ELSEVIER Mathematical Biosciences 150 (1998) 131–151

Mathematical Biosciences
an international journal

Analysis of a dengue disease transmission model

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Received 1 July 1997; received in revised form 26 January 1998

Abstract

A model for the transmission of dengue fever in a constant human population and variable vector population is discussed. A complete global analysis is given, which uses the results of the theory of competitive systems and stability of periodic orbits, to establish the global stability of the endemic equilibrium. The control measures of the vector population are discussed in terms of the threshold condition, which governs the existence and stability of the endemic equilibrium.

Keywords: Dengue disease; Endemic equilibrium; Global stability; Competitive systems; Threshold number

1. Introduction

Dengue disease is a common arboviral disease in tropical regions of the world. It is transmitted to humans by the bite of *Aedes* mosquitoes. Four types of virus have been identified, denoted by I, II, III, and IV. Infection by any single type apparently produces permanent immunity to it, but only temporary

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0025-5564/98/$19.00
PII: S0025-5564(98)10003-2

cross immunity to the others. The mosquitoes never recover from the infection since their infective period ends with their death [1]. Vertical transmission in the main vector of dengue, *A. aegypti*, has been observed only at a relatively low rate [2,3].

In the past 40 years, a severe form of the disease, dengue hemorrhagic fever (DHF) and its associated, dengue shock syndrome (DSS), have become a major public health problem in Southeast Asia [1,4]. There is evidence that a similar increase in the disease severity may be occurring in the Americas [5].

Epidemiological evidence suggests that an important risk factor for DHF is the presence of preexisting antibodies at subneutralizing levels [1]. This led to the formulation of the *secondary infection or immune enhancement hypothesis*. Briefly stated, this hypothesis says that DHF appears in persons who have had a previous infection with an heterologous serotype. The World Health Organization has warned about the danger of the appearance of DHF epidemics in regions invaded with a particular serotype of dengue. This situation has been observed in some countries of Latin America. Méndez Galván [5] mentions that serotype I has been around in México since 1978, and important outbreaks of DHF have emerged in this country recently.

For the above reasons, it is worth studying the mechanisms that allow the invasion and persistence of a serotype of dengue in a region. Appropriate mathematical models can provide a qualitative assessment for this problem. In this paper we give a detailed derivation of a model for the dynamics of dengue disease, when only one type of virus is present and the disease-related death rate is negligible.

The model is closely related to the models proposed by Bailey [6] and Dietz [7]. Here we assume that the human population is constant, but for the vector population we suppose a constant recruitment rate and deaths proportional to the population size.

We make a global analysis of the model equations. In particular, we follow closely the ideas of Li and Muldowney [8] who use the general theory of competitive systems and compound matrices, to establish the global stability of the endemic equilibrium. We find a threshold parameter R_0 which determines the global dynamical behavior: if $R_0 < 1$, the disease-free equilibrium is globally stable, namely, the disease will die out; if $R_0 > 1$ the unique endemic equilibrium is globally stable, which implies that disease will always remain endemic above the threshold value. This threshold is further used in the last section to discuss the effectiveness of various control strategies.

2. Formulation of the model

Let N_H and N_V be the human and vector population sizes, respectively. We assume that the human population has constant size with birth and death rate

constant equal to μ_H. For the mosquito population we assume a constant recruitment rate A, independent of the actual number of adult mosquitoes. This assumption seems reasonable, since only a fraction of a large reservoir of eggs and larvae matures to the adult stage, and this process does not depend directly on the size of the adult mosquito population. Total deaths in the mosquito population occur at a rate $\mu_V N_V$, where μ_V is the per capita mortality rate of mosquitoes. The differential equation that governs the population dynamics of the vector population is

$$N_V' = A - \mu_V N_V.$$

It is well known that the solutions N_V of this equation approach the equilibrium A/μ_V as $t \to \infty$.

Let $\overline{S}_H(t), \overline{I}_H(t)$ and $\overline{R}_H(t)$ denote the number of susceptibles, infectives and immunes in the human population; and $\overline{S}_V(t), \overline{I}_V(t)$, the number of susceptibles and infectives in the vector population. Recall that mosquitoes never recover from infection. Since vertical transmission seems to be not relevant in the most important species of mosquitoes from the point of view of transmission to man, we do not consider it in the model. Flow from the susceptible to the infectious class, for each species, depends on the biting rate of the mosquitoes, the transmission probabilities, as well as the number of infectives and susceptibles of each species. The biting rate b of mosquitoes is the average number of bites per mosquito per day. This rate depends on a number of factors, in particular climatic ones, but here b is assumed to be constant (typical values are once every two or three days [1]). The transmission probability is the probability that an infectious bite produces a new case in a susceptible member of the other species.

Let m denote the number of alternative hosts available as blood sources, then the probability that a mosquito chooses a human individual as a host is given by $N_H/(N_H + m)$. Thus a human receives $b(N_V/N_H)N_H/(N_H + m)$ bites per unit of time, and a mosquito takes $bN_H/(N_H + m)$ human blood meals per unit of time. Then, the infection rates per susceptible human and susceptible vector are given by

$$\beta_H b \frac{N_V}{N_H} \frac{N_H}{N_H + m} \frac{\overline{I}_V}{N_V} = \frac{\beta_H b}{N_H + m} \overline{I}_V,$$

$$\beta_V b \frac{N_H}{N_H + m} \frac{\overline{I}_H}{N_H} = \frac{\beta_V b}{N_H + m} \overline{I}_H,$$

respectively, where β_H is the transmission probability from vector to human, β_V is the transmission probability from human to vector.

Finally, we assume that infected humans recover (or get treated) at a constant rate γ_H.

Therefore, the model is described by the following system of differential equations:

$$
\begin{aligned}
\overline{S}'_{\mathrm{H}}(t) &= \mu_{\mathrm{H}} N_{\mathrm{H}} - \frac{\beta_{\mathrm{H}} b}{N_{\mathrm{H}} + m} \overline{S}_{\mathrm{H}} \overline{I}_{\mathrm{V}} - \mu_{\mathrm{H}} \overline{S}_{\mathrm{H}}, \\
\overline{I}'_{\mathrm{H}}(t) &= \frac{\beta_{\mathrm{H}} b}{N_{\mathrm{H}} + m} \overline{S}_{\mathrm{H}} \overline{I}_{\mathrm{V}} - (\mu_{\mathrm{H}} + \gamma_{\mathrm{H}}) \overline{I}_{\mathrm{H}}, \\
\overline{R}'_{\mathrm{H}}(t) &= \gamma_{\mathrm{H}} \overline{I}_{\mathrm{H}} - \mu_{\mathrm{H}} \overline{R}_{\mathrm{H}}, \\
\overline{S}'_{\mathrm{V}}(t) &= A - \frac{\beta_{\mathrm{V}} b}{N_{\mathrm{H}} + m} \overline{S}_{\mathrm{V}} \overline{I}_{\mathrm{H}} - \mu_{\mathrm{V}} \overline{S}_{\mathrm{V}}, \\
\overline{I}'_{\mathrm{V}}(t) &= \frac{\beta_{\mathrm{V}} b}{N_{\mathrm{H}} + m} \overline{S}_{\mathrm{V}} \overline{I}_{\mathrm{H}} - \mu_{\mathrm{V}} \overline{I}_{\mathrm{V}},
\end{aligned}
\tag{1}
$$

with the two conditions

$$N_{\mathrm{H}} = \overline{S}_{\mathrm{H}} + \overline{I}_{\mathrm{H}} + \overline{R}_{\mathrm{H}} \quad \text{and} \quad N_{\mathrm{V}} = \overline{S}_{\mathrm{V}} + \overline{I}_{\mathrm{V}}.$$

The first orthant in the $\overline{S}_{\mathrm{H}} \overline{I}_{\mathrm{H}} \overline{R}_{\mathrm{H}} \overline{S}_{\mathrm{V}} \overline{I}_{\mathrm{V}}$ space is positively invariant for system (1), since the vector field on the boundary does not point to the exterior. Therefore the model is well posed.

