) Similarly, we have

$$\begin{aligned}
\left(r - 1 + \frac{\Lambda}{\mu\widetilde{\Psi}}\right)e^{-\mu\widetilde{\tau}} &= \frac{\Lambda}{\mu\widetilde{\Psi}} - 1,\\
\widetilde{\tau} &= -\frac{1}{\mu}\ln\left[\frac{\Lambda - \mu\widetilde{\Psi}}{\Lambda + \mu\widetilde{\Psi}(r-1)}\right].
\end{aligned} \tag{4.14}$$

□

It follows that we can find the minimal spraying effectiveness or the minimal spraying period, in terms of the birth and death rates of mosquitoes and the spraying effectiveness.

Theorem 4.4. *If spraying occurs at nonfixed times, then, assuming the two previous spraying events are known, the population of mosquitoes can be reduced below the threshold* $\widetilde{\Psi}$ *if the next spraying event satisfies*

$$t_{n+1} \leq t_n - \frac{1}{\mu}\ln\left[\frac{2 - r - \mu\widetilde{\Psi}/\Lambda}{1 + r(1-r)e^{-\mu(t_n - t_{n-1})}}\right]. \tag{4.15}$$

Proof. For n large,

$$\Psi_n^{-} \approx \frac{\Lambda}{\mu}\left(1 - \sum_{i=1}^{n-1} r(1-r)^{n-i-1}e^{-\mu(t_n - t_i)}\right) \tag{4.16}$$

since $(1-r)^{n-1} \approx 0$ and $e^{-\mu(t_n - t_0)} \approx 0$. If we assume $e^{-\mu(t_n - t_{n-2})}$ is small, then, using (4.5), we have

$$\begin{aligned}
\Psi_n^- &< \frac{\Lambda}{\mu}\left(1 - e^{-\mu(t_n - t_{n-1})}\right), \\
\Psi_{n+1}^+ &< \frac{\Lambda}{\mu}\left(1 - e^{-\mu(t_{n+1} - t_n)}\right) + (1-r)\Psi_n^- e^{-\mu(t_{n+1} - t_n)} \\
&< \frac{\Lambda}{\mu}\left(1 - e^{-\mu(t_{n+1} - t_n)}\right) + (1-r)\frac{\Lambda}{\mu}\left(1 - re^{-\mu(t_n - t_{n-1})}\right)e^{-\mu(t_{n+1} - t_n)}.
\end{aligned} \tag{4.17}$$

Define

$$\widetilde{\Psi} \equiv \frac{\Lambda}{\mu}\left(1 - e^{-\mu(t_{n+1} - t_n)}\right) + (1-r)\frac{\Lambda}{\mu}\left(1 - re^{-\mu(t_n - t_{n-1})}\right)e^{-\mu(t_{n+1} - t_n)}. \tag{4.18}$$

Thus,

$$\begin{aligned}
\frac{\Lambda}{\mu}\left(1 + (1-r)\right) - \widetilde{\Psi} &= e^{-\mu(t_{n+1} - t_n)}\frac{\Lambda}{\mu}\left(1 + r(1-r)e^{-\mu(t_n - t_{n-1})}\right), \\
e^{-\mu(t_{n+1} - t_n)} &= \frac{2 - r - \mu\widetilde{\Psi}/\Lambda}{1 + r(1-r)e^{-\mu(t_n - t_{n-1})}}, \\
t_{n+1} &= t_n - \frac{1}{\mu}\ln\left[\frac{2 - r - \mu\widetilde{\Psi}/\Lambda}{1 + r(1-r)e^{-\mu(t_n - t_{n-1})}}\right].
\end{aligned} \tag{4.19}$$

Hence, if spraying occurs at t_{n+1} or earlier, then the number of mosquitoes will be less than or equal to $\widetilde{\Psi}$, immediately after the $(n+1)$th spraying event. □

Thus, we can derive the "next best" spraying events for nonfixed spraying, by assuming that the time between the current spraying and two sprayings events previously is sufficiently large.

