Population dynamics of disease-transmitting mosquitoes exposed to insecticides: susceptible and resistant interaction

E Salazar¹, E Gómez-Hernández¹, and E Ibarguen-Mondragón²
¹ Facultad de Ciencias Exactas, Universidad Católica del Maule, Talca, Chile
² Facultad de Ciencias Básicas, Universidad de Nariño, Pasto, Colombia

E-mail: edwin.salazar@alu.ucm.cl, edbargun@gmail.com

Abstract. One of the first biological topics that have attracted physicists’ attention is population dynamics. Researchers have approached these topics through dynamical systems, which have its origin in 15th-century physics, with the invention of Newton’s differential equations. In particular, we are interested in studying mosquitoes transmitting diseases such as Anopheles, Aedes and Culex as they cause serious public health problems worldwide. One of the strategies to control these diseases has been the use of insecticides. These spraying programs were initially successful. However, the evolution of resistance threatens efforts to control these epidemics. Therefore, this article proposes a dynamic system that includes continued use of an insecticide, assuming a proportion of mosquitoes not killed by spraying but acquire resistance. In addition, the genetic predisposition of mosquitoes to be more susceptible or more resistant is incorporated in the model utilizing a ratio that allows differentiating mosquitoes that are born susceptible from those that are born resistant. The dynamic system analysis shows that population persistence depends on growth thresholds that depend on resistance parameters. Therefore, according to the model, to avoid epidemics caused by mosquitoes, the emergence of resistant mosquito populations must be prevented.

1. Introduction

Vector-borne diseases generate serious consequences worldwide; about 80% of people are at risk. Mosquito-borne diseases are the major contributors to the vector-borne disease burden [1, 2]. Mosquitoes include mainly three genera, Anopheles, Aedes and Culex. Anopheles transmits malaria to humans (around 212 million cases per year). Aedes transmits dengue (around 96 million cases per year), chikungunya (around 693.000 cases per year), Zika (around 500.000 cases per year) and yellow fever (around 130.000 cases per year). Culex transmits Japanese encephalitis (around 42.000 cases per year) and West Nile fever (around 2.500 cases per year). All three genera transmit lymphatic filariasis disease (around 38 million cases per year) [3]. The figures, although alarming, underestimate the human hardship caused by these diseases since mosquitoes thrive best in conditions where water is unsafe and the environment is polluted, having a more significant impact on human populations suffering from economic and social hardship [4, 5].

Globally, mosquito-borne diseases are increasing in incidence and geographic distribution [1]. Several factors can explain the spread of these diseases: population growth, land-use change,
urbanization in tropical areas, poor sanitary conditions, and inadequate mosquito control efforts. Among these factors, the most relevant is poor mosquito control management associated with insecticides [6, 7]. Since the 1940s, insecticides have been the primary strategy to control mosquitoes. However, the evolution of resistance is jeopardizing efforts to prevent epidemics [4, 8, 9].

Recent studies have addressed the problem of resistance by considering genetic factors. In particular, mosquitoes have variable genetics, within which there are some individuals that are more resistant, and there are others that are more susceptible depending on their genetic structure. The repeated application of an insecticide on the population eliminates susceptible individuals, and the resistant ones increase their allele frequency within the population [10, 11]. Therefore, resistance is the selection of a heritable trait in a mosquito population that causes the repeated failure of an insecticide to achieve the appropriate level of control [12, 13]. So we hypothesize that the proportion of resistant individuals before application determines the decrease in allele frequency of susceptible mosquitoes. Therefore, our objective is to incorporate a proportion of resistant individuals before using insecticides in a dynamic system.

The approach proposed in this article is a mathematical model in ordinary differential equations for the dynamics of susceptible and resistant mosquitoes to insecticides that describe resistance and selection pressure evolution. We model the model considering that there are naturally individuals with genetic characteristics that allow them to survive exposure to a new insecticide in the initial population. After the first exposure, most of the susceptible individuals die, while the resistant ones survive. As resistant mosquitoes have more opportunity to reproduce, the frequency of susceptible genes decreases. Thus the treatment is not effective in the offspring since the expression of the specific genes has been selected to eliminate susceptible individuals.