The subset T defined by the equations

$$\overline{S}_{\mathrm{H}} + \overline{I}_{\mathrm{H}} + \overline{R}_{\mathrm{H}} = N_{\mathrm{H}}, \qquad \overline{S}_{\mathrm{V}} + \overline{I}_{\mathrm{V}} = \frac{A}{\mu_{\mathrm{V}}}$$

is an invariant region for system (1), because any solution starting in T satisfies

$$(\overline{S}_{\mathrm{H}}(t) + \overline{I}_{\mathrm{H}}(t) + \overline{R}_{\mathrm{H}}(t))' = 0, \quad (\overline{S}_{\mathrm{V}}(t) + \overline{I}_{\mathrm{V}}(t))' = 0.$$

Moreover, since N_{H} remains constant and $N_{\mathrm{V}} \to A/\mu_{\mathrm{V}}$, all paths approach T. Therefore, it is enough to study the asymptotic behavior of solutions of Eq. (1) in this invariant set (see also Ref. [9]).

The human and vector populations remain constant in T; therefore, without loss of generality, we can work with the proportions

$$S_{\mathrm{H}} = \frac{\overline{S}_{\mathrm{H}}}{N_{\mathrm{H}}}, \quad I_{\mathrm{H}} = \frac{\overline{I}_{\mathrm{H}}}{N_{\mathrm{H}}}, \quad R_{\mathrm{H}} = \frac{\overline{R}_{\mathrm{H}}}{N_{\mathrm{H}}}, \quad S_{\mathrm{V}} = \frac{\overline{S}_{\mathrm{V}}}{A/\mu_{\mathrm{V}}}, \quad I_{\mathrm{V}} = \frac{\overline{I}_{\mathrm{V}}}{A/\mu_{\mathrm{V}}}.$$

Since $R_{\mathrm{H}} = 1 - S_{\mathrm{H}} - I_{\mathrm{H}}$ and $S_{\mathrm{V}} = 1 - I_{\mathrm{V}}$, system (1) in the invariant space T can be written as the equivalent three-dimensional non-linear system of ODEs:

$$
\begin{aligned}
S'_{\mathrm{H}}(t) &= \mu_{\mathrm{H}}(1 - S_{\mathrm{H}}) - b\beta_{\mathrm{H}} \frac{A/\mu_{\mathrm{V}}}{N_{\mathrm{H}} + m} S_{\mathrm{H}} I_{\mathrm{V}}, \\
I'_{\mathrm{H}}(t) &= b\beta_{\mathrm{H}} \frac{A/\mu_{\mathrm{V}}}{N_{\mathrm{H}} + m} S_{\mathrm{H}} I_{\mathrm{V}} - (\gamma_{\mathrm{H}} + \mu_{\mathrm{H}}) I_{\mathrm{H}}, \\
I'_{\mathrm{V}}(t) &= b\beta_{\mathrm{V}} \frac{N_{\mathrm{H}}}{N_{\mathrm{H}} + m} (1 - I_{\mathrm{V}}) I_{\mathrm{H}} - \mu_{\mathrm{V}} I_{\mathrm{V}}
\end{aligned}
\tag{2}
$$

System (2) was used by Bailey [6] and Dietz [7] as a model of arbovirus diseases. Here we give a more thorough analysis of the system.

3. Equilibrium points of the model

First, note that the region of biological interest

$$\Omega = \{(S_H, I_H, I_V)\colon\ 0 \leqslant I_V \leqslant 1,\ \ 0 \leqslant S_H,\ \ 0 \leqslant I_H,\ \ S_H + I_H \leqslant 1\}$$

is positively invariant under the flow induced by Eq. (2), as the vector field on the boundary does not point to the exterior.

Our next result concerns the existence of equilibrium points of system (2). From the first and third equations of (2) with the right-hand side equal to zero, it can be seen that the equilibrium points must satisfy the following relations:

$$S_H = \frac{\beta I_H + 1}{(\beta + MR_0)I_H + 1}, \tag{3}$$

$$I_V = \frac{\beta I_H}{\beta I_H + 1}, \tag{4}$$

where

$$\beta = \frac{b\beta_V N_H}{\mu_V(N_H + m)}, \quad M = \frac{\gamma_H + \mu_H}{\mu_H}, \quad R_0 = \frac{b^2\beta_H\beta_V N_H A/\mu_V}{(N_H + m)^2\mu_V(\gamma_H + \mu_H)}. \tag{5}$$

Substituting Eqs. (3) and (4) and $(\beta b\beta_H A/\mu_V)/(N_H + m) = R_0(\gamma_H + \mu_H)$ in the second equation of (2), we obtain that I_H must be a solution of the following quadratic equation:

$$-(\beta + MR_0)I_H^2 + (R_0 - 1)I_H = 0. \tag{6}$$

Substituting the solutions $I_H = 0$ and $I_H = (R_0 - 1)/(\beta + MR_0)$ of Eq. (6) in Eqs. (3) and (4) we obtain the equilibrium points of Eq. (2):

$$E_1 = (1, 0, 0) \quad \text{and} \quad E_2 = (S_H^*, I_H^*, I_V^*),$$

where

$$S_H^* = \frac{\beta + M}{\beta + MR_0}, \quad I_H^* = \frac{R_0 - 1}{\beta + MR_0}, \quad I_V^* = \frac{\beta(R_0 - 1)}{R_0(\beta + M)}. \tag{7}$$

E_1 is the disease-free equilibrium and E_2 corresponds to the endemic value. If $R_0 \leqslant 1$, then E_1 is the only equilibrium in Ω; if $R_0 > 1$ then the endemic equilibrium E_2 will also lie in Ω.

The quantity $\tilde{R}_0 = \sqrt{R_0}$ is called the *basic reproductive number* of the disease, since it represents the average number of secondary cases that one case can produce if introduced into a susceptible population. This can be seen as follows: an infective human introduced into the susceptible population is bitten, during his infective period, by $(b(A/\mu_V)/(N_H + m))(1/(\gamma_H + \mu_H))$ mosquitoes; a proportion, $(\beta_V b(A/\mu_V)/(N_H + m))(1/(\gamma_H + \mu_H))$, of these mosquitoes becomes infectious. Similarly, an infective mosquito distributes $bN_H/(N_H + m)$ $(1/\mu_V)$ bites in the human population during the rest of its life and a proportion,

$\beta_H b N_H/(N_H+m)\ (1/\mu_V)$, of these bites becomes new infections in the human population. Therefore, the geometric mean of these quantities, which is equal to $\tilde{R}_0$, gives the number of secondary infections.

Recently, Diekmann et al. [10] defined the basic reproductive number of a disease as the spectral ratio of the one-generator map. According to this, the basic reproductive number of a vector transmission disease is precisely $\tilde{R}_0$. This definition has also been used by Velasco-Hernández [11] for a Chagas disease model.