Theorem 4.5. *If nonfixed spraying occurs indefinitely, then there exists a minimum spraying effectiveness r_0, satisfying $0 < r_0 < 1$, such that variable spraying is only effective for $r_0 \le r \le 1$. Furthermore, on this interval, the minimum spraying interval for indefinite nonfixed spraying is always less than the minimum spraying interval for regular spraying.*

Proof. First, note that, for regular spraying, we have

$$\begin{aligned}
\widetilde{\tau} &= -\frac{1}{\mu}\ln\left[\frac{\Lambda - \mu\widetilde{\Psi}}{\Lambda + \mu\widetilde{\Psi}(r-1)}\right], \\
\widetilde{\tau}|_{r=0} &= -\frac{1}{\mu}\ln\left[\frac{\Lambda - \mu\widetilde{\Psi}}{\Lambda - \mu\widetilde{\Psi}}\right] = 0,
\end{aligned} \tag{4.20}$$

$$\widetilde{\tau}|_{r=1} = -\frac{1}{\mu}\ln\left[\frac{\Lambda - \mu\widetilde{\Psi}}{\Lambda}\right] = -\frac{1}{\mu}\ln\left[1 - \frac{\mu\widetilde{\Psi}}{\Lambda}\right]. \tag{4.21}$$

However, $\Psi = M + N$. So, if there is no impulse, then, from (4.2), $\lim_{t\to\infty}\Psi(t) = \Lambda/\mu$. Thus, we can assume that $\widetilde{\Psi} < \Lambda/\mu$. Hence,

$$0 < 1 - \frac{\mu\widetilde{\Psi}}{\Lambda} < 1, \tag{4.22}$$

and thus $\widetilde{\tau}|_{r=1} > 0$.

If nonfixed spraying occurs indefinitely, then let $\tau_{\mathrm{nf}} \equiv t_{n+1} - t_n = t_n - t_{n-1}$. The minimum spraying effectiveness then satisfies

$$\tau_{\mathrm{nf}} = -\frac{1}{\mu}\ln\left[\frac{2 - r - \mu\widetilde{\Psi}/\Lambda}{1 + r(1-r)e^{-\mu\tau_{\mathrm{nf}}}}\right]. \tag{4.23}$$

If $\tau_{\mathrm{nf}} = 0$, then

$$\begin{aligned}
-\frac{1}{\mu}\ln\left[\frac{2 - r - \mu\widetilde{\Psi}/\Lambda}{1 + r(1-r)}\right] &= 0,\\
2 - r - \frac{\mu\widetilde{\Psi}}{\Lambda} &= 1 + r(1-r),\\
r^2 - 2r + 1 - \frac{\mu\widetilde{\Psi}}{\Lambda} &= 0,\\
r &= 1 \pm \sqrt{\frac{\mu\widetilde{\Psi}}{\Lambda}}.
\end{aligned} \tag{4.24}$$

Clearly, the larger root exceeds unity and can hence be discounted. The smaller root, $r_0 \equiv 1 - \sqrt{\mu\widetilde{\Psi}/\Lambda}$, satisfies $0 < r_0 < 1$ by (4.22). It follows that spraying is only effective in the range $r_0 \le r \le 1$.

Next, we have

$$\tau_{\mathrm{nf}}|_{r=1} = -\frac{1}{\mu}\ln\left[\frac{1 - \mu\widetilde{\Psi}/\Lambda}{1}\right] = \widetilde{\tau}|_{r=1}, \tag{4.25}$$

from (4.21).

Note that $\Lambda + \mu\widetilde{\Psi}(r-1)$ and $(2-r)\Lambda - \mu\widetilde{\Psi}$ are both positive on $0 < r < 1$, since $\Lambda - \mu\widetilde{\Psi} > 0$. Since $e^{-\mu\tau_{\mathrm{nf}}} < 1$, we have

$$\frac{\Lambda - \mu\widetilde{\Psi}}{\Lambda + \mu\widetilde{\Psi}(r-1)} \cdot \frac{1 + r(1-r)e^{-\mu\tau_{\mathrm{nf}}}}{2 - r - \mu\widetilde{\Psi}/\Lambda} < \frac{\Lambda(\Lambda - \mu\widetilde{\Psi})}{\Lambda + \mu\widetilde{\Psi}(r-1)} \cdot \frac{1 + r(1-r)}{(2-r)\Lambda - \mu\widetilde{\Psi}}. \tag{4.26}$$

