Models for Dengue Transmission and Control

F. Sánchez, M. Engman, L. Harrington, and C. Castillo-Chávez

Abstract. The transmission dynamics of dengue, a mosquito-transmitted disease is studied via a model that includes a simplified view of the life-history of the vector. It is shown that selective biological vector control measures can support multiple vector densities. The role of seasonality in the implementation of transmission rates is explored. The implications of model results to dengue dynamics and its control are discussed.

1. Introduction

Dengue is a mosquito-transmitted disease that is endemic in Asia, Africa, Latin America and the tropics. Four recognized dengue strains coexist in various parts of the world [14]. These serotypes are antigenically distinct, that is, infection with one type does not provide immunity to infection to other strains. However, there is some evidence that sequential infections may “cross-react” producing (on relatively rare occasions) a severe (even fatal) form of the symptoms called Dengue Haemorrhagic Fever (DHF). The Centers for Disease Control and Prevention (CDC) [28] report between 50 to 100 million suspected cases of dengue fever (the symptoms associated with dengue infection) per year around the world (a rate that may substantially underestimate dengue’s incidence). Previous modeling work on dengue [7, 9, 10, 11, 12] has not included the life history of the vector. Here, we incorporate in a simplified manner, the egg/larval stage of the mosquito. Since there is no “real” evidence of vertical transmission, it is assumed that eggs/larvae do not carry dengue. Also egg/larvae populations are assumed to be functions of vector densities. The possibility of multiple levels of vector densities as a result of the selective application of control measures (non-uniform spraying of areas where vector densities are high) is illustrated. In nature, vector densities are in part, a function of the distribution of breeding sites, the frequency and levels of precipitation, and temperature. Theoretical work that incorporates and tests the importance of these factors are still needed.

The article is organized as follows: Section 2 briefly reviews the life-history and ecology of the vector and the epidemiology of dengue; Section 3 introduces a simple model for the transmission dynamics of dengue that includes two life-history

2000 Mathematics Subject Classification. Primary 54C40, 14E20; Secondary 46E25, 20C20. Key words and phrases. Vector-transmitted diseases, epidemiology, dengue fever, differential equations, biological control.

The second author was supported in part by NSF Grant MIE (Models Institute of Excellence).
stages of the vector; Section 4 studies the impact of selective control measures and seasonality; Section 5 summarizes our conclusions and outlines future directions.

2. Ecology of *Aedes aegypti* and the Epidemiology of Dengue

Dengue is an arbovirus within the family flaviridae. At least two species of mosquitoes have been identified as vectors for the dengue virus: *Aedes aegypti* and *Aedes albopictus*. *Aedes aegypti*, the main vector, has a life cycle that consists of four stages and can lay 100–200 eggs at once (about 1,400 eggs over her lifetime). Eggs are laid in natural and artificial containers just above the water line (breeding sites). Eggs can survive in the dry state for six months to one year. Females fed approximately every two to three days and develop a batch of eggs several days after feeding depending on the ambient temperature. Eggs hatch after flooding with water releasing larvae. Seven to ten day old larva change to pupa and eventually surviving pupae reach the adult stage. A few days after adult emergence, females seek a blood meal. Males can feed on plants and flowers while females primarily feed on vertebrate blood. Research has shown that *Ae. aegypti* prefers to feed on humans [32, 33]. The adult stage may last from fifteen and twenty days. *Aedes aegypti* mosquitoes bite during the day and often approach the host from behind feeding on the feet or back. The vector lives wherever water collects albeit *Ae. aegypti* does not typically breed in contaminated waters [14]. *Ae. aegypti* breeding sites are mostly generated by human activity (provisional water storage containers) and rainfall.

The “first” recorded dengue outbreaks may have taken place between 1779 – 1780. It was a “global” outbreak since epizootic events were reported in Asia, Africa and North America “simultaneously”. The periods between recorded epidemic outbreaks used to be large (10 to 40 years) [14]. Today, cases of dengue fever are continuously reported. Dengue may afflict 100 million people annually. The exact number of cases is not known because a large proportion of cases are asymptomatic [18]. Underreporting is also a problem.

Four distinct serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) coexist in the world [11]. Individuals, upon recovery, acquire permanent immunity to each strain that infects them, but, there is no evidence of cross-immunity (reduced susceptibility to new strains conferred by past history of infections). Dengue has its biggest impact in urban settings [17]. Tropical and subtropical regions experiencing high levels of urbanization and increased deforestation have impacted the vectors habitat. The dynamics of breeding sites seems to be driven by urban dynamics. Vectors have adapted quite well and thrive in cities.