Thus, in this article, we evaluate the complexity of the allele frequency of resistant mosquitoes by qualitative analysis of the model based on mosquito population growth thresholds, which determine whether the population dies out or persists over time. The thresholds depend on the intrinsic growth rate, the death rate, the proportion of mosquitoes that pass to the adult stage while being resistant, and the proportion of mosquitoes that survive insecticide exposure. The results show that if the proportion of susceptible mosquitoes is high, i.e., they are at the first insecticide application, then the population of resistant mosquitoes increases slowly over time. In contrast, if the proportion of susceptible mosquitoes is low, i.e., after constant and repeated exposure to the insecticide, then the resistant ones increase their allele frequency within the population.

2. Mathematical model

This section presents a mathematical model based on ordinary differential equations to study the dynamics of susceptible mosquitoes \( x \) and insecticide-resistant mosquitoes \( y \). The mosquito population \( x + y \) has a logistic growth with carrying capacity \( k \), of which an initial proportion \( \gamma \) is susceptible and the remaining proportion \( (1 - \gamma) \) passes to the adult stage being resistant. The intrinsic rate of growth is \( \beta \). A proportion \( q \) of the susceptible mosquitoes acquire resistance to insecticides and the insecticide kills a proportion \( (1 - q) \). Susceptibles exit their stage at a rate of \( \alpha \). Resistant mosquitoes die naturally at a rate of \( \mu \).

Figure 1 shows the inflows and outflows of each of the variables. We observe that the total population has an inflow associated with the parameter \( \beta \) and the outflow associated with the parameters \( \alpha \) and \( \mu \). Therefore whether the total population persists or not depends on the value of \( \beta/(\alpha + \mu) \), which will be called a growth threshold \( \phi_1 \). In addition, Figure 1 shows that \( \phi_2 = \beta \gamma/\alpha + \beta \gamma/\alpha \cdot q/\mu + \beta (1 - \gamma)/\mu \) is also a threshold. The first term refers to the inflow and outflow of the susceptible population and the last two terms refer to the inflow and outflow of the resistant population.
Figure 1. Flow-chart of the dynamics of susceptible and resistant mosquitoes to insecticides.

The above description associated to the flow chart of Figure 1 leads to the dynamical system given by Equation (1) and Equation (2).

\[
\frac{dx}{dt} = \beta \gamma (x + y) \left(1 - \frac{x + y}{k}\right) - \alpha x, \quad (1)
\]

\[
\frac{dy}{dt} = \beta (1 - \gamma) (x + y) \left(1 - \frac{x + y}{k}\right) + \alpha qx - \mu y. \quad (2)
\]

where \( \alpha, \beta, \gamma, k \) and \( \mu \) are positive parameters. The proposition 1 details the positively invariant region for the system given by Equation (1) and Equation (2).

**Proposition 1.** The set \( \Omega = \{(x, y) \in \mathbb{R}^2 : x \geq 0, y \geq 0, x + y \leq k\} \), is positively invariant for the system given by Equation (1) and Equation (2).

**Proof.** The total population variation is given by Equation (3).

\[
\frac{d(x + y)}{dt} = \beta (x + y) \left(1 - \frac{x + y}{k}\right) - \alpha x - \mu y. \quad (3)
\]

Then \( d(x + y)/dt \leq \beta (x + y) (1 - (x + y)/k) \). We have Bernoulli’s equation for the case of equality, whose solution is given by Equation (4).

\[
(x + y)(t) = \left(\frac{1}{x(0) + y(0)} - \frac{1}{k}\right) \exp\left(-\beta t\right) + \frac{1}{k} \right)^{-1}. \quad (4)
\]

Taking the limit we have the Equation (5).

\[
\lim_{t \to \infty} (x + y)(t) \leq \lim_{t \to \infty} \left(\frac{1}{x(0) + y(0)} - \frac{1}{k}\right) \exp\left(-\beta t\right) + \frac{1}{k} \right)^{-1} = k. \quad (5)
\]

Therefore, \( (x + y)(t) \leq k \) for all \( 0 < t < \infty \) if \( (x + y)(0) \leq k \).