Thus,

$$\frac{\Lambda(\Lambda - \mu\widetilde{\Psi})}{\Lambda + \mu\widetilde{\Psi}(r-1)} \cdot \frac{1 + r(1-r)}{(2-r)\Lambda - \mu\widetilde{\Psi}} - 1 = \frac{\gamma}{\left[\Lambda + \mu\widetilde{\Psi}(r-1)\right]\left[(2-r)\Lambda - \mu\widetilde{\Psi}\right]}, \tag{4.27}$$

where

$$\begin{aligned}
\gamma &= -\Lambda^2(r-1)^2 + 2\mu\widetilde{\Psi}\Lambda(r-1)^2 + \mu^2\widetilde{\Psi}^2(r-1)\\
&= -(r-1)\left[\Lambda^2(r-1) - 2\mu\widetilde{\Psi}\Lambda(r-1) - \mu^2\widetilde{\Psi}^2\right].
\end{aligned} \tag{4.28}$$

For $0 < r < 1$, $r - 1 < 0$. Furthermore, if $\Lambda - 2\mu\tilde{\Psi} > 0$, then the quantity in the square brackets is increasing and hence the maximum value it attains on the interval $0 < r < 1$ is $-\mu^2\tilde{\Psi}^2$ at $r = 1$. Conversely, if $\Lambda - 2\mu\tilde{\Psi} < 0$, then the quantity in the square brackets is decreasing and hence the maximum value it attains on the interval $0 < r < 1$ is $-(\Lambda - \mu\tilde{\Psi})^2$ at $r = 0$. In either case, $\gamma < 0$ on the interval $0 < r < 1$.

Consequently,

$$\frac{\Lambda - \mu\tilde{\Psi}}{\Lambda + \mu\tilde{\Psi}(r-1)} \cdot \frac{1 + r(1-r)e^{-\mu\tau_{\mathrm{nf}}}}{2 - r - \mu\tilde{\Psi}/\Lambda} < 1, \tag{4.29}$$

and hence

$$\tilde{\tau} - \tau_{\mathrm{nf}} = -\frac{1}{\mu} \ln \left[\frac{\Lambda - \mu\tilde{\Psi}}{\Lambda + \mu\tilde{\Psi}(r-1)} \cdot \frac{1 + r(1-r)e^{-\mu\tau_{\mathrm{nf}}}}{2 - r - \mu\tilde{\Psi}/\Lambda} \right] > 0. \tag{4.30}$$

Thus, $\tilde{\tau} > \tau_{\mathrm{nf}}$ for $0 < r < 1$. □

It follows that nonfixed spraying is always worse than regular spraying—even in the best-case scenario where such spraying is applied at regular intervals—and is only defined for a sufficiently effective insecticide.

5. The impact of climate change

As global temperatures increase, one of the major impacts will be an increase in the birth rate of mosquitoes [23, 24]. Consequently, we examine the impact of increasing the birth rate on the minimal effective period of IRS required to maintain mosquitoes at given thresholds.

If the mosquito birth rate is increased from Λ to $\Lambda + \Lambda_1$, then the recursion relation (4.5), with regular spraying, becomes

$$\Psi_{k+1}^{-} = \frac{\Lambda + \Lambda_1}{\mu}\left(1 - e^{-\mu\tau}\right) + (1-r)\Psi_k^{-}e^{-\mu\tau}. \tag{5.1}$$

This has solution

$$\tilde{\Psi}^{-} = \frac{\Lambda + \Lambda_1}{\mu} \cdot \frac{1 - e^{-\mu\tau}}{1 + (r-1)e^{-\mu\tau}}. \tag{5.2}$$

Rearranging, we have

$$\tilde{\tau} = -\frac{1}{\mu} \ln \left[\frac{\Lambda + \Lambda_1 - \mu\tilde{\Psi}}{\Lambda + \Lambda_1 + \mu\tilde{\Psi}(r-1)} \right]. \tag{5.3}$$