Dengue transmission occurs when an infectious mosquito bites an un-infected human. Once the virus is in the mosquito it replicates (a period of 8 to 12 days [14]). Infected mosquitoes transmit the virus by biting “unsuspecting” hosts. The virus may produce symptoms that can last up to 14 days on infected hosts. There is no vaccine or cure.

The most severe cases of dengue experience Dengue Haemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS).

Several factors have contributed to the global emergence of DHF including the absence of effective and sustained vector control measures; uncontrolled urbanization; and, population growth [17]. The simulations carried out in subsequent sections used parameter estimates found in the literature (see [10], [12], [14], [16]).
3. The Model

Several models of dengue have been developed in the past [9, 10, 11, 12], with most of them in the tradition of Ross [21]. Knowledge of life history of the vector (closely connected to the distribution, size and dynamics of breeding sites) is the key to the development of potentially effective control measures. Yet, the vector life history has rarely been included by theoreticians. A model that includes a detailed account of the life history of the vector may not be amenable to analysis. Instead, the classical Ross model is expanded to include a simplified version of the vector’s life history. The impact of selective vector control measures on dengue dynamics is explored. The model assumes that (female) vectors may be found in three states: the egg/larvae state, E; the uninfected vector state, V; and the infected vector state, I. The host (humans) disease dynamics are modeled via an SIR model (see [2] and [3]), where \( S(t) \) denotes the susceptible human population at time \( t \); \( I(t) \) the infected (assumed infectious) host population at time \( t \); and \( R(t) \) the recovered individuals (with assumed permanent immunity) at time \( t \). The model is given by following non-linear system:

\[
\begin{align*}
\frac{dE}{dt} &= f(E) - (\mu_E + \delta)E = f_1(E, V, S, R, J, I) \\
\frac{dV}{dt} &= \delta E - \mu_v V - \alpha V \frac{E}{L} = f_2(E, V, S, R, J, I) \\
\frac{dS}{dt} &= \mu N - \beta S \frac{I}{L} - \mu S = f_3(E, V, S, R, J, I) \\
\frac{dR}{dt} &= \gamma I - \mu R = f_4(E, V, S, R, J, I) \\
\frac{dJ}{dt} &= \alpha V \frac{E}{L} - \mu_m J = f_5(E, V, S, R, J, I) \\
\frac{dI}{dt} &= \beta S \frac{I}{L} - (\mu + \gamma) I = f_6(E, V, S, R, J, I)
\end{align*}
\]

where \( L = V + J \) and \( N = S + I + R \) denote the total adult vector and host populations respectively. \( N \) is assumed to be constant, a valid assumption when the time scale of interest is short in relation to the life-span of the host but \( L \) is not assumed to be constant. In fact, the net egg/larvae recruitment function \( f(L) \) is of Kolmogorov type, that is \( f(L) = L g(L) \) with \( g : \mathbb{R}^+ \rightarrow \mathbb{R}^+ \) a differentiable function such that \( g(0) > 0 \), and \( g(\infty) = 0 \). Dengue is not assumed to increase vector death rates.

Selective control measures (Section 4) are modeled by replacing the more general function \( g \) with \( g_c(L) \equiv g(L) - c(L) \), where \( g_c(L) \) represents a (strictly decreasing) per-capita mosquito fertility rate and \( c(L) \) the per-capita vector death rate that results from selective control efforts. Control efforts are modeled in a phenomenological way via the function \( c(L) \) which captures, in a rough manner, the impact of measures geared towards the elimination of the adult vector population. These measures may include selective spraying of areas where vector density is high. Furthermore, it is assumed that such measures negatively impact the net egg/larvae recruitment functions. Consequently, \( g_c^{-1}(y) \) denotes the, possibly multiple valued, inverse image of \( y \) under control regime \( c \), that is, shifting vector densities via control measures is a possibility. The parameters used in the model are defined in Table 1. Naturally, a reasonable model that includes the life-history of the vector must be able to support a critical mass of vectors. Enough hosts must also be available for dengue to prosper. Since our focus is primarily on the study of dengue in endemic regions with characteristics similar to those found in Puerto Rico, \( N \) is large “enough”. Conditions that guarantee the establishment of a “critical” mass of vectors are tied into the nature of \( f(L) \). Certainly, such a critical mass exists in places where dengue is endemic (like the Caribbean). The existence of a
Table 1. Parameter List

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
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<tbody>
<tr>
<td>$\delta$</td>
<td>per-capita rate at which viable eggs become adult vectors</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>contact rate (human-vector)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>contact rate (vector-human)</td>
</tr>
<tr>
<td>$\mu_e$</td>
<td>per-capita egg mortality rate</td>
</tr>
<tr>
<td>$\mu_m$</td>
<td>per-capita adult mosquito mortality rate</td>
</tr>
<tr>
<td>$\mu$</td>
<td>per-capita natural human mortality rate</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>per-capita recovery rate</td>
</tr>
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The minimal critical mass of vectors depends on the demographic threshold $R_d(0)$ (see below). $R_d(s)$ will govern the existence and stability of vector densities at level $s$ where $s \geq 0$.

