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Comparing malaria surveillance with periodic spraying in the presence of insecticide-resistant mosquitoes: Should we spray regularly or based on human infections?

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ABSTRACT

There is an urgent need for more understanding of the effects of surveillance on malaria control. Indoor residual spraying has had beneficial effects on global malaria reduction, but resistance to the insecticide poses a threat to eradication. We develop a model of impulsive differential equations to account for a resistant strain of mosquitoes that is entirely immune to the insecticide. The impulse is triggered either due to periodic spraying or when a critical number of malaria cases are detected. For small mutation rates, the mosquito-only submodel exhibits either a single mutant-only equilibrium, a mutant-only equilibrium and a single coexistence equilibrium, or a mutant-only equilibrium and a pair of coexistence equilibria. Bistability is a likely outcome, while the effect of impulses is to introduce a saddle-node bifurcation, resulting in persistence of malaria in the form of impulsive periodic orbits. If certain parameters are small, triggering the insecticide based on number of malaria cases is asymptotically equivalent to spraying periodically.

1. Introduction

It has been estimated that one in two humans who ever lived has been killed by malaria [7]. Three billion people — almost half the world's population — are at risk of malaria [13,20,22]. 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 [16]; 90% of deaths due to malaria occur in sub-Saharan Africa [17], 75% of whom are African children [6]. In 2015, it caused more than 214 million acute illnesses and 438,000 deaths [26]. This represents a 37% reduction in cases over the previous 15 years [26].

This reduction has been largely driven by vector-control methods, primarily insecticide-treated bednets and indoor residual spraying (IRS) [9,25]; both are known to be highly effective [14]. The latter involves spraying houses and structures with insecticides, thereby killing mosquitoes after they have fed, in an effort to stop transmission of the disease. Recent data reconfirm the efficacy and effectiveness of IRS in malaria control in countries where it was implemented well [25]. 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. 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 for timely, good-quality spraying is greater than six months [25].

Using these methods, malaria was eradicated or greatly reduced in many countries in the world between the 1940s and 1960s. Due to its success, DDT was rapidly introduced into public-health and malaria-control campaigns, and was the main insecticide used in the malaria-eradication campaign carried out between 1955 and 1969 [24]. There is evidence of resistance, but spraying with multiple insecticides has been successful in controlling *Anopheles funestus, Anopheles gambiae* and *Anopheles melas* in Equatorial Guinea, for example [19].

Surveillance is an important tool in disease management [10]; this is particularly true of malaria, which is spatially heterogeneous [2]. The World Health Organization has identified effective surveillance as a critical component in malaria elimination and has called for stronger surveillance systems to track and prevent outbreaks in endemic regions [26]. However, the majority of scientific and surveillance efforts are focused on countries that are unlikely to be the location of important emerging infectious diseases [10].

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Furthermore, many countries with a high burden of malaria have weak surveillance systems and are not in a position to assess disease distribution and trends [26].

We assume that spraying occurs at times t_k. The effect of the insecticide is assumed to be instantaneous, resulting in a system of impulsive differential equations. Impulsive differential equations consist of a system of ordinary differential equations (ODEs), together with difference equations. Between impulses, 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 spatio-temporal conditions are met [3–5,12]. This is related to the use of pulse vaccinations [1], seasonal skipping in recurrent epidemics [23], antiretroviral drug treatment [15] and birth pulses in animals [18]. Impulse times may be fixed or non-fixed [21] and may be either time- or state-dependent.

This paper is organized as follows. In Section 2, we introduce the impulsive model in its general form, detailing key assumptions. In Section 3, we develop preliminary results, such as existence and uniqueness properties. In Section 4, we analyze a non-impulsive submodel consisting only of mosquito dynamics. In Section 5, we analyze the mosquito-only submodel with impulsive effects. In Section 6 we illustrate our theoretical results with numerical simulations. In Section 7, we determine global results for periodic orbits under a simplifying assumption. We conclude with a discussion and relegate all proofs to the appendix.

2. The model

All humans are either susceptible (S), infected (I) or partially immune (R). Humans are born susceptible at a constant background birth rate π, independent of the population size. The background death rate is μ_H. Susceptible humans can become infected after being bitten by infected mosquitoes at rate β. Infected humans die from the disease at rate γ, recover without immunity at rate h or acquire immunity at rate α. Humans with temporary immunity lose their immunity at rate δ. All rates are per capita rates, unless otherwise mentioned.

