

Einführung in die Mathematische Epidemiologie: Introduction to Mathematical Epidemiology: Further Examples

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1 Introduction

We consider further examples of deterministic compartmental models of infectious diseases here.

2 Asymptomatic Infections

In many diseases, some proportion of the infectious population does not develop symptoms, or show any outward signs of disease, though the hosts are infectious to susceptible individuals. For example, about 90% of people infected with the poliovirus show no signs of disease though they can still transmit the virus on to other people (though at a lower probability).

We can model such an infection by adding a new compartment for asymptomatic individuals that are infected and infectious (though possibly with a different infectivity and recovery rate than the “normal” infectious individuals). We show a schematic of such a model in Figure 2.1; a summary of model variables in Table 2.1 and parameters in Table 2.2.

Table 2.1: Description of state variables of an infectious disease model with asymptomatic individuals.

S : Susceptible humans
 I : Infectious humans
 A : Asymptomatic humans
 R : Recovered humans

The full model is described by,

$$\frac{dS}{dt} = \Lambda - r \left(\beta_A \frac{A}{N} + \beta_I \frac{I}{N} \right) S - \mu S, \quad (2.1a)$$

$$\frac{dA}{dt} = \varphi r \left(\beta_A \frac{A}{N} + \beta_I \frac{I}{N} \right) S - (\gamma_A + \mu) A, \quad (2.1b)$$

$$\frac{dI}{dt} = (1 - \varphi) r \left(\beta_A \frac{A}{N} + \beta_I \frac{I}{N} \right) S - (\gamma_I + \mu) I, \quad (2.1c)$$

$$\frac{dR}{dt} = \gamma_A A + \gamma_I I - \mu R, \quad (2.1d)$$

Table 2.2: Description of parameters of an infectious disease model with asymptomatic individuals.

- r : Number of contacts per unit time. Dimension: Time^{-1} .
- φ : Proportion of infected individuals that become asymptomatic.
- β_A : Probability of disease transmission from an asymptomatic individual per contact.
- β_I : Probability of disease transmission from an infectious individual per contact.
- γ_A : Per-capita recovery rate of asymptomatic individuals. Dimension: Time^{-1} .
- γ_I : Per-capita recovery rate of infectious individuals. Dimension: Time^{-1} .
- Λ : Constant recruitment rate. Dimension: $\text{Humans}/\text{Time}$.
- μ : Per-capita removal rate. Dimension: Time^{-1} .

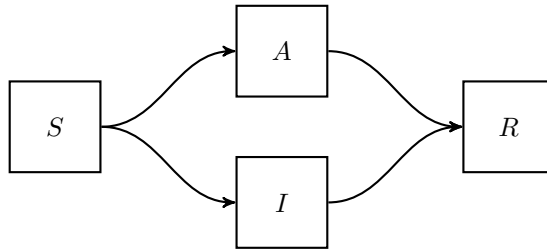


Figure 2.1: A schematic of an infectious disease model that allows asymptomatic infections. Arrows representing birth and death are not shown here.

with $N = S + A + I + R$. The dynamics of the total population size are given by,

$$\frac{dN}{dt} = \Lambda - \mu N, \quad (2.2)$$

with a globally asymptotically stable equilibrium point,

$$N^* = \frac{\Lambda}{\mu}. \quad (2.3)$$

For the rest of this analysis, we assume that the initial conditions are such that the total population size is fixed at N^* ¹.

The model (2.1) has two equilibrium points: a disease-free equilibrium point, $S^* = N^*$, $A^* = I^* = R^* = 0$; and an endemic equilibrium point. Although it is possible to solve for the endemic equilibrium, and the explicit expression can be useful for analyses like sensitivity analysis, we do not show the long expressions here. Instead, we calculate the basic reproductive number using the next generation operator approach from van den Driessche and Watmough [5].