In the absence of control measures ($g_c = g_0$) only two vector densities may be possible $L_\infty \equiv 0$ and $L_\infty > 0$. $R_d(s)$, the vector demographic number at vector density $L_\infty = s$, is given by

$$R_d(s) = \frac{f'(s)}{\phi} \text{ where } \phi = \frac{(\mu_e + \delta)\mu_m}{\delta}.$$

Where $f$ is the net egg/larvae recruitment function described above. $R_d(0)$ denotes the invasion demographic reproductive number. $R_d(0) > 1$ corresponds to the situation where a vector population can successfully invade a habitat. In fact, $R_d(0) > 1$ guarantees the existence of a critical mass of vectors (positive and stable). It is assumed throughout that $R_d(0)$ is always greater than one. That is, the possibility of vector extinction is excluded in this study.

The issue of whether or not a disease can invade a host population and remain endemic requires the introduction of a second threshold. Disease invasion and persistence are typically intimately connected to the disease’s basic reproductive number $R_0$. This number or “ratio” is a dimensionless quantity that gives the number of secondary infections generated by a “typical” infectious individual (vector or host) in populations at demographic equilibrium. $R_0$ involves the parameters that drive the “invasion” process. Hence, its study (sensitivity and uncertainty) helps identify key parameters and evaluate the relative effectiveness of various control measures. $R_0$ can be computed in various ways. Here, we use the next generation operator method [5], [8], and obtain that

$$R_0 = \sqrt{\frac{\alpha \beta}{\mu_m (\mu + \gamma)}}.$$

It is shown ($R_d(0) > 1$) that the disease’s basic reproductive number $R_0$ is the key. The condition $R_0 < 1$ is, at least, a necessary condition for a globally asymptotically stable disease free state. On the other hand, $R_0 > 1$ allows the possibility of multiple stable endemic states.

Control is modeled, in the endemic case, as an adult (vectors) harvesting process with a maximal harvesting rate (effort) $\epsilon$. Although, the economics of control are not included, it is implicitly assumed that the cost of increasing $\epsilon$, that is, the cost of eliminating a larger number of adults per unit of time, may grow fast as $\epsilon$ increases. Limitations on our ability to implement control efforts (measured by $\epsilon$)
may have a severe impact the vector’s dynamics, a point that will be illustrated below.

4. Disease Dynamics and Control

In this section it is assumed that the vector has become established, that is, that $R_d(0) > 1$. We also assumed that we have plenty of hosts, $N >> 0$. The infection-free equilibrium is

$$E_\infty = \frac{\mu_m}{\delta} g_c^{-1}(\phi), \quad L_\infty = V_\infty = g_c^{-1}(\phi), \quad S_\infty = N, \quad R_\infty = J_\infty = I_\infty = 0.$$  \hfill (4)

The “mosquito-free” and “disease-free” state $(0, 0, N, 0, 0, 0)$, is an essential singular point of the system is therefore not considered\(^1\) (see [1]). Conditions for the existence of positive (disease present) equilibria are immediate from the formulae:

$$
\begin{align*}
E_\infty &= \frac{\mu_m}{\delta} g_c^{-1}(\phi), \\
V_\infty &= \frac{\mu + \beta}{\mu R_0 + \beta} g_c^{-1}(\phi), \\
S_\infty &= \frac{N(\beta + \mu R_0)}{\alpha(\mu + \beta)}, \\
R_\infty &= \frac{\mu R_0^2 + \beta}{\mu R_0^2 + \beta} g_c^{-1}(\phi), \\
J_\infty &= \frac{\mu N \mu m (R_0^2 - 1)}{\alpha(\mu + \beta)}, \\
I_\infty &= \frac{\mu N \mu m (R_0^2 - 1)}{\alpha(\mu + \beta)}.
\end{align*}
$$

Clearly, positive (endemic) equilibria are possible whenever $R_0 > 1$. The role of $R_0$ is fundamental in both the free and “controlled” host-vector system as the following series of results show. The proofs are in the appendix.