It follows that

$$\frac{\partial\tilde{\tau}}{\partial\Lambda_1} = -\frac{r\tilde{\Psi}}{(\Lambda + \Lambda_1 - \mu\tilde{\Psi})(\Lambda + \Lambda_1 - \mu\tilde{\Psi} + r\mu\tilde{\Psi})} < 0 \tag{5.4}$$

since $\tilde{\Psi} < \Lambda/\mu$. Thus, as the mosquito birth rate increases, the minimal effective spraying period will always be reduced, for a fixed mosquito threshold $\tilde{\Psi}$. In particular, we have

$$\lim_{\Lambda_1 \to 0} \tilde{\tau} = 0. \tag{5.5}$$

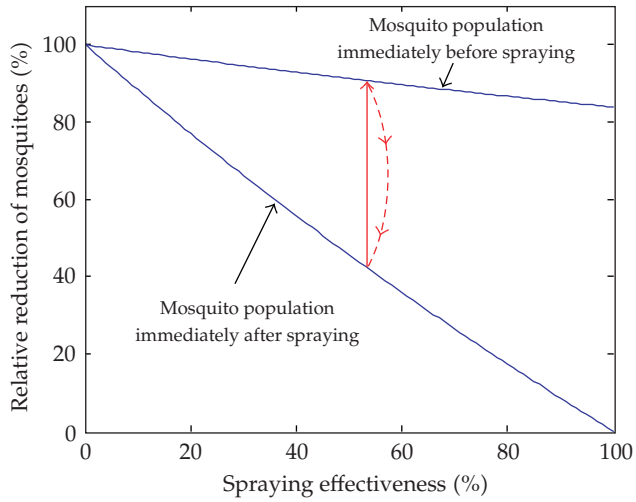

Figure 2: The relative reduction of mosquitoes as a function of the spraying effectiveness. The two curves indicate the maximum and minimum numbers of mosquitoes, given by Ψ^- and $\Psi^+ = (1-r)\Psi^-$, respectively. Parameters used were $\Lambda = 1000$ mosquitoes $\cdot$ years^{-1}, $\mu = 1/7.3$ days^{-1}, and spraying that occurred every three months. Note that there is a discontinuity at the right endpoint due to the impulsive nature of the solutions; if spraying is 100% effective, then the mosquito population will be zero.

6. Numerical simulations

The average lifespan of a mosquito is of the order of days to weeks [25]; we chose an intermediate value of 7 days. The birth rate of mosquitoes is the carrying capacity divided by the lifespan [26]. With a lifespan of 7 days and a carrying capacity of 20 000 [26], this results in 1400 females per year. Correcting for those not reached by spraying (e.g., those who feed away from houses), we assumed 1000 females per year. The probability of infection is the product of the biting rate times the probability that a bite is infectious. The former value is 0.7 per day and the latter is 0.75 [27], resulting in an infection probability for humans of 0.5 per day. The value for mosquito infection is assumed to be one tenth of the value for humans. The total duration of malaria infection in humans is 3–7 days [28]. We chose recovery, immunity, and mortality rates so that the total duration of infection was 3 days.

The dependency of the mosquito population upon the spraying effectiveness is illustrated in Figure 2. The two curves indicate the maximum and minimum mosquito populations if an insecticide is used which reduces mosquitoes by the percentage on the x-axis, when sprayed every three months. These are the long-term outcomes of fixed spraying. The greater the spraying effectiveness is, the more variation in the overall mosquito population exists, but the lower the average mosquito population will be. We chose parameters to simulate a small spraying region, since mosquito spraying may occur at different times.

Varying the period of spraying will result in a change of strategy, as shown in Figure 3. A mosquito control program aiming to reduce the maximum number of mosquitoes by 15% would require an insecticide that reduced mosquitoes by 92% per spraying if spraying occurred three times a year, or by 54% if spraying occurred 2.3 times a year.

The dependency of the mosquito population upon the spraying effectiveness, for both regular and nonfixed spraying, is illustrated in Figure 4. If spraying is fixed, then

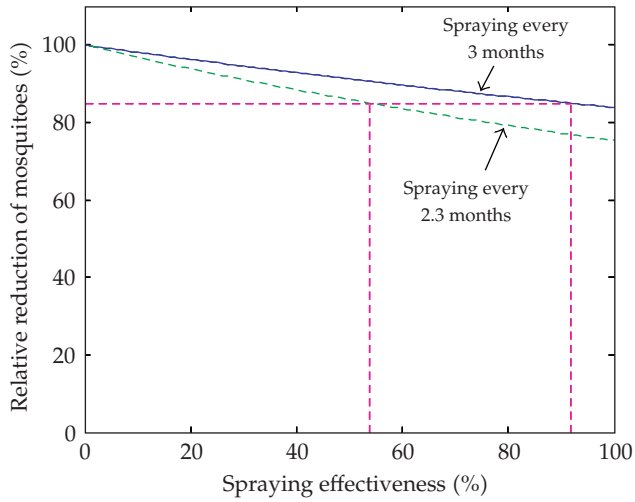

Figure 3: Two spraying options: every three months (solid curve) and every 2.3 months (dashed curve). A mosquito-control program aiming to reduce the number of mosquitoes by 15% would require a 92% effective insecticide if spraying occurred every three months, or 54% if spraying occurred every 2.3 months. Note that these curves illustrate the maximum number of mosquitoes in each case, showing the worst-case scenario.