We define the asymptomatic and infectious classes as the two infected classes and order the system as,

$$\begin{aligned} x_1 &= A, \\ x_2 &= I, \\ x_3 &= R, \\ x_4 &= S, \end{aligned}$$

and write the system of equations (2.1) in the form,

$$\frac{dx_i}{dt} = \mathcal{F}_i(x) - \mathcal{V}_i(x), \quad (2.4)$$

¹Though this assumption is not necessary for calculating equilibrium points or the basic reproductive number, it makes the analysis easier.

with disease-free equilibrium point,

$$x_{dfe} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ N^* \end{pmatrix}. \quad (2.5)$$

The rate of new infections is,

$$\mathcal{F}(x) = \begin{pmatrix} \varphi r (\beta_A \frac{A}{N} + \beta_I \frac{I}{N}) S \\ (1 - \varphi) r (\beta_A \frac{A}{N} + \beta_I \frac{I}{N}) S \\ 0 \\ 0 \end{pmatrix}, \quad (2.6)$$

the rate of movement into compartments by other means is,

$$\mathcal{V}^+(x) = \begin{pmatrix} 0 \\ 0 \\ \gamma_A A + \gamma_I I \\ \Lambda \end{pmatrix}, \quad (2.7)$$

and the rate of movement out of each compartment is,

$$\mathcal{V}^-(x) = \begin{pmatrix} (\gamma_A + \mu) A \\ (\gamma_I + \mu) I \\ \mu R \\ r (\beta_A \frac{A}{N} + \beta_I \frac{I}{N}) S + \mu S \end{pmatrix}. \quad (2.8)$$

It is easy to see that these functions satisfy assumptions (A1)–(A4). For assumption (A5), we calculate the Jacobian of the righthand side of (2.4) at x_{dfe} with $\mathcal{F}(x)$ set to zero,

$$J = \begin{pmatrix} -(\gamma_A + \mu) & 0 & 0 & 0 \\ 0 & -(\gamma_I + \mu) & 0 & 0 \\ \gamma_A & \gamma_I & -\mu & 0 \\ -r\beta_A & -r\beta_I & 0 & -\mu \end{pmatrix}. \quad (2.9)$$

Since this matrix is lower triangular, the eigenvalues are given by the diagonal elements, which are all negative. Therefore, assumption (A5) is satisfied.

Following the method of van den Driessche and Watmough [5], we calculate,

$$F = \begin{pmatrix} \varphi r \beta_A & \varphi r \beta_I \\ (1 - \varphi) r \beta_A & (1 - \varphi) r \beta_I \end{pmatrix}, \quad (2.10)$$

and,

$$V = \begin{pmatrix} \gamma_A + \mu & 0 \\ 0 & \gamma_I + \mu \end{pmatrix}. \quad (2.11)$$

Then,

$$V^{-1} = \begin{pmatrix} \frac{1}{\gamma_A + \mu} & 0 \\ 0 & \frac{1}{\gamma_I + \mu} \end{pmatrix}, \quad (2.12)$$

and,

$$FV^{-1} = \begin{pmatrix} \frac{\varphi r \beta_A}{\gamma_A + \mu} & \frac{\varphi r \beta_I}{\gamma_I + \mu} \\ \frac{(1 - \varphi) r \beta_A}{\gamma_A + \mu} & \frac{(1 - \varphi) r \beta_I}{\gamma_I + \mu} \end{pmatrix}, \quad (2.13)$$