**RESULT 4.1.** Consider the system (1) with $f(L) = L g_c(L)$ where $g_c$, is differentiable. Assume $\{g_c^{-1}(\phi)\}$ is non-empty, and let $n = \text{card}\{g_c^{-1}(\phi)\}$ (i.e. the number of positive vector densities) then

a. If $R_0 \leq 1$ then the system has $n$ positive disease-free equilibria (at various vector densities) and no endemic equilibria.

b. If $R_0 > 1$ then the system has $n$ positive disease-free equilibria and $n$ endemic equilibria (at distinct vector densities).

In other words, control measures may support various stable vector densities (a function of the effort and related parameters). Result 4.1 suggests that as long as there is a critical stable mass of vectors (and a large host population) the disease will survive if $R_0 > 1$. Specific conditions are set in Result 4.2 and 4.3 below.

**RESULT 4.2.** Let $\vec{x}_\infty(DF) = (E_\infty, V_\infty, N, 0, 0, 0)$ be a disease free equilibrium of (1) then $\vec{x}_\infty(DF)$ is locally asymptotically stable if $R_0 < 1$ and $R_d(g_c^{-1}(\phi)) < 1$. If either of $R_0$ or $R_d(g_c^{-1}(\phi))$ are greater than 1 then the corresponding equilibrium is unstable.

**RESULT 4.3.** Let $\vec{x}_\infty = (E_\infty, V_\infty, S_\infty, R_\infty, J_\infty, I_\infty)$ be an endemic equilibrium of (1) then $V_\infty + J_\infty \in \{g_c^{-1}(\phi)\}$, $R_0 > 1$ and $\vec{x}_\infty$ is locally asymptotically stable if $R_d(g_c^{-1}(\phi)) < 1$ and unstable if $R_d(g_c^{-1}(\phi)) > 1$. Note that $R_d(g_c^{-1}(\phi)) < 1$ simply states that we have a stable vector population (an attractor).

\(^1\)However, the use of DDT was probably responsible for the disappearance, over many decades, of dengue in Costa Rica (L. Harrington; personal communication)
The condition in Result 4.4 (below) follows from the observation that since $f(L) = L g_c(L)$ then
\begin{equation}
 f'(g_c^{-1}(\phi)) = \phi + g_c^{-1}(\phi)g'_c(g_c^{-1}(\phi)).
\end{equation}
Dividing by $\frac{1}{\phi}$ gives
\begin{equation}
 \mathcal{R}_d(g_c^{-1}(\phi)) = 1 + \frac{1}{\phi} g_c^{-1}(\phi)g'_c(g_c^{-1}(\phi)).
\end{equation}
Hence, $\mathcal{R}_d(g_c^{-1}(\phi)) < 1$ if and only if $g'_c(g_c^{-1}(\phi)) < 0$, that is:

**Result 4.4.** Let $\bar{x}_\infty = (E_\infty, V_\infty, S_\infty, R_\infty, J_\infty, I_\infty)$ be a (positive disease free or endemic) equilibrium of (1) then $\mathcal{R}_d(g_c^{-1}(\phi)) < 1$ if and only if $g'_c(V_\infty + J_\infty) < 0$.

In the absence of control measures the system behaves as expected, that is, if $\mathcal{R}_d(0) > 1$ and $\mathcal{R}_0 < 1$ then the unique positive disease-free equilibrium, $\bar{x}_\infty$, given by (4), is globally asymptotically stable in the domain $\Omega = \{(E, V, S, R, J, I) | E > 0, V > 0, S + I + R = N\} \subset \mathbb{R}_+^6$.

We note that the same result can be obtained under the weaker hypotheses: $\text{card}(g_c^{-1}(\phi)) = 1$ and $\mathcal{R}_d(g_c^{-1}(\phi)) < 1$.

Vector control is modeled as adult “harvesting” on the “recruitment” function $f(L)$. In fact, if $f(L)$ is replaced by $L(g(L) - c(L))$ then the choice of $c(L)$ can impact the qualitative dynamics of the system. The following result outlines some possibilities.