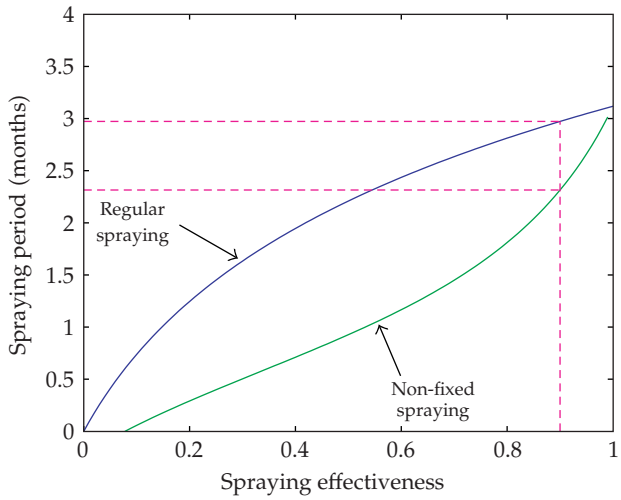

Figure 4: The minimum spraying intervals, for both regular spraying and nonfixed spraying, to reduce the overall mosquito population by 15% of the levels without spraying. While regular spraying can theoretically be applied for any spraying effectiveness, nonfixed spraying is only applicable if the spraying is 8% effective or greater. An insecticide that reduced mosquitoes by 90% at each spraying would have to be applied every three months, if it were applied regularly, but not more than every 2.3 months if spraying was not fixed.

any spraying effectiveness may theoretically be used, when the insecticide is applied with sufficient frequency. If spraying is not fixed, then there is minimum spraying effectiveness that must be satisfied. A 90% effective insecticide should be sprayed at three-month intervals