The local stability of the disease-free equilibrium E_1 is governed by the matrix

$$\mathrm{D}F(E_1) = \begin{bmatrix} -\mu_H & 0 & -\frac{b\beta_H A/\mu_V}{N_H+m} \\ 0 & -(\gamma_H+\mu_H) & \frac{b\beta_H A/\mu_V}{N_H+m} \\ 0 & \frac{b\beta_V N_H}{N_H+m} & -\mu_V \end{bmatrix}, \tag{8}$$

where $\mathrm{D}F$ denotes the derivative of the vector field F given by the right-hand side of Eq. (2). The eigenvalues of Eq. (8) are given by

$$-\mu_H,\ \frac{-(\gamma_H+\mu_H+\mu_V) \pm \sqrt{(\gamma_H+\mu_H+\mu_V)^2 - 4\mu_V(\gamma_H+\mu_H)(1-R_0)}}{2}.$$

Therefore E_1 is locally asymptotically stable for $R_0 < 1$. We can actually show that it is globally asymptotically stable in Ω for $R_0 \leqslant 1$. To prove this, we use the Lyapunov function

$$V = \left(\frac{b\beta_H A/\mu_V}{(N_H+m)\mu_V}\right) I_V + I_H. \tag{9}$$

The orbital derivative of V is given by

$$\dot{V} = -\frac{b\beta_H A/\mu_V}{N_H+m}(1-S_H)I_V - (\gamma_H+\mu_H)[1-R_0(1-I_V)]I_H, \tag{10}$$

which is less or equal to zero in Ω. The subset of Ω where $\dot{V}=0$, is defined by the equations

$$(1-S_H)I_V = 0, \quad I_H = 0 \text{ if } R_0 < 1,$$

$$(1-S_H)I_V = 0, \quad I_V I_H = 0 \text{ if } R_0 = 1.$$

From inspection of system (2), it can be seen that $\{E_1\}$ is the only invariant set contained in $\dot{V}=0$. Therefore, from the LaSalle–Lyapunov Theorem [12], it follows that E_1 is locally stable and all trajectories starting in Ω approach E_1 as t goes to infinity. This proof establishes the global asymptotical stability of E_1 for $R_0 \leqslant 1$.

For $R_0 > 1$, the equilibrium E_1 becomes an unstable hyperbolic point, and the endemic equilibrium E_2 emerges in Ω. The local stability for this point is governed by the matrix

$$\mathrm{D}F(E_2) = \begin{bmatrix} -\mu_{\mathrm{H}}\left(\frac{\beta+MR_0}{\beta+M}\right) & 0 & -\frac{\mu_{\mathrm{H}}MR_0}{\beta}\left(\frac{\beta+M}{\beta+MR_0}\right) \\ \frac{\mu_{\mathrm{H}}M(R_0-1)}{\beta+M} & -\mu_{\mathrm{H}}M & \frac{\mu_{\mathrm{H}}MR_0}{\beta}\left(\frac{\beta+M}{\beta+MR_0}\right) \\ 0 & \frac{\mu_{\mathrm{V}}\beta}{R_0}\left(\frac{\beta+MR_0}{\beta+M}\right) & -\mu_{\mathrm{V}}R_0\left(\frac{\beta+M}{\beta+MR_0}\right) \end{bmatrix}, \tag{11}$$

where β and M are given in Eq. (5).

The characteristic polynomial of Eq. (11) is given by

$$p(\lambda) = \lambda^3 + A\lambda^2 + B\lambda + C, \tag{12}$$

where

$$A = -\mathrm{Tr}(\mathrm{D}F(E_2)), \quad B = \begin{vmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{vmatrix} + \begin{vmatrix} a_{11} & a_{13} \\ a_{31} & a_{33} \end{vmatrix} + \begin{vmatrix} a_{22} & a_{23} \\ a_{32} & a_{33} \end{vmatrix},$$

$$C = -\det(\mathrm{D}F(E_2)).$$

After some calculations we obtain

$$A = \frac{\mu_{\mathrm{H}}(\beta + MR_0)}{\beta + M} + \mu_{\mathrm{H}}M + \frac{\mu_{\mathrm{V}}R_0(\beta + M)}{\beta + MR_0},$$

$$B = \frac{\mu_{\mathrm{H}}^2 M(\beta + MR_0)}{\beta + M} + \mu_{\mathrm{V}}\mu_{\mathrm{H}}R_0 + \frac{\mu_{\mathrm{V}}\mu_{\mathrm{H}}M\beta(R_0 - 1)}{\beta + MR_0},$$

$$C = \mu_{\mathrm{V}}\mu_{\mathrm{H}}^2 M(R_0 - 1).$$

We notice that for $R_0 > 1$ the coefficients of Eq. (12) are positive. Also it is easy to verify that

$$AB > \mu_{\mathrm{V}}\mu_{\mathrm{H}}^2 MR_0 > C.$$

Then, the Routh–Hurwitz conditions for the polynomial Eq. (12) are satisfied if $R_0 > 1$, therefore E_2 is locally asymptotically stable.

In Section 4, we shall prove that $\Omega - \{(S_{\mathrm{H}}, 0, 0):\ 0 \leqslant S_{\mathrm{H}} \leqslant 1\}$ is an asymptotic stability region for the endemic equilibrium E_2.

4. Global stability of the endemic equilibrium

The global stability of an endemic equilibrium of an SIR model with several populations, has only been conjectured [13]. In this section we will prove this fact for our two population model.

We state the main result of this section:

Theorem 4.1. *If $R_0 > 1$, the endemic equilibrium E_2 is globally asymptotically stable in* $\mathrm{int}(\Omega)$.

To establish Theorem 4.1 we shall use some results about competitive systems and about the stability of periodic orbits.

We need to recall some definitions and results, before presenting our proof.

Let $D \subset \mathbb{R}^n$ be an open set, and $\overline{x} \mapsto f(\overline{x}) \in \mathbb{R}^n$ be a C^1 function defined in D. We consider the autonomous system in $\mathbb{R}^n$ given by

$$\overline{x}' = f(\overline{x}). \tag{13}$$

System Eq. (13) is *competitive* in D [14] if, for some diagonal matrix $H = \mathrm{diag}(\epsilon_1, \ldots, \epsilon_n)$, where each ϵ_i is either 1 or -1, $H(\mathrm{D}F(\overline{x}))H$ has non-positive off-diagonal elements for $\overline{x} \in D$, where $\mathrm{D}F(\overline{x})$ is the Jacobian of Eq. (13). It is shown in Ref. [14] that, if D is convex, the flow of such a system preserves for $t < 0$ the partial order in $\mathbb{R}^n$ defined by the orthant

$$K = \{(x_1, \ldots, x_n) \in \mathbb{R}^n\colon\ \epsilon_i x_i \geqslant 0\}.$$

By looking at its Jacobian matrix and choosing the matrix H as

$$H = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

we can see that system (2) is competitive in Ω, with respect to the partial order defined by the orthant

$$K = \{(S_{\mathrm{H}}, I_{\mathrm{H}}, I_{\mathrm{V}}) \in R^3\colon\ S_{\mathrm{H}} \geqslant 0, I_{\mathrm{H}} \leqslant 0, I_{\mathrm{V}} \geqslant 0\}.$$

Hirsch [15] and Smith [14] proved that three-dimensional competitive systems that live in convex sets have the Poincaré–Bendixson property [16], that is, any non-empty compact omega limit set that contains no equilibria must be a closed orbit.