3. Equilibrium solutions and stability

The equilibrium solutions of model given by Equation (1) and Equation (2) are obtained by finding the solutions of the homogeneous system and are given by \( E_0 = (0, 0) \) and \( E_1 \) described in Equation (6).

\[
E_1 = \left(\frac{\gamma k \beta (\phi_2 - 1)}{\alpha \phi_2^2}, \frac{k \beta (\gamma q + 1 - \gamma)(\phi - 1)}{\mu \phi_2^2}\right), \quad (6)
\]

**Proposition 2.** If \( \phi_i < 1 \), for \( i = 1, 2 \), then \( E_0 \) is locally and asymptotically stable in \( \Omega \).
Proof. Jacobian of system given by Equation (1) and Equation (2) evaluated at the equilibrium $E_0$ is given by Equation (7).

$$ J(E_0) = \begin{bmatrix} \beta \gamma - \alpha & \beta \gamma \\ \alpha q - \beta \gamma + \beta & -\beta \gamma + \beta - \mu \end{bmatrix}. $$

(7)

The determinant of $J(E_0)$ is given by Equation (8).

$$ \det(J(E_0)) = -\alpha \beta \gamma q + \alpha \beta \gamma - \beta \gamma \mu - \alpha \beta + \alpha \mu. $$

(8)

Simplifying we have the Equation (9).

$$ \det(J(E_0)) = (1 - \phi_2) \alpha \mu. $$

(9)

The trace of the matrix $J(E_0)$ is given by Equation (10).

$$ \text{tr}(J(E_0)) = -\alpha + \beta - \mu. $$

(10)

Simplifying in terms of $\phi_1$ we have the Equation (11).

$$ \text{tr}(J(E_0)) = (\phi_1 - 1)(\alpha + \mu). $$

(11)

Hence, $\det(J(E_0)) > 0$ and $\text{tr}(J(E_0)) < 0$ if $\phi_i < 1$, $i = 1, 2$. Therefore, the given conditions for the growth thresholds guarantee local asymptotic stability.

**Proposition 3.** If the following two conditions are met

$$ 1 < \phi_2 < 2 \text{ and } \phi_1 < -\phi_2/(\phi_2 - 2), $$

(12)

$$ \phi_1 > 0 \text{ and } \phi_2 \geq 2. $$

(13)

Then $E_1$ is locally and asymptotically stable in $\Omega$.

Proof. Jacobian of system given by Equation (1) and Equation (2) evaluated at the equilibrium $E_1$ is given by Equation (14).

$$ J(E_1) = \begin{bmatrix} \gamma \beta \left(\frac{2}{\phi_2} - 1\right) - \alpha & \gamma \beta \left(\frac{2}{\phi_2} - 1\right) \\ \left(\frac{2}{\phi_2} - 1\right) (1 - \gamma) \beta + \alpha q & \left(\frac{2}{\phi_2} - 1\right) (1 - \gamma) \beta - \mu \end{bmatrix}. $$

(14)

The determinant of $J(E_1)$ is given by Equation (15).

$$ \det(J(E_1)) = \alpha \beta \gamma q - \alpha \beta \gamma + \beta \gamma \mu + \alpha \beta - \alpha \mu. $$

(15)

This equation can be written in terms of $\phi_2$ as the Equation (16).

$$ \det(J(E_1)) = (\phi_2 - 1) \alpha \mu. $$

(16)

The trace of the matrix $J(E_1)$ is given by Equation (17).

$$ \text{tr}(J(E_1)) = \gamma \beta \left(\frac{2}{\phi_2} - 1\right) - \alpha + \left(\frac{2}{\phi_2} - 1\right) (1 - \gamma) \beta - \mu. $$

(17)

This equation can be written in terms of $\phi_1$ and $\phi_2$ as the Equation (18).
\[
\text{tr}(J(E_1)) = \left[ \left( \frac{2}{\phi_2} - 1 \right) \phi_1 - 1 \right] (\alpha + \mu).
\] (18)

If \( \left( \frac{2}{\phi_2} - 1 \right) \phi_1 - 1 < 0 \) then the trace \( \text{tr}(J(E_1)) < 0 \). Now let us observe that the solutions of the inequality \( \left( \frac{2}{\phi_2} - 1 \right) \phi_1 - 1 < 0 \) are:

(i) \( 0 < \phi_2 < 2 \) and \( \phi_1 < -\phi_2 / (\phi_2 - 2) \).

(ii) \( \phi_2 > 2 \) and \( \phi_1 < -\phi_2 / (\phi_2 - 2) \).

(iii) \( \phi_1 > 0 \) and \( \phi_2 \geq 2 \).