In the absence of humans (and therefore new infections), mosquitoes undergo logistic growth with competition and a small probability of unidirectional mutation at birth. There is no competitive advantage or disadvantage to being infected with malaria. Malaria infection has a negligible effect on the lifespan of mosquitoes. Therefore, if M_w and M_m denote the population sizes of wild-type and mutant susceptible mosquitoes, N_w and N_m denote the corresponding infected mosquitoes, and $V_w = M_w + N_w$ and $V_m = M_m + N_m$ denote the total populations of wild-type and mutant mosquitoes (susceptible and infected), then we assume

$$\begin{aligned}
\dot{M}_w &= ((1-\epsilon)b_w - d_w)M_w + (1-\epsilon)b_w N_w,\\
\dot{M}_m &= (b_m - d_m)M_m + b_m N_m + \epsilon b_w M_w + \epsilon b_w N_w,\\
\dot{N}_w &= -d_w N_w,\\
\dot{N}_m &= -d_m N_m,
\end{aligned}$$

where $0 < \epsilon \ll 1$ is the mutation rate. The birth and death rates are

$$\begin{aligned}
b_w &= b_w^0 - K_{bww}V_w - K_{bwm}V_m, \qquad d_w = d_w^0 + K_{dww}V_w + K_{dwm}V_m,\\
b_m &= b_m^0 - K_{bmm}V_m - K_{bmw}V_w, \qquad d_m = d_m^0 + K_{dmm}V_m + K_{dmw}V_w,
\end{aligned}$$

where all parameters are assumed to be positive. There is no vertical malaria transmission among mosquitoes. Notice that the above is not the usual, elegant definition of logistic growth. However, this parameter-heavy definition is necessary to take into account the correct mutation rate.

Wild-type mosquitoes are more evolutionarily fit in the absence of insecticide: Define the *intrinsic growth rates*

$$r_w = b_w^0 - d_w^0, \quad r_m = b_m^0 - d_m^0, \tag{1}$$

carrying capacities

$$K_w = \frac{r_w}{K_{bww} + K_{dww}}, \quad K_m = \frac{r_m}{K_{bmm} + K_{dmm}}, \tag{2}$$

and *competition coefficients*

$$\alpha_{wm} = \frac{K_{bwm} + K_{dwm}}{K_{bww} + K_{dww}}, \quad \alpha_{mw} = \frac{K_{bmw} + K_{dmw}}{K_{bmm} + K_{dmm}}. \tag{3}$$

It is assumed that these bulk parameters satisfy the inequalities

$$r_w \geq r_m, \quad K_w \geq K_m, \quad \alpha_{mw} \geq \alpha_{wm}, \tag{4}$$

and at least one of the inequalities is strict.

Susceptible mosquitoes can become infected by biting an infectious human at rate β_M, which may depend on the sizes of human and mosquito subpopulations. The infection rate of humans by mosquitoes, β, is positively correlated to the population of infected mosquitoes. The infection rate of mosquitoes by humans, β_M, is positively correlated with the population of infected humans. Infection rates are assumed to be smooth functions of the population variables. All infection rates are nonnegative.

The probability of passive surveillance efforts detecting a given human malaria infection is given by η. Insecticide is sprayed if the number of reported malaria cases since the previous insecticide application reaches a critical level, $\overline{\Theta}$. Application of the insecticide instantaneously decreases the population of wild-type mosquitoes by a factor of $q \in (0, 1)$. The insecticide has no effect on the mutant strain.

With these assumptions in place, we obtain the following system of impulsive differential equations:

$$\begin{aligned}
\dot{S} &= \pi - \beta(P)S + hI + \delta R - \mu_H S, && \Theta \neq \overline{\Theta}\\
\dot{I} &= \beta(P)S - hI - \alpha I - (\mu_H + \gamma)I, && \Theta \neq \overline{\Theta}\\
\dot{R} &= \alpha I - \delta R - \mu_H R, && \Theta \neq \overline{\Theta}\\
\dot{M}_w &= ((1-\epsilon)b_w - d_w)M_w + (1-\epsilon)b_w N_w - \epsilon b_w M_w\\
&\quad - \beta_M(P)M_w, && \Theta \neq \overline{\Theta}\\
\dot{M}_m &= (b_m - d_m)M_m + \epsilon b_w(M_w + N_w) + b_m N_m\\
&\quad - \beta_M(P)M_m, && \Theta \neq \overline{\Theta}\\
\dot{N}_w &= \beta_M(P)M_w - d_w N_w, && \Theta \neq \overline{\Theta}\\
\dot{N}_m &= \beta_M(P)M_m - d_m N_m, && \Theta \neq \overline{\Theta}\\
\dot{\Theta} &= \eta\beta(P)S, && \Theta \neq \overline{\Theta}\\
\Delta M_w &= -qM_w, && \Theta = \overline{\Theta}\\
\Delta N_w &= -qN_w, && \Theta = \overline{\Theta}\\
\Delta\Theta &= -\overline{\Theta}, && \Theta = \overline{\Theta}
\end{aligned} \tag{5}$$

Here S, I and R represent the number of susceptible, infected and temporarily immune humans, and $P = (S, I, R, M_w, N_w, M_m, N_m)$.

Due to the model assumptions, we may assume the infection rates satisfy

$$\frac{\partial\beta}{\partial N_w} > 0, \quad \frac{\partial\beta}{\partial N_m} > 0, \quad \frac{\partial\beta_M}{\partial I} > 0,$$
$$\beta(S, I, R, M_w, M_m, 0, 0) = \beta_M(S, 0, R, M_w, M_m, N_w, N_m) = 0.$$

3. Preliminary results

3.1. Existence and uniqueness of solutions and the biological domain

To properly discuss existence, uniqueness and boundedness of solutions of (5), it is necessary to adequately describe the