We recall additional definitions that we will use later. Suppose Eq. (13) has a periodic solution $\gamma(t)$ with minimal period $\omega > 0$ and orbit $\gamma = \{\gamma(t)\colon\ 0 \leqslant t \leqslant \omega\}$. This orbit is *orbitally stable* iff for each $\epsilon > 0$, there exists a $\delta > 0$ such that any solution $\overline{x}(t)$, for which the distance of $\overline{x}(0)$ from γ is less than δ, remains at a distance less than ϵ from γ, for all $t \geqslant 0$. It is *asymptotically orbitally stable*, if the distance of $\overline{x}(t)$ from γ also tends to zero as t goes to infinity [12].

System (13) is *persistent* in the sense described in Ref. [17], iff each solution $\overline{x}(t)$ starting in $\mathrm{int}(\Omega)$, has the property that $\liminf_{t\to\infty} \overline{x}(t)$ is at a positive distance from the boundary of Ω.

We shall now introduce a new definition. We say that system (13) has the *property of stability of periodic orbits*, iff the orbit of any periodic solution $\gamma(t)$, if it exists, is asymptotically orbitally stable. This concept allows us to generalize the results for the SEIR model given in Ref. [8] to systems that are competitive, persistent and have the property of stability of periodic orbits.

The following theorem is the main tool to prove the global stability of the endemic equilibrium.

Theorem 4.2. *Assume that $n=3$, D convex and bounded. Suppose Eq. (13) is competitive, persistent and has the property of stability of periodic orbits. If $\bar{x}_0$ is the only equilibrium point in* $\mathrm{int}(D)$*, and if it is locally asymptotically stable, then it is globally asymptotically stable in* $\mathrm{int}(D)$.

The proof of this theorem is the same of Theorems 2.1 and 4.2 in Ref. [8].

In accordance with Theorem 4.2, Theorem 4.1 would be established, if we show that system (2) is persistent for $R_0 > 1$ and has the property of stability of periodic orbits. In order to prove the persistence of system (2) we shall prove the following proposition.

Proposition 4.1. *On the boundary of Ω, system (2) has only one omega-limit point which is the equilibrium E_1. Moreover for $R_0 > 1$, E_1 cannot be the omega-limit of any orbit in* $\mathrm{int}(\Omega)$.

Proof. The vector field is transversal to the boundary of Ω, except in the S_H-axis which is invariant with respect Eq. (2). On the S_H-axis we have

$$S'_H = \mu_H(1 - S_H),$$

which implies that $S_H(t) \to 1$ as $t \to \infty$. Therefore E_1 is the only omega limit point on the boundary of Ω.

To prove the second part of the proposition, we consider the function

$$V = I_V + \frac{\mu_V(N_H + m)(1 + R_0)}{2b\beta_H A/\mu_V} I_H, \tag{14}$$

whose derivative along solutions is given by

$$\dot{V} = \left[(1 - I_V) - \frac{1}{2}\left(\frac{1}{R_0} + 1\right)\right] b\beta_V \frac{N_H}{N_H + m} I_H + \left[S_H. - \frac{2}{1 + R_0}\right] \frac{\mu_V(1 + R_0)}{2} I_V.$$

Since $R_0 > 1$, then $\frac{1}{2}(1/R_0 + 1)$ and $2/(1 + R_0)$ are less than one, therefore there exists a neighborhood U of E_1 such that for $(S_H, I_H, I_V) \in U \cap \mathrm{int}(\Omega)$ the expressions inside the brackets are positive. In this neighborhood we have that $\dot{V} > 0$ unless $I_H + I_V = 0$. On the other hand, the level sets of V are the planes

$$I_V + \frac{\mu_V(N_H + m)(1 + R_0)}{2b\beta_H A/\mu_V} I_H = c,$$

which go away from the S_H-axis as c increases. Since V is increasing along the orbits starting in $U \cap \mathrm{int}(\Omega)$, we conclude that they go away from E_1.

This proves the proposition, and therefore, the persistence of system (2) when $R_0 > 1$.

Proposition 4.2. *The system (2) has the property of stability of periodic orbits.*

Proof. In accordance with the criterion given by Muldowney in Ref. [18], for the asymptotic orbital stability of a periodic orbit of a general autonomous system, it is sufficient to prove that the linear non-autonomous system

$$\overline{X}'(t) = (\mathrm{D}F^{[2]}(\gamma(t)))\overline{X}(t), \tag{15}$$

is asymptotically stable, where $\mathrm{D}F^{[2]}$ is the second additive compound matrix of the Jacobian $\mathrm{D}F$ (see Appendix A for a definition of compound matrix and examples in dimension three).

The Jacobian of Eq. (2) is given by

$$\mathrm{D}F = \begin{bmatrix} -(\mu_{\mathrm{H}} + a_{\mathrm{H}} b\beta_{\mathrm{H}} I_{\mathrm{V}}) & 0 & -a_{\mathrm{H}} b\beta_{\mathrm{H}} S_{\mathrm{H}} \\ a_{\mathrm{H}} b\beta_{\mathrm{H}} I_{\mathrm{V}} & -(\gamma_{\mathrm{H}} + \mu_{\mathrm{H}}) & a_{\mathrm{H}} b\beta_{\mathrm{H}} S_{\mathrm{H}} \\ 0 & a_{\mathrm{V}} b\beta_{\mathrm{V}}(1 - I_{\mathrm{V}}) & -(\mu_{\mathrm{V}} + a_{\mathrm{V}} b\beta_{\mathrm{V}} I_{\mathrm{H}}) \end{bmatrix},$$

where

$$a_{\mathrm{H}} = \frac{A/\mu_{\mathrm{V}}}{N_{\mathrm{H}} + m}, \qquad a_{\mathrm{V}} = \frac{N_{\mathrm{H}}}{N_{\mathrm{H}} + m}.$$

For the solution $\gamma(t)$, Eq. (15) becomes

$$\begin{aligned} X' &= -(\mu_{\mathrm{H}} + a_{\mathrm{H}} b\beta_{\mathrm{H}} I_{\mathrm{V}} + \gamma_{\mathrm{H}} + \mu_{\mathrm{H}})X + a_{\mathrm{H}} b\beta_{\mathrm{H}} S_{\mathrm{H}} Y + a_{\mathrm{H}} b\beta_{\mathrm{H}} S_{\mathrm{H}} Z, \\ Y' &= a_{\mathrm{V}} b\beta_{\mathrm{V}}(1 - I_{\mathrm{V}})X - (\mu_{\mathrm{H}} + a_{\mathrm{H}} b\beta_{\mathrm{H}} I_{\mathrm{V}} + \mu_{\mathrm{V}} + a_{\mathrm{V}} b\beta_{\mathrm{V}} I_{\mathrm{H}})Y, \\ Z' &= a_{\mathrm{H}} b\beta_{\mathrm{H}} I_{\mathrm{V}} Y - (\mu_{\mathrm{V}} + a_{\mathrm{V}} b\beta_{\mathrm{V}} I_{\mathrm{H}} + \gamma_{\mathrm{H}} + \mu_{\mathrm{H}})Z. \end{aligned} \tag{16}$$

In order to prove that Eq. (16) is asymptotically stable, we shall use the following Lyapunov function which is similar to the one found in Ref. [8] for the SEIR model.

$$V(X(t), Y(t), Z(t), S_{\mathrm{H}}(t), I_{\mathrm{H}}(t), I_{\mathrm{V}}(t)) = \left\| \left(X(t), \frac{I_{\mathrm{H}}(t)}{I_{\mathrm{V}}(t)} Y(t), \frac{I_{\mathrm{H}}(t)}{I_{\mathrm{V}}(t)} Z(t)\right) \right\|, \tag{17}$$

where $\|\cdot\|$ is the norm in R^3 defined by

$$\|(X, Y, Z)\| = \sup\{|X|, |Y| + |Z|\}.$$

From Proposition 4.1, we obtain that the orbit of $\gamma(t)$ remains at a positive distance from the boundary of Ω; therefore

$$I_{\mathrm{V}}(t) \geqslant K \text{ and } I_{\mathrm{H}}(t) \geqslant K \text{ with } 0 < K < 1.$$