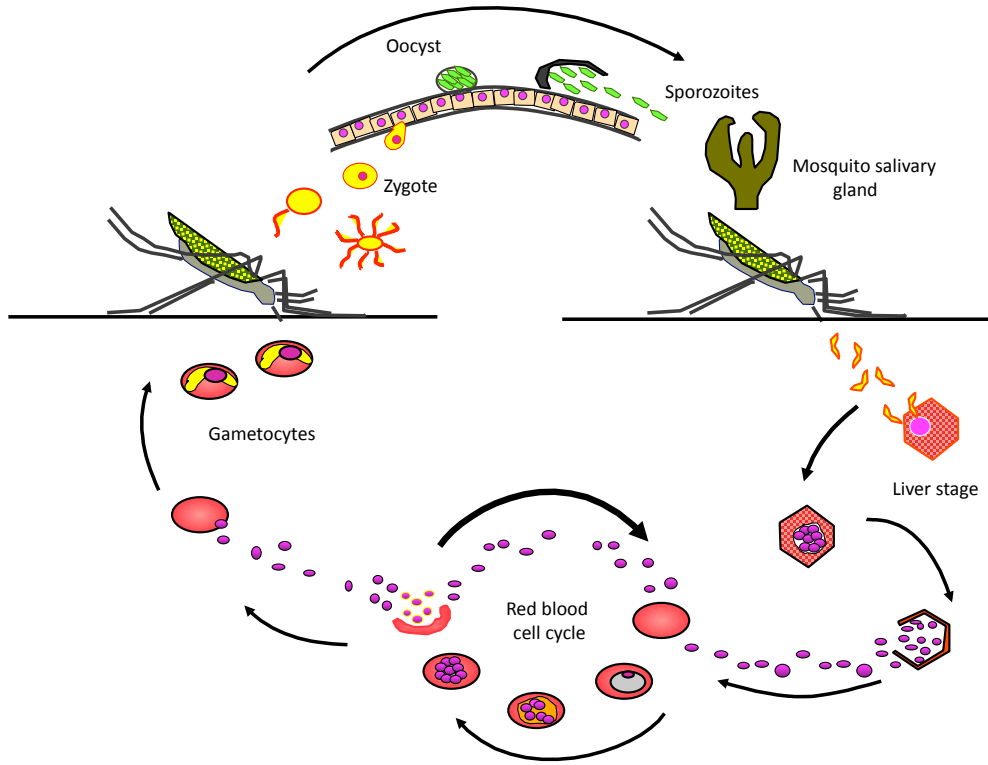


Figure 3.1: A schematic of the malaria life cycle.

with eigenvalues,

$$\lambda_1 = \frac{r\beta_A\varphi}{\gamma_A + \mu} + \frac{r\beta_I(1 - \varphi)}{\gamma_I + \mu}, \quad (2.14)$$

$$\lambda_2 = 0, \quad (2.15)$$

so the basic reproductive number is,

$$R_0 = \frac{r\beta_A\varphi}{\gamma_A + \mu} + \frac{r\beta_I(1 - \varphi)}{\gamma_I + \mu}. \quad (2.16)$$

From [5], we know that the disease-free equilibrium point, x_{dfe} is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. R_0 has the nice interpretation of the weighted average of the number of new infections from the asymptomatic and infectious classes (weighted by the proportion that become either asymptomatic or infectious). If the proportion that enter the asymptomatic class, φ , is large (as is the case with polio), then eradication efforts should focus on asymptomatic carriers (depending on the values of the other parameters).

3 Malaria

3.1 Overview of Malaria

Malaria is an infectious disease caused by the *Plasmodium* parasite and transmitted between humans through the bites of female *Anopheles* mosquitoes. A schematic of the malaria life cycle is shown in Figure 3.1. An

estimated 40% of the world's population live in malaria endemic areas and malaria killed about 655 000 people in 2010 [6]. An estimate of global prevalence of *P. falciparum* malaria in children in 2010 is shown in Figure 3.2.