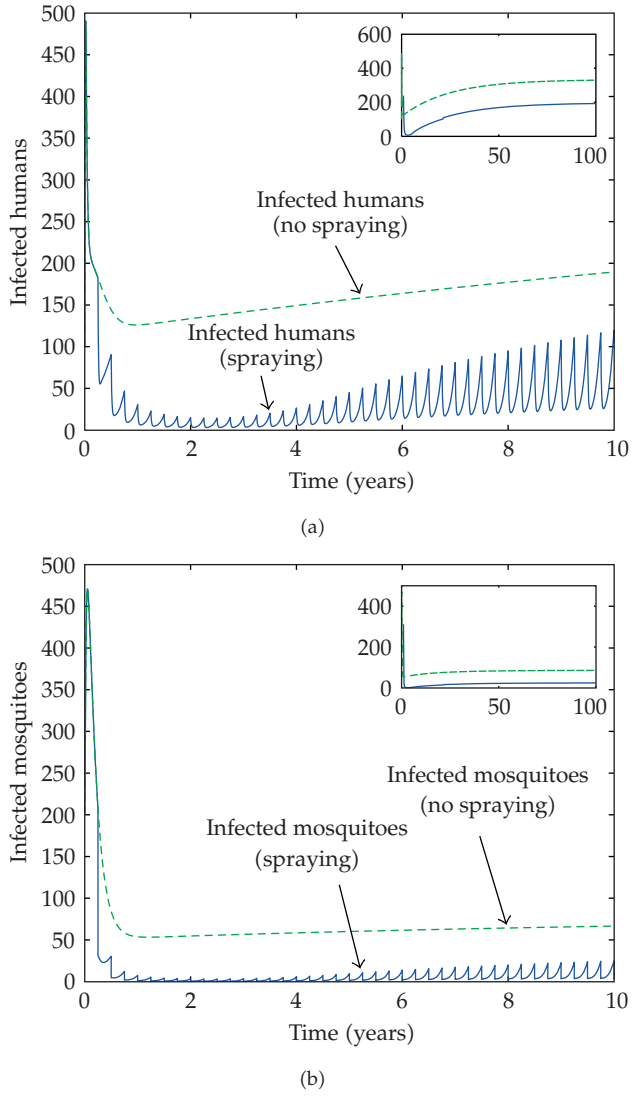

Figure 5: (a) Number of infected humans, over a ten year period, for no spraying (dashed curve) and regular, three-monthly spraying (solid curve) Inset: Mean number of infected humans over a 100 year period. (b) Number of infected mosquitoes over a ten year period, for no spraying (dashed curve) and regular, three-monthly spraying (solid curve). Inset: Mean number of infected mosquitoes over a 100 year period. Data used were $\Lambda = 1000$ mosquitoes $\cdot$ years^{-1}, $\beta_M = 0.05$ mosquitoes^{-1} days^{-1}, $h = 1/9$ days^{-1}, $\delta = 1/30$ days^{-1}, $\mu_H = 1/30$ years^{-1}, $\alpha = 1/8$ days^{-1}, $\gamma = 1/20$ days^{-1}, $\mu = 1/7.3$ days^{-1}, $\pi = 100$ humans $\cdot$ years^{-1}, $\beta_H = 0.5$ humans^{-1} days^{-1}, $r = 0.85$ and $\tau = 0.25$ years.

for regular spraying, or every 2.3 months for nonfixed spraying, to reduce the overall mosquito population to 85% of that of the mosquito population without spraying.

To illustrate this, model (2.1) was simulated, over a period of 100 years. Regular spraying occurred every three months, for an insecticide that was 85% effective. Regular spraying significantly reduced the number of malaria cases in humans (Figure 5(a)) and the number of infected mosquitoes (Figure 5(b)). Nonfixed spraying was also illustrated, for

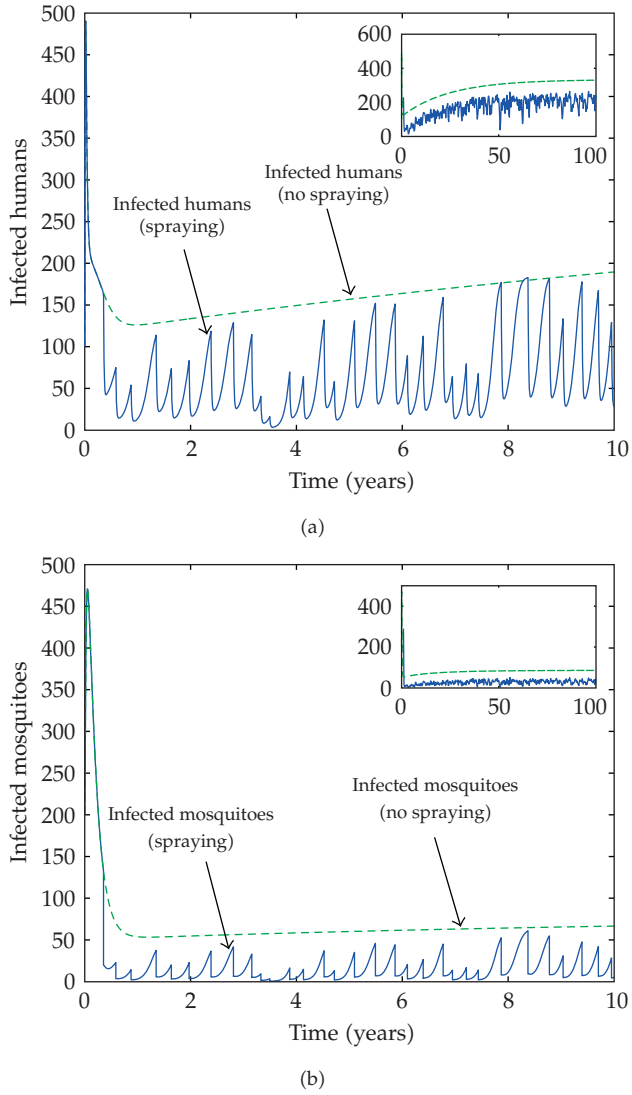

Figure 6: (a) Number of infected humans, over a 25-year period, for no spraying (dashed curve) and nonfixed spraying (solid curve). (b) Number of infected mosquitoes over a 25-year period, for no spraying (dashed curve) and nonfixed spraying (solid curve). Data used were identical to those in Figure 5, except for the time of spraying. These times were randomly generated from a normal distribution, with a mean of 4 months and a standard deviation of 1.2 months.

a spraying program with random spraying events chosen from a normal distribution with a mean of 4 months and a standard deviation of 1.2 months. In this case, the number of malaria cases in both humans and mosquitoes was also reduced significantly (Figure 6). However, during some periods where the gap between spraying events was excessive, the peaks of infection matched the number of infections without spraying.