Hence the function V is well defined along $\gamma(t)$ and

$$V(X, Y, Z; S_{\mathrm{H}}, I_{\mathrm{H}}, I_{\mathrm{V}}) \geqslant K\|(X, Y, Z)\|. \tag{18}$$

Along a solution $(X(t), Y(t), Z(t))$ of Eq. (16), V becomes

$$V(t) = \sup\{|X(t)|, \frac{I_H(t)}{I_V(t)}(|Y(t)| + |Z(t)|)\}.$$

Similarly as was done in Ref. [8] we found the following inequalities. (Full details are in Ref. [19].)

$$\begin{aligned} D_+|X(t)| &\leqslant -(\mu_H + a_H b\beta_H I_V + \gamma_H + \mu_H)|X(t)| + a_H b\beta_H S_H(|Y(t)| + |Z(t)|) \\ &\leqslant -(\mu_H + a_H b\beta_H I_V + \gamma_H + \mu_H)|X(t)| \\ &\quad + a_H b\beta_H S_H \frac{I_V}{I_H}\left(\frac{I_H}{I_V}(|Y(t)| + |Z(t)|)\right), \end{aligned} \tag{19}$$

$$D_+|Y(t)| \leqslant a_V b\beta_V(1 - I_V)|X(t)| - (\mu_H + a_H b\beta_H I_V + \mu_V + a_V b\beta_V I_H)|Y(t)|, \tag{20}$$

$$D_+|Z(t)| \leqslant a_H b\beta_H I_V|Y(t)| - (\mu_V + a_V b\beta_V I_H + \gamma_H + \mu_H)|Z(t)|. \tag{21}$$

From Eqs. (20) and (21) we get

$$\begin{aligned} D_+[|Y(t)| + |Z(t)|] \leqslant & -(\mu_H + \mu_V + a_V b\beta_V I_H)(|Y(t)| + |Z(t)|) \\ & + a_V b\beta_V(1 - I_V)|X(t)|, \end{aligned}$$

therefore

$$\begin{aligned} D_+\left[\frac{I_H}{I_V}(|Y(t)| + |Z(t)|)\right] &= \left(\frac{I'_H}{I_H} - \frac{I'_V}{I_V}\right)\frac{I_H}{I_V}(|Y(t)| + |Z(t)|) + \frac{I_H}{I_V}D_+(|Y(t)| \\ &\quad + |Z(t)|) \leqslant \frac{I_H}{I_V}a_V b\beta_V(1 - I_V)|X(t)| \\ &\quad + \left(\frac{I'_H}{I_H} - \frac{I'_V}{I_V} - \mu_H - \mu_V - a_V b\beta_V I_H\right)\frac{I_H}{I_V}(|Y(t)| \\ &\quad + |Z(t)|). \end{aligned} \tag{22}$$

From Eqs. (19) and (22) we get:

$$D_+V(t) \leqslant \sup\{h_1(t), h_2(t)\}V(t), \tag{23}$$

where

$$h_1(t) = -(\mu_H + a_H b\beta_H I_V + \gamma_H + \mu_H) + a_H b\beta_H S_H \frac{I_V}{I_H},$$

$$h_2(t) = \frac{I_H}{I_V}a_V b\beta_V(1 - I_V) + \frac{I'_H}{I_H} - \frac{I'_V}{I_V} - \mu_H - \mu_V - a_V b\beta_V I_H.$$

We rewrite the last two equations of (2) as

$$a_H b\beta_H S_H \frac{I_V}{I_H} = \frac{I'_H}{I_H} + \gamma_H + \mu_H, \tag{24}$$

$$a_V b\beta_V(1-I_V)\frac{I_H}{I_V}=\frac{I_V'}{I_V}+\mu_V. \tag{25}$$

From Eqs. (24) and (25) we find

$$\sup\{h_1(t),h_2(t)\}\leqslant -\mu_H+\frac{I_H'}{I_H}$$

and thus, from Eq. (23) and Gronwall's inequality, we obtain

$$V(t)\leqslant V(0)I_H(t)e^{-\mu_H t}\leqslant V(0)e^{-\mu_H t},$$

which implies that $V(t)\to 0$ as $t\to\infty$. By Eq. (18) it turns out that

$$(X(t),Y(t),Z(t))\to 0 \text{ as } t\to\infty.$$

This implies that the linear system Eq. (16) is asymptotically stable and therefore the periodic solution is asymptotically orbitally stable. This proves Proposition 4.2.

As it was noted before, this result proves Theorem 4.1.

From Proposition 4.1 and Theorem 4.1 we can prove the next theorem, which completely determines the dynamical behavior of the solutions of system (2) when $R_0>1$.

Theorem 4.3. *Consider system (2). If $R_0>1$, then $\Omega-\{(S_H,0,0):\ 0\leqslant S_H\leqslant 1\}$ is an asymptotic stability region for the endemic equilibrium E_2. Moreover, all trajectories starting in the S_H-axis approach the disease-free equilibrium E_1.*

Proof. The first part of the theorem follows from the transversality of the vector field of (2) on $\Omega-\{(S_H,0,0):\ 0\leqslant S_H\leqslant 1\}$ and Theorem 4.1. The second part is proved in Proposition 4.1.

Fig. 1 illustrates the typical behavior of the proportions of susceptible humans, infective humans and infective mosquitoes initially positive. In Fig. 1(a) and (b), $R_0=0.84$ whereas in Fig. 1(c) and (d), $R_0=10.6$. We observe in the first case that the susceptible proportion increases to one, and the infectious proportions decline exponentially to zero. In the second case, they approach the endemic proportions $S_H^*=0.095$, $I_H^*=0.00028$ and $I_V^*=0.00057$.

The graphs shown were obtained after the numerical integration of the equivalent equations in the variables S_H, R_H and S_V since, numerically, this system is less stiff than system (2) analyzed theoretically.

We notice that the temporal courses of the proportions in Fig. 1(c) and (d) present damped oscillations. In the numerical simulations μ_H happens to be very small with respect to the other parameters, since the average expected life in humans is about 60 years, whereas the length of the infected period is a few days. We shall prove that under this situation there exist damped oscillations for $R_0>1$.