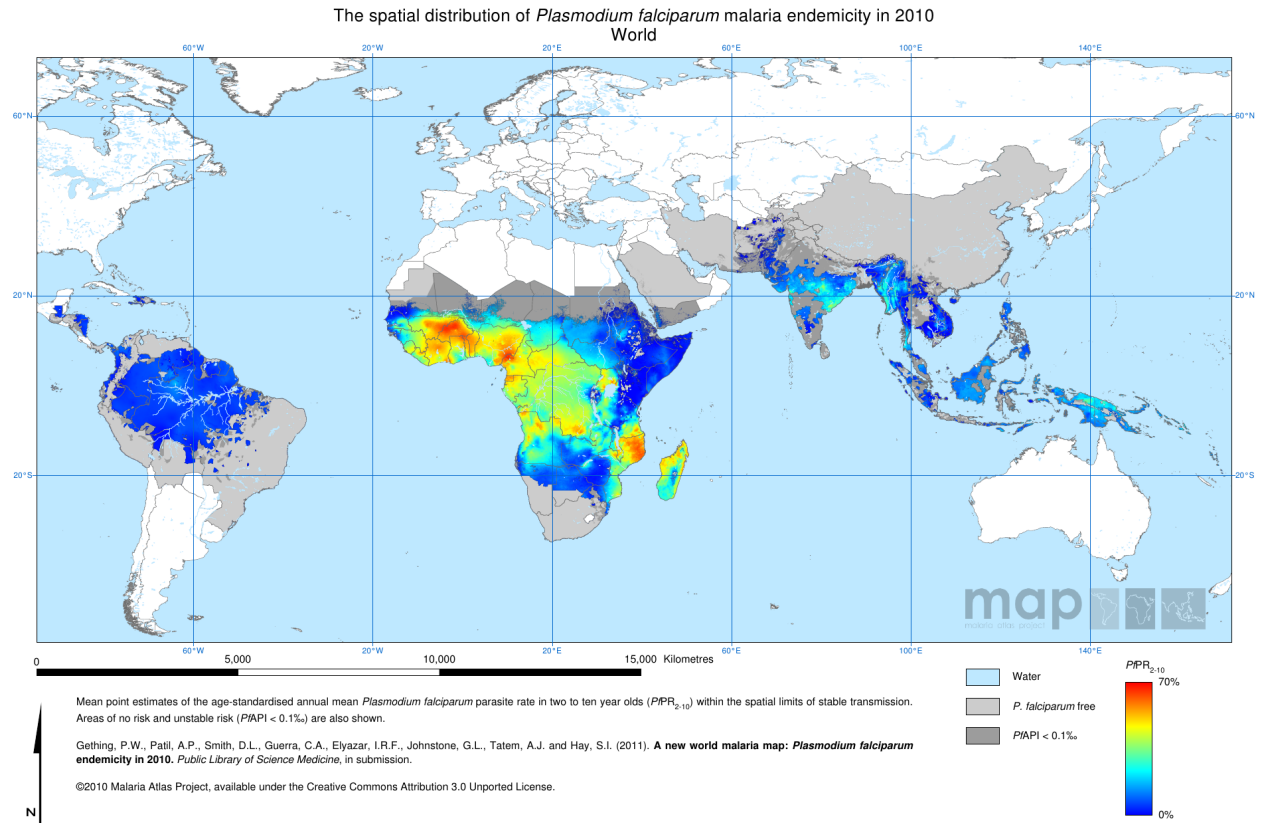


Figure 3.2: Global distribution of prevalence of *P. falciparum* malaria in children aged between 2 and 10 years. This map is reproduced from http://www.map.ox.ac.uk/browse-resources/endemicity/Pf_mean/world/.

3.2 History of Malaria Modeling

In the early 20th Century, Ronald Ross published a differential equation model [4] for malaria transmission. Ross introduced the idea of a threshold condition in epidemiology: “a critical density of mosquitoes,” below which the malaria parasite would die out. Ross’s mathematical models drove the first few decades of malaria control where efforts focused on larviciding and destruction of larval breeding sites. In the middle of the 20th Century, George Macdonald tested Ross’s theory with epidemiological [1] and entomological [2] field data. Macdonald’s analysis helped to explain that spraying of insecticide worked because it greatly reduced the number of mosquitoes that lived long enough to become infectious and transmit malaria [3]. From then on, a lot of malaria control activities focussed on killing adult mosquitoes.

3.3 The Ross-Macdonald Model

We now consider a delay differential equation (DDE) version of the Ross-Macdonald model, assuming susceptible-infectious-susceptible (SIS) dynamics for the human population and susceptible-exposed-infectious (SEI) dynamics for the mosquito population as shown in Figure 3.3. The classes described are:

- S_H : susceptible humans
- I_H : infectious humans
- S_V : susceptible mosquitoes
- E_V : exposed mosquitoes
- I_V : infectious mosquitoes.

Since the time scales of human birth and death are far greater than the time scales of mosquito birth and death, we include birth and death in mosquitoes but not in humans. We also assume mosquitoes have constant and equal birth and death rates and that the total mosquito population is at equilibrium.

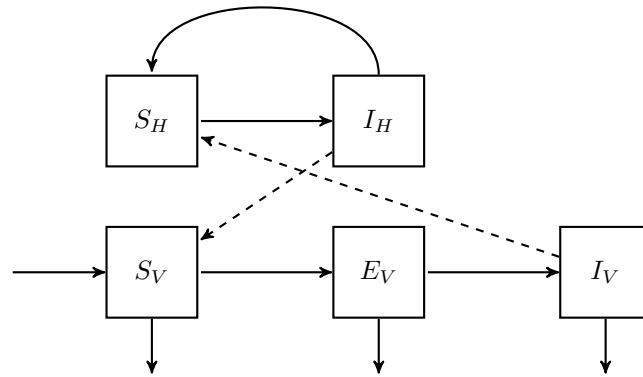


Figure 3.3: A schematic of the Ross-Macdonald model assuming SIS dynamics for humans and SEI dynamics for mosquitoes. We ignore birth and death in humans because the time scales in which these occur are far greater than those of mosquito population dynamics.