The effects of increasing the mosquito birth rate are illustrated in Figure 7. The minimal effective spraying period for regular spraying will always decrease as the mosquito birth rate

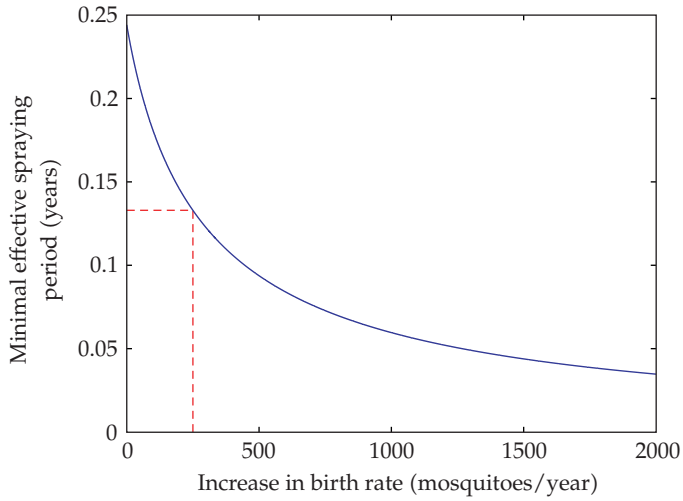

Figure 7: The amount of IRS required to maintain present mosquito levels, as the mosquito birth rate increases. If the mosquito birth rate is increased by 25%, then the minimal effective spraying period for regular spraying decreases by about half (dashed red lines). If the mosquito birth rate doubles, then the minimal effective spraying period is reduced by three quarters. As the mosquito birth rate continues to increase, the minimal effective spraying period is driven to zero. In this case, identical parameters were used to Figure 2.

increases; however, even a small increase in the mosquito birth rate has a significant effect on the reduction of the minimal effective spraying period.

Finally, sensitivity to the other significant parameter, the mosquito death rate, is illustrated in Figure 8. As the death rate increases, the minimal effective spraying period decreases. There is a vertical asymptote at $\mu = \Lambda/\Psi$, since $\Psi \leq \Lambda/\mu$, the equilibrium level from the nonimpulsive system. That is, if $\mu > \Lambda/\Psi$, then $d\Psi/dt < 0$ and thus the number of mosquitoes would never increase.

7. Discussion

We derived minimal effective spraying times for either fixed or variable spraying. Once the birth and death rates of mosquitoes and spraying effectiveness of the insecticide are known, the minimal effective spraying period can be determined, using (4.12). This is a simple formula that can be easily calculated by policy makers and health officials.

If spraying occurs at regular, known intervals (e.g., every six months), then the minimal insecticide effectiveness or spraying period can be derived (Corollary 4.3). If spraying does not occur at fixed intervals, then the optimal result would depend on knowing the entire history of spraying in the area. Since this is not possible, we assume that only the previous two spraying events are known. In this case, the next best spraying is given by Theorem 4.4. While this provides a recipe for coping with the "next best" outcome, it should be noted (from Theorem 4.5) that (a) nonfixed spraying is always less optimal than regular spraying and (b) only applies for a sufficiently effective insecticide.