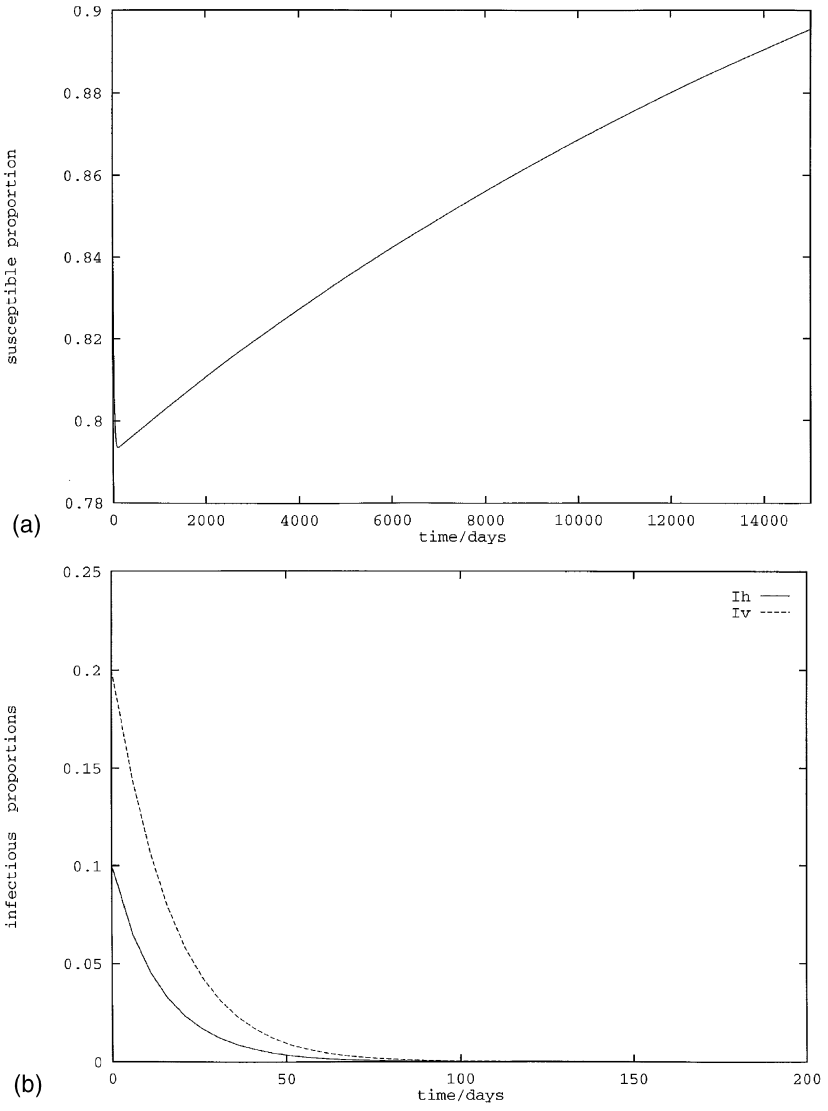
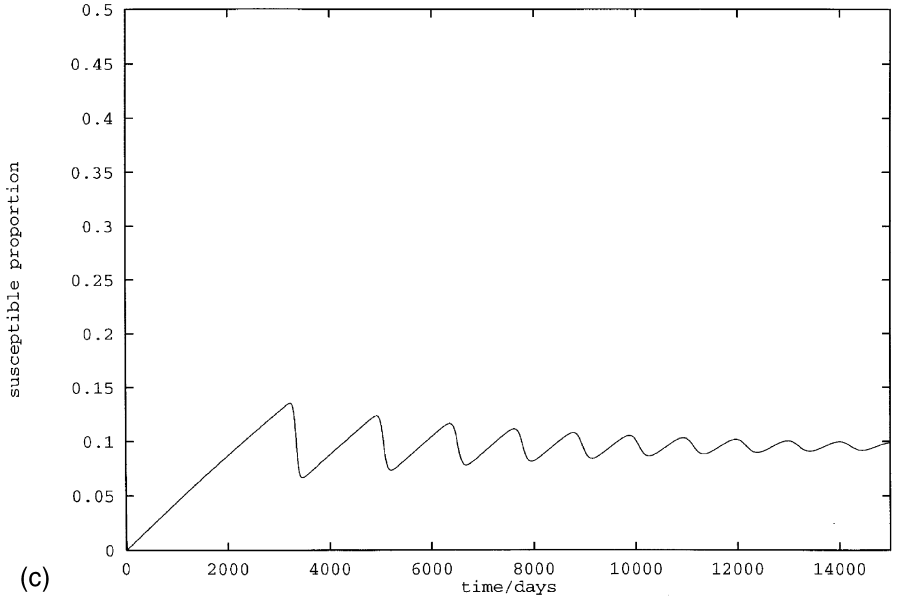


Fig. 1. Numerical solution of model (1). The graphs show the proportion of susceptible humans, infective humans and infective vectors versus time. The parameters in the simulation are: (a), (b) $\mu_H = 0.0000457$/day, $\mu_V = 0.25$/day, $b = 0.5$, $\beta_H = 0.75$, $\beta_V = 1$, $m = 0$, $\gamma_H = 0.1428$/day, $N_H = 10,000$, $A = 400$. In this case $R_0 = 0.84$ and $\tilde{R}_0 = 0.91$. (c), (d) $\mu_H = 0.0000457$/day, $\mu_V = 0.25$/day, $b = 0.5$, $\beta_H = 0.75$, $\beta_V = 1$, $m = 0$, $\gamma_H = 0.1428$/day, $N_H = 10,000$, $A = 5000$. In this case $R_0 = 10.5$ and $\tilde{R}_0 = 3.24$.



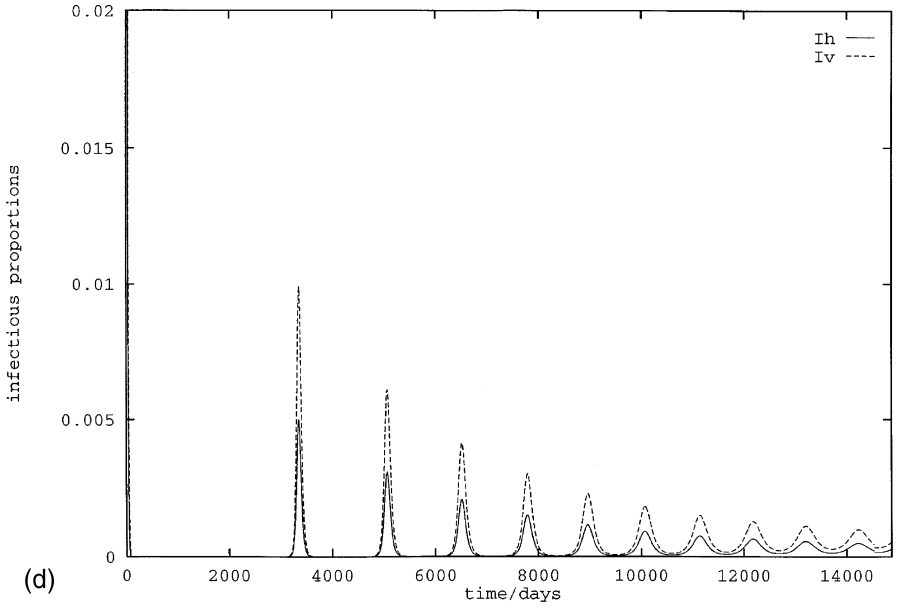


Fig. 1. (*continued*)

Theorem 4.4. *Assume $R_0 > 1$ and $\mu_H \ll 1$, then the solutions of system (2) oscillate to the endemic equilibrium.*

Proof. The existence of oscillations around the equilibrium E_2 depends on whether the polynomial Eq. (12) has eigenvalues with imaginary part different from zero. Recall that a polynomial of degree three has eigenvalues with imaginary part different from zero if the discriminant

$$\Delta = \frac{1}{4}q^2 + \frac{1}{27}p^3 \tag{26}$$

is bigger than zero [20], where

$$q = \frac{2}{27}A^3 - \frac{AB}{3} + C, \quad p = B - \frac{A^2}{3}.$$

We substitute M and R_0 in the coefficients A, B and C and expand them in Taylor series around $\mu_H = 0$. After some calculations we obtain the following approximations:

$$A = \mu_V + \gamma_H + \left[\frac{\mu_V}{\lambda\gamma_H}(\beta\lambda - \gamma_H) + \frac{\beta\lambda}{\gamma_H} + 1\right]\mu_H + O(\mu_H^2),$$

$$B = \left[\frac{\mu_V}{\lambda}(\beta\lambda - \gamma_H) + \beta\lambda\left(\frac{\mu_V + \gamma_H}{\gamma_H}\right)\right]\mu_H + O(\mu_H^2),$$

$$C = \mu_V(\beta\lambda - \gamma_H)\mu_H + O(\mu_H^2),$$

where $\lambda = (b\beta_H A/\mu_V)/(N_H + m)$.