We show the state variables of the Ross-Macdonald model in Table 3.1 and the parameters in Table 3.2.

Table 3.1: Description of state variables for the Ross-Macdonald model.

- $x(t)$: Proportion of infectious humans at time t . $x(t) = I_H(t)/(S_H(t) + I_H(t))$.
- $y(t)$: Proportion of infected but not yet infectious mosquitoes at time t . $y(t) = E_V/(S_V + E_V + I_V)$.
- $z(t)$: Proportion of infectious mosquitoes at time t . $z(t) = I_V/(S_V + E_V + I_V)$.

Table 3.2: Description of parameters for the Ross-Macdonald model.

- m : Number of female mosquitoes per human host.
- a : Number of bites per mosquito per unit time. Dimension: Time^{-1} .
- b : Probability of transmission of infection from infectious mosquitoes to humans per bite.
- c : Probability of transmission of infection from infectious humans to mosquitoes per bite.
- γ : Recovery rate of humans. Dimension: Time^{-1} .
- μ : Death rate of mosquitoes. Dimension: Time^{-1} .
- τ : Extrinsic incubation period. Dimension: Time.

$$\frac{dx(t)}{dt} = mabz(t)(1 - x(t)) - \gamma x(t) \quad (3.1a)$$

$$\frac{dy(t)}{dt} = acx(t)(1 - y(t) - z(t)) - \mu y(t) - acx(t - \tau)(1 - y(t - \tau) - z(t - \tau))e^{-\mu\tau} \quad (3.1b)$$

$$\frac{dz(t)}{dt} = acx(t - \tau)(1 - y(t - \tau) - z(t - \tau))e^{-\mu\tau} - \mu z(t) \quad (3.1c)$$

Representing the movement of mosquitoes from the exposed to the infectious class with a constant per-capita rate, as is usually done in ordinary differential equations, assumes an exponential distribution for the time spent in the exposed class. Here, using delay differential equations, we can model the extrinsic incubation period (the amount of time it takes an infected mosquito to become infectious) as a fixed duration, though still allowing for an exponential distribution of survival.

This model (3.1) has two equilibrium points: the disease-free equilibrium point,

$$x_0 = 0, \quad (3.2a)$$

$$y_0 = 0, \quad (3.2b)$$

$$z_0 = 0, \quad (3.2c)$$

and the endemic equilibrium point,

$$x^* = \frac{ma^2bce^{-\mu\tau} - \gamma\mu}{ma^2bce^{-\mu\tau} + ac\gamma}, \quad (3.3a)$$

$$y^* = \left(\frac{1 - e^{-\mu\tau}}{e^{-\mu\tau}} \right) \left(\frac{ma^2bce^{-\mu\tau} - \gamma\mu}{ma^2bc + mab\mu} \right), \quad (3.3b)$$

$$z^* = \frac{ma^2bce^{-\mu\tau} - \gamma\mu}{ma^2bc + mab\mu}. \quad (3.3c)$$

We can simplify this system of delay differential equations (3.1) to a system of ordinary differential equations (ODE) by ignoring the time delay and assuming that the ratio of the proportion of exposed mosquitoes to infectious mosquitoes is at equilibrium. This implies,

$$y(t) = \left(\frac{1 - e^{-\mu\tau}}{e^{-\mu\tau}} \right) z(t). \quad (3.4)$$

Substituting (3.4) into (3.1) and ignoring the delay, leads to,

$$\frac{dx}{dt} = mabz(1 - x) - \gamma x, \quad (3.5a)$$

$$\frac{dz}{dt} = acx \left(1 - \left(\frac{1 - e^{-\mu\tau}}{e^{-\mu\tau}} \right) z - z \right) e^{-\mu\tau} - \mu z, \quad (3.5b)$$

which simplifies to,

$$\frac{dx}{dt} = mabz(1 - x) - \gamma x, \quad (3.6a)$$

$$\frac{dz}{dt} = acx (e^{-\mu\tau} - z) - \mu z. \quad (3.6b)$$

This ODE Ross-Macdonald model has the equivalent equilibrium points as the DDE Ross-Macdonald model. Using the method of van den Driessche and Watmough [5], we can define a basic reproductive number, R_0 , where the disease-free equilibrium point loses stability.