These thresholds are analytical, so their application may vary, depending on the region in which they are applied. However, we provide an illustrative example: an insecticide which reduces mosquitoes by 90% at each spraying will ultimately result in a 15% reduction in

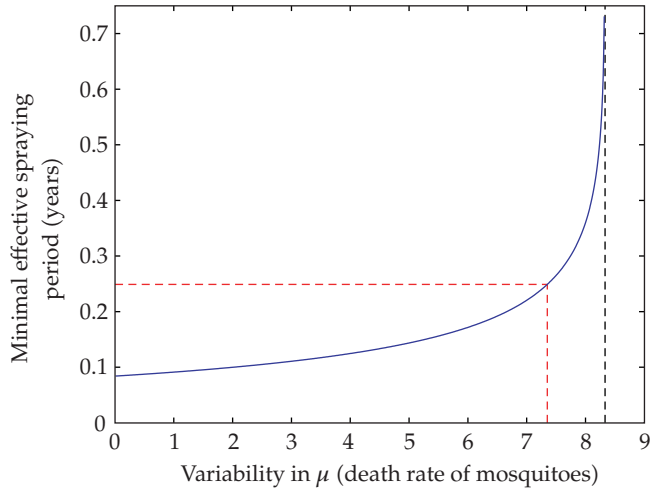

Figure 8: Sensitivity of IRS to changes in the mosquito death rate. Parameters used are identical to Figure 2 and the median case illustrated by the dashed red line. As the death rate decreases, the minimal effective spraying period decreases, but it is bounded below by $\tau_{\min} = 0.085$ years. Thus, if regular spraying occurs every month, then mosquitoes would be eradicated even if they never died due to any other cause. Conversely, as the death rate increases, the minimal effective IRS period is increased. There is a vertical asymptote at $\mu = \Lambda/\Psi$; above this level, mosquitoes would be dying faster than they were born—an unrealistic scenario.

mosquitoes if sprayed every three months. If the same insecticide is used, but with nonfixed spraying, then the insecticide should be applied at 2.3-month intervals to achieve a 15% reduction.

The mosquito birth rate may increase due to a variety of factors; one of those factors will be the impact of climate change, as global temperatures increase. The effect of global warming will have an increasingly heavy burden on the resulting change in strategy; if the mosquito birth rate increased by one quarter, as a result of temperate changes, then the minimal effective IRS period would be reduced by roughly half. If the mosquito birth rate doubled, then the minimal effective IRS period would be reduced by about three quarters. Since the spraying of insecticide consumes valuable and limited resources [29], we therefore conclude that global warming will have a disproportionately detrimental effect in malaria-endemic countries. However, it should be noted that the effects of climate change are likely to be significantly more complicated than considered here.

The dependence of the minimal effective spraying period upon mosquito birth rates is also a measure of the sensitivity of the results to changes in the latter. Since the thresholds for the insecticide effectiveness and spraying period also serve as sensitivity analyses to their respective parameters, we thus performed a sensitivity analysis on the only remaining significant parameter, the death rate of mosquitoes. The result is reasonably sensitive to changes in the death rate (Figure 8), but this is unsurprising; many models are sensitive to changes in death rates (see [30] for more discussion on this topic), but we do not expect the death rate to vary enormously.

We use a simple SIR model for humans, with mass action terms, but the bulk of the analysis only depends on the form of the mosquito interactions. Thus, the results are independent of the mass-action condition, and will be similar for other models, as long as the

total mosquito population satisfies (4.1). In particular, the model could easily accommodate a separate, exposed, class, and specific biting rates of mosquitoes, with the ODEs for mosquitoes satisfying

$$\begin{aligned}\frac{dM}{dt} &= \Lambda - \mu M - \beta_M b \frac{MI}{\Sigma},\\ \frac{dE}{dt} &= \beta_M b \frac{MI}{\Sigma} - \theta E,\\ \frac{dN}{dt} &= \theta E - \mu N,\end{aligned} \tag{7.1}$$

where E is the exposed (but noninfectious) class, b is the biting rate of mosquitoes, θ is the duration of exposure, and Σ is the total human population. These more complicated dynamics for mosquitoes still satisfy (4.1), and thus our results still apply. Similarly, if only a single household were modelled, the dynamics for humans would not be well approximated by ordinary differential equations, whereas the dynamics of mosquitoes still might be, if sufficiently prevalent. In this case, the human interactions might take other forms, such as network models.

Future work will examine the impact of spatial variation on the implementation of IRS, including the reemergence of disease from point sources missed from the previous spraying. More complex criteria for nonfixed spraying will also be considered.

In conclusion, regular spraying is clearly superior to nonfixed spraying, but either will result in a significant reduction in the overall number of mosquitoes, as well as the number of malaria cases in humans. We thus recommend that the use of indoor spraying be reexamined for widespread application in malaria-endemic areas.

Acknowledgments

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