On the other hand, in terms of the coefficients A, B and C, from Eq. (26) we have

$$\Delta = \frac{A^3C}{27} - \frac{A^2B^2}{108} - \frac{ABC}{6} + \frac{B^3}{27} + \frac{C^2}{4}. \tag{27}$$

Substituting A, B and C in Eq. (27), and collecting terms $O(\mu_H^2)$, we get

$$\Delta = \frac{1}{27}(\mu_V + \gamma_H)^3\mu_V(\beta\lambda - \gamma_H)\mu_H + O(\mu_H^2).$$

The term $\beta\lambda - \gamma_H$ is bigger than zero since $R_0 > 1$, therefore

$$\lim_{\mu_H \to 0} \frac{\Delta}{\mu_H} > 0$$

which implies that for μ_H sufficiently small and positive, $\Delta > 0$. This proves the theorem.

For the simulation shown in Fig. 1(c) and (d) the imaginary part of the complex roots is approximately 0.0062. Therefore, we can estimate the period of the oscillations as they approach E_2 by means of the solutions of the linearized system, obtaining $2\pi/0.0062 \approx 2.77$ years. As can be observed in the same figure, this value is a good approximation to the period of the solutions.

In Fig. 2 we show the bifurcation diagram for the equilibria of model (2) with respect to R_0. For $R_0 > 1$ we plot the proportion of infective humans I_H^*

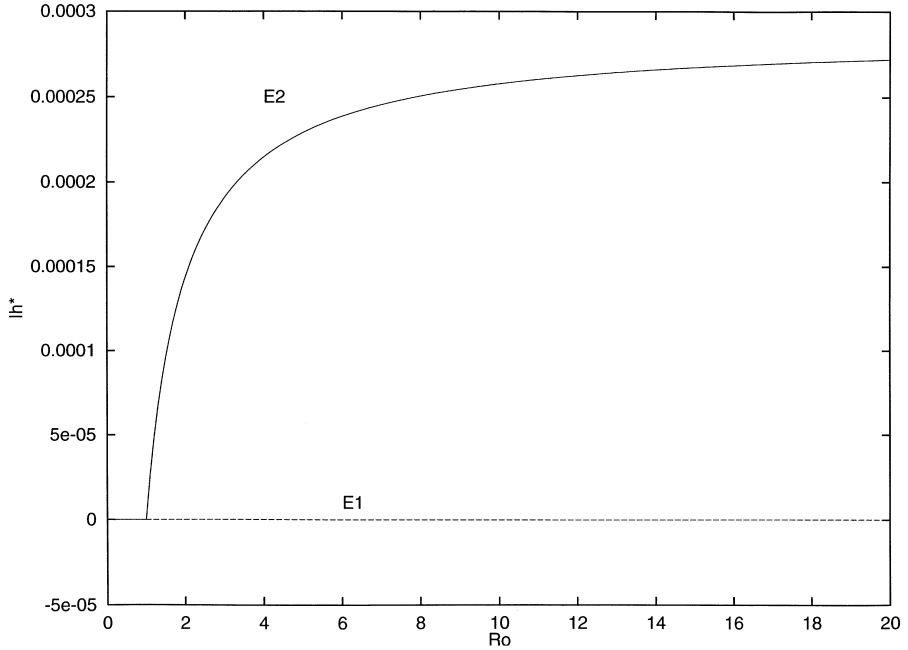


Fig. 2. Bifurcation diagram for model (1). The parameters are given in the text. —— represents the stable solution, and - - - - the unstable one.

given in Eq. (7), and we fixed the parameters $b = 0.5$/day, $\beta_V = 1$, $1/\mu_V = 4$ days, $1/\gamma_H = 7$ days, $1/\mu_H = 67$ years and $m = 0$; then $\beta = b\beta_V/\mu_V = 2$ and $M = (\gamma_H + \mu_H)/\mu_H = 3494$. From Eq. (7) it is clear that the bifurcation diagram will be qualitatively the same for different values of β and M.

5. Conclusions

We have analyzed a model for dengue disease. In this model we assume that the human population is constant. The vector population has a constant recruitment rate, which depends upon the fractions of eggs and larvae that mature to the adult stage, and a constant per capita mortality. Therefore, the vector population is asymptotically constant.

For this model we found that

$$R_0 = \frac{b^2\beta_H\beta_V N_H A/\mu_V}{(N_H + m)^2\mu_V(\gamma_H + \mu_H)}$$

is the threshold condition for the existence of the endemic state. $\tilde{R}_0 = \sqrt{R_0}$ is the basic reproductive number of the disease.

For $R_0 \leqslant 1$ (or equivalently $\tilde{R}_0 \leqslant 1$), the disease free equilibrium is globally asymptotically stable. In the case $R_0 > 1$ (or equivalently $\tilde{R}_0 > 1$) we proved, using results about competitive systems and stability of periodic orbits, that this state is globally asymptotically stable.

Fig. 1 illustrates the typical behavior of the proportion of susceptible humans, infective humans and infective vectors initially positive. In the region of admissible values, the solutions asymptotically approach to the disease free equilibrium for $R_0 \leqslant 1$, whereas for $R_0 > 1$ they oscillate to the endemic state.

The behavior mentioned above can be explained intuitively in terms of the basic reproduction number $\tilde{R}_0$. If this number is less or equal than one, so that an infective replaces itself with less than one new infective, then the disease dies out. Moreover, the susceptible fraction approaches one since everyone is susceptible when the disease has disappeared and all the removed people who are immune have died.

On the other hand, if the basic reproductive number is greater than one, and the initial fraction of susceptibles $S = S_H + S_V$ satisfies $\tilde{R}_0 S > 1$, then S decreases and the infection proportion $I = I_H + I_V$ first increases to a peak and then decreases because there are not sufficient susceptibles to be infected. When the susceptible fraction gets large enough due to births of new susceptibles, there are secondary smaller epidemics and, thus, the solutions spiral to the endemic equilibrium.

The threshold number R_0 is directly proportional to the carrying capacity of the mosquito population. We also note that R_0 is linear with respect to the ratio between the human population and the total number of hosts available as blood sources for the mosquitoes; that means that in the urban centers, where alternative hosts are scarce, the probability of dengue epidemics in the human population is higher than in the rural regions. Therefore, it is not surprising that mosquitoes that are adapted to urban environments such as the *A. aegypti* have become a major public health problem.

Since no vaccine is yet available for dengue fever, the efforts to control the disease focus on the vector. One of the methods to control *A. aegypti* population has been source reduction, that is, the vector breeding sites are reduced [1,4,5]. A. *aegypti* is a highly domestic species and thrives in places where water is stored or accumulated in the domestic environment. Thus, elimination of man-made larval habitats may eliminate or at least greatly reduce the density of the species. Early programs using this labor-intensive approach have proved to be effective [21].

Since the late 1960s, ultra low volume (ULV) application of insecticides to kill the adult population of mosquitoes [4,22] has been the standard method of control of *A. aegypti* in most parts of the world. However, there is much controversy over the impact of ULV insecticide application on *A. aegypti* population. Studies made in several countries of Asia and the Americas

[21,23,24] indicate that, after the application of ULV, the adult population of mosquitoes returned to pretreatment levels within two weeks.