We rewrite (3.6) in terms of functions,

$$\mathcal{F}(\mathbf{x}) = \begin{pmatrix} mabz(1-x) \\ acx(e^{-\mu\tau} - z) \end{pmatrix}, \quad (3.7)$$

$$\mathcal{V}(\mathbf{x})^+ = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \quad (3.8)$$

$$\mathcal{V}(\mathbf{x})^- = \begin{pmatrix} \gamma x \\ \mu z \end{pmatrix}. \quad (3.9)$$

We can verify that these functions satisfy all assumptions, (A1)–(A5). We calculate,

$$F = \begin{pmatrix} 0 & mab \\ ace^{-\mu\tau} & 0 \end{pmatrix}, \quad (3.10)$$

$$V = \begin{pmatrix} \gamma & 0 \\ 0 & \mu \end{pmatrix}. \quad (3.11)$$

Then,

$$FV^{-1} = \begin{pmatrix} 0 & mab/\mu \\ ace^{-\mu\tau}/\gamma & 0 \end{pmatrix}. \quad (3.12)$$

The two eigenvalues of FV^{-1} are,

$$\lambda_{1,2} = \pm \sqrt{\frac{ma^2bce^{-\mu\tau}}{\gamma\mu}}, \quad (3.13)$$

and,

$$R_0 = \sqrt{\frac{ma^2bce^{-\mu\tau}}{\gamma\mu}}. \quad (3.14)$$

However, frequently, the basic reproductive number for malaria from the Ross-Macdonald model is defined as,

$$\hat{R}_0 = \frac{ma^2bce^{-\mu\tau}}{\gamma\mu}. \quad (3.15)$$

The two definitions satisfy the same threshold conditions because when $R_0 = 1$, $R_0^2 = \hat{R}_0 = 1$. While R_0 estimates the number of new infections in the next generation of mosquitoes (or humans) caused by one infectious human (or mosquito), \hat{R}_0 estimates the number of new infections in the next generation of humans caused by one infectious human through a generation of infections in mosquitoes, thus leading to the square of R_0 . This definition may be represented as,

$$\begin{aligned} \hat{R}_0 &= \begin{pmatrix} \text{Number of} \\ \text{mosquito bites} \\ \text{per human} \\ \text{per time} \end{pmatrix} \begin{pmatrix} \text{Probability of} \\ \text{transmission} \\ \text{from human} \\ \text{to mosquito} \end{pmatrix} \begin{pmatrix} \text{Duration of} \\ \text{infection} \\ \text{in humans} \end{pmatrix} \\ &\quad \times \begin{pmatrix} \text{Probability} \\ \text{of surviving} \\ \text{exposed} \\ \text{stage} \end{pmatrix} \begin{pmatrix} \text{Number of} \\ \text{bites on humans} \\ \text{per mosquito} \\ \text{per time} \end{pmatrix} \begin{pmatrix} \text{Probability of} \\ \text{transmission} \\ \text{from mosquito} \\ \text{to human} \end{pmatrix} \begin{pmatrix} \text{Expected} \\ \text{infectious} \\ \text{life span} \\ \text{of mosquitoes} \end{pmatrix}, \\ &= (ma)(c) \left(\frac{1}{\gamma}\right) (e^{-\mu\tau}) (a)(b) \left(\frac{1}{\mu}\right), \\ &= \frac{ma^2bce^{-\mu\tau}}{\gamma\mu}. \end{aligned}$$

The disease-free equilibrium point is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. We can also see that the endemic equilibrium point is positive if and only if $R_0 > 1$. Thus to eliminate malaria, control activities need to reduce R_0 to a value below 1. The expression for R_0 shows that to eliminate malaria, increasing the mosquito death rate, μ , or reducing the mosquito biting rate, a , is more effective than reducing the mosquito density, m .

References

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