We discard item (ii) because all the parameters are positive and therefore \( \phi_1 \) is positive. On the other hand, we know that the determinant \( \det(J(E_1)) \) is greater than zero if \( \phi_2 > 1 \) therefore we have that the region of item (i) reduces to \( 1 < \phi_2 < 2 \) and \( \phi_1 < -\phi_2 / (\phi_2 - 2) \) which corresponds to the region \( R_1 \) of the Figure 2. Item (iii) corresponds to region \( R_2 \) of the Figure 2. Hence, \( \det(J(E_1)) > 0 \) and \( \text{tr}(J(E_1)) < 0 \) if the conditions are met of the Equation (12) and Equation (13), corresponding to the \( R_1 \) and \( R_2 \) of the Figure 2, respectively. Therefore, the given conditions for the growth thresholds guarantee local asymptotic.

**Figure 2.** Values of \( \phi_1 \) and \( \phi_2 \) that guarantee the local asymptotic stability of the equilibrium \( E_1 \).

4. Simulations

In this section, we present numerical simulations to illustrate the persistence of the system given by Equation (1) and Equation (2) by varying the values of \( \gamma \) and \( q \), using the Matlab function ode45. For numerical simulations, we set parameters as \( k = 5000 \), \( \beta = 0.0558 \) and \( \mu = 0.0039 \) taken from the article [14], we also fix the value of \( \alpha \) to 0.02. Then, we consider the effect of the variation of \( \gamma \) and \( q \). Figure 3(a) and Figure 3(b) show the directional behavior of system, including the stability of the persistence equilibrium point \( E_1 \) of the mosquito population. Figure 3(a) shows the variation of the initial conditions of the susceptible mosquitoes \( x \) between 500 and 2000 and the variation of the initial conditions of the resistant population \( y \) between 2500 and 4000, the value of \( \gamma \) is 0.8, the growth thresholds are \( \phi_1 = 0.94 \) and \( \phi_2 = 2.86 \), therefore according to proposition 3, we have that \( E_1 = (1155.3258) \) is locally and asymptotically stable since the thresholds satisfy condition of Equation (13). Figure 3(b) shows the variation of the initial conditions of the susceptible mosquitoes \( x \) between 50 and 250, and the variation of the initial conditions of the resistant population \( y \) between 4000 and 4800, the value of \( \gamma \) is 0.2, the growth thresholds are \( \phi_1 = 0.94 \) and \( \phi_2 = 1.78 \), therefore according to proposition 3 we have that \( E_1 = (200.4411) \) is locally and asymptotically stable since the thresholds fulfill the condition of Equation (12).
Figure 3(c) and Figure 3(d) show the evolution of the mosquito population for \( q = 0.3 \) and with different values for the proportion of mosquitoes that are born susceptible \( \gamma \), showing that the higher the proportion of resistant mosquitoes \( (1 - \gamma) \), the lower the susceptible population and the higher the resistant population. Figure 3(e) and Figure 3(f) show the evolution of the mosquito population for \( (1 - \gamma) = 0.8 \) and with different values for the proportion of susceptible mosquitoes acquiring resistance \( q \), it is shown that the higher the proportion \( q \), the population of susceptibles decreases while the population of resistant ones increases.

**Figure 3.** Numerical solution for model given by Equation (1) and Equation (2) for \( k = 5000 \), \( \beta = 0.0558 \), \( \mu = 0.0039 \) and \( \alpha = 0.02 \). (a) Phase-plane portrait for \( \gamma = 0.2 \) and \( q = 0.3 \). (b) Phase-plane portrait for \( \gamma = 0.8 \) and \( q = 0.3 \). (c) The evolution of susceptible population with different values of the proportion of susceptibles \( \gamma \). (d) Evolution of resistant population with different values of the proportion of susceptibles \( \gamma \). (e) The evolution of susceptible population with different values of the proportion of mosquitoes acquiring resistance \( q \). (f) Evolution of resistant population with different values of the proportion of mosquitoes acquiring resistance \( q \).

5. Conclusion

Disease-transmitting mosquitoes such as Anopheles, Aedes and Culex cause serious public health problems worldwide. One of the strategies to control these diseases has been insecticides. These spraying programs were initially successful. However, the evolution of resistance threatens efforts to control these epidemics. Therefore, this article proposes a model that includes the effect of continuous use of an insecticide, assuming a proportion of mosquitoes that are not killed by spraying and instead acquire resistance. In addition, we incorporate the genetic predisposition of mosquitoes to be more susceptible or more resistant through a ratio that allows us to differentiate mosquitoes that are born susceptible from those that are born resistant. Analysis of the model shows that population persistence depends on growth thresholds that depend on parameters associated with resistance. Therefore, according to the model proposed, the ecological study related to genetic predisposition is essential before initiating an insecticide spraying process.
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