We simulate the ULV application of insecticide by an abrupt increase of the mortality μ_V of vector population in model (1), when the prevalence (number of cases at a given time in the human population) exceeds 1% of the total population. This increase lasts for seven days and thereafter it returns to pre-treated levels.

Fig. 3 demonstrates the effect of raising the mortality rate of vector population from (i) 0.25/day to (ii) 0.50/day and (iii) 0.90/day. In the simulations $A = 1250$ and the other parameters are as in Fig. 1(a). Here we show only the first epidemic peak. The basic reproductive number decreases temporally from 1.61 to 0.8 and 0.45, respectively, which shows the great sensitivity of this number to changes in the mortality of vector population.

We observe in Fig. 3 that in all cases, application of ULV results in a transient depression of prevalence, but after the treatment the epidemic resumes again. As the mortality rate increases, the epidemic diminishes and it is delayed for several days. However, even if we raise the mortality to 0.90/day (that corresponds to increase the mortality 3.6 times of its original value), the maximum prevalence is delayed by 23 days and only 63 cases are prevented.

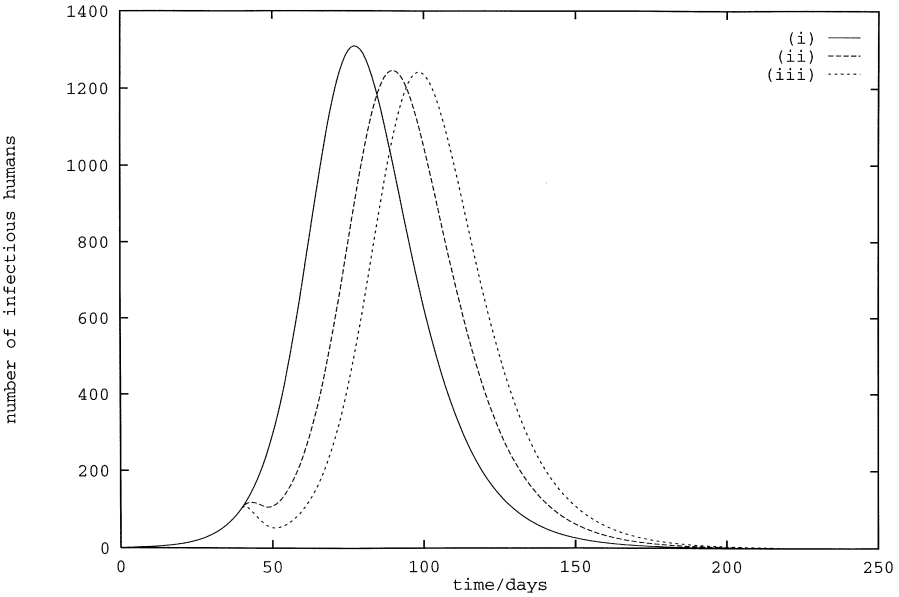


Fig. 3. Impact of ULV insecticide treatment applied during seven days when prevalence is 1% of the total human population. The application raises the mortality rate of vectors μ_V from (i) 0.25/day to (ii) 0.50/day and (iii) 0.90/day. In the simulations, $A = 1250$ and the other parameters are as in Fig. 1. The initial conditions are $\overline{S}_H = 9999$, $\overline{S}_V = 4500$, $\overline{I}_H = \overline{I}_V = 1$.

The above results agree with the ones obtained by Newton and Reiter [25] who used a similar model to study the impact of ULV application of insecticide. Their numerical simulations suggest that even with multiple applications of ULV, the impact on the incidence of the disease is very small.

The control measures for the vector population can be explained in terms of the basic reproductive number. If an outbreak of dengue starts in an endemic region, the basic reproductive number is greater than one. When the ULV treatment is applied during a short period of time, the mortality rate of adult mosquitoes μ_V will increase, and in consequence, the basic reproduction number will decrease temporarily to levels below one. The infective mosquitoes will diminish, and in turn the infective humans will also decrease. But once the treatment is concluded, the basic reproduction number will return to levels above one, and due to the global stability of the endemic equilibrium, the infectious populations will increase to the endemic state again.

Consequently, decreasing the carrying capacity of the environment for mosquitoes by frequent reduction of the vector breeding sites, seems to be the more effective way to control the disease. Unfortunately, during the periods of low transmission, most people, including government agencies, lose interest in mosquito control and as a result mosquito densities are allowed to increase.

Acknowledgements

We are grateful to Professor Herbert W. Hethcote for his very valuable comments during the preparation of the manuscript. We also want to thank two anonymous referees for their careful reading that helped us to improve the paper.

Appendix A

In this appendix we shall give the definition of an additive compound matrix. A survey of properties of additive compound matrices together with their connections to differential equations may be found in Ref. [18].

We start recalling the definition of a kth exterior power or multiplicative compound of a matrix.

Definition A.1. Let A be a $n \times m$ matrix of real or complex numbers. Let $a_{i_1 \ldots i_k,\, j_1 \ldots j_k}$ be the minor of A determined by the rows $(i_1, \ldots, i_k)$ and the columns $(j_1, \ldots, j_k)$, $1 \leqslant i_1 < i_2 < \cdots < i_k \leqslant n$, $1 \leqslant j_1 < j_2 < \cdots < j_k \leqslant m$. The *kth multiplicative compound matrix* $A^{(k)}$ of A is the $\binom{n}{k} \times \binom{m}{k}$ matrix whose entries, written in lexicographic order are $a_{i_1,\ldots,i_k,\, j_1,\ldots j_k}$.

In particular, when A is a $n \times k$ matrix with columns $a_1, a_2, \ldots, a_k$, $A^{(k)}$ is the exterior product $a_1 \wedge a_2 \wedge \cdots \wedge a_k$.

In the case $m = n$, the additive compound matrices are defined in the following way.

Definition A.2. Let A be a $n \times n$ matrix. The kth *additive compound* $A^{[k]}$ of A is the $\binom{n}{k} \times \binom{n}{k}$ matrix given by

$$A^{[k]} = D(I + hA)^{(k)}|_{h=0}, \tag{A.1}$$

where D denotes the derivative with respect to h.

If $B = A^{[k]}$, it can be deduced from Eq. (A.1) the following formula for $b_{i,j}$. For any integer $i = 1, \ldots, \binom{n}{k}$, let $(i) = (i_1, i_2, \ldots, i_k)$ be the ith member in the lexicographic ordering of all k-tuples of integers such that $1 \leqslant i_1 < i_2 < \cdots < i_k \leqslant n$. Then

$$b_{i,j} = \begin{cases} a_{i_1,i_1} + \cdots + a_{i_k,i_k} & \text{if } (i) = (j), \\ (-1)^{r+s} a_{i_s,j_r} & \text{if exactly one entry } i_s \text{ in } (i) \text{ does not occur in } (j) \text{ and } j_r \text{ does not occur in } (i), \\ 0 & \text{if } (i) \text{ differs from } (j) \text{ in two or more entries.} \end{cases}$$

In the extreme cases when $k = 1$ and $k = n$, we have $A^{[1]} = A$ and $A^{[n]} = \operatorname{tr}(A)$.

For $n = 3$ the matrices $A^{[k]}$ are as follows:

$$A^{[1]} = A, \quad A^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}, \quad A^{[3]} = a_{11} + a_{22} + a_{33}.$$

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