**Result 4.6.** Suppose $\mathcal{R}_d(0) > 1$, and that $f(L) = L g_c(L)$. Assume that $g_c(L) = \phi$ for an increasing, finite sequence $\{V_\infty^1, V_\infty^2, \cdots, V_\infty^{2n+1}\}$ where $g'_c(V_\infty^{2j+1}) < 0$ for all $0 \leq j \leq n$ and $g'_c(V_\infty^{2j+1}) > 0$ for all $1 \leq j \leq n$. If $\mathcal{R}_0 < 1$, then there are $n+1$ locally asymptotically stable positive disease free equilibria for the system (1). These equilibria are given by $\bar{x}_\infty^{2j+1} = (\frac{e}{a} V_\infty^{2j+1}, V_\infty^{2j+1}, N, 0, 0, 0)$, $0 \leq j \leq n$ and the basins of attraction for these equilibria are given by $\Omega_{2j+1} = \{(E, V, S, R, J, I) | E > 0, V > 0, S + I + R = N, V_\infty^{2j+1} < V + J < V_\infty^{2j+2}\}$, for each $0 \leq j \leq n$, where, for convenience $V_\infty^0$ is defined to be 0 and $V_\infty^{2n+2} = \infty$.

**Proof.** Result 4.6 implies that the condition $g'_c(V_\infty^{2j+1}) < 0$ is equivalent to the condition $\mathcal{R}_d(g_c^{-1}(\phi)) < 1$. The proof follows by observing that the conditions in the comment after Result 4.5 hold in each set $\Omega_{2j+1}$. That is, in sets that exclude unstable equilibria ($V_\infty^j$ and $V_\infty^{2j+2}$).

Similar results have been obtained before. In [23], Wu and Feng constructed models for Schistosomiasis that support alternating stable and unstable equilibria and computed their corresponding basins of attraction.

In order to provide an explicit illustration to the above results, we take $g(L) = \rho e^{-\omega L}$ and $c(L) = \frac{\epsilon L}{a^2 + L^2}$, that is,
\begin{equation}
 f(L) = \rho L e^{-\omega L} - \frac{\epsilon L^2}{a^2 + L^2}
\end{equation}
where $\epsilon$ is interpreted as the maximal “harvesting” rate (value of $L_c(L)$ as $L \to \infty$) $a^2$ is a parameter associated with the time needed to handle of or search for adult
vectors, and ρ is the maximal per-capita vector egg-reproduction rate. Equilibria are solutions of
\[ \rho e^{-\omega L} - \frac{\epsilon L}{\alpha^2 + L^2} = \phi, \]
that is, this explicit "φ" corresponds to the generic φ in (5). There are at most three positive equilibria. Figure 1 illustrates the case when there are three (two stable and one unstable). The incorporation of seasonality effects on the transmission dynamics of dengue is important [30], [31]. Seasonality may directly impact host to vector transmission rates (β); the per capita fertility rate (ρ) and possibly the maximal “control” rate (ε) (possibly higher when vector densities are higher). Here, we briefly illustrate its potential role on each of these parameters via simulations. Three sets of independent simulations are conducted. The artificial introduction of seasonality effects in the equation is as follows: ε is replaced by \( \bar{\epsilon} = \epsilon_0(\epsilon_1 + \sin(\frac{2\pi t}{180})) \), β by \( \bar{\beta} = \beta_0(\beta_1 + \sin(\frac{2\pi t}{180})) \) and α is replaced by \( \bar{\alpha} = \alpha_0(\alpha_1 + \sin(\frac{2\pi t}{180})) \). These selections are not driven by particular explicit scenarios or systematically explored. Our objective here is to illustrate the potential role of fluctuations on key parameters. Seasonal variations in ε may derive from the observation that (vectors’) “harvesting” efforts may not be equal over the entire year. They may be higher during the rainy (or dry) season. Here, ε is varied independently while all the other parameters remain fixed. Simulations that include simultaneous fluctuations on both transmission rates, α and β, are also considered.

Figures 2c, 2d illustrate effects of seasonality on infected host class levels due to regular fluctuations on the intensity of control efforts (ε). The vector population exhibits oscillatory behavior with a period of six months (same as that of ε). Figures 2c and 2d illustrate the impact of periodic harvesting effects. The dynamics become regular (oscillatory) after the transients are “gone” (1000 days). Seasonally-dependent harvesting via the control parameter ε forces the vector population to jump from the low demographic equilibrium \( V_{\infty}^{\text{low}} = 0.4099141 \) to the high \( V_{\infty}^{\text{high}} = 10.99821 \) where it remains afterwards. In the absence of seasonality, vector levels remain at the lower equilibria. Although vector levels (infected and uninfected) shift the corresponding host-infection levels remain unchanged. That is, the host endemic levels found in Figures 2c and 2d correspond to both vector levels as illustrated in Figures 3c and 3d. Moderate, independent or simultaneous changes in transmission rates (α and β) do not drive shifts in vector population levels (from either the low demographic equilibrium \( E_0^{\text{low}} = 0.230129, V_0^{\text{low}} = 0.4099141 \) and \( J_0^{\text{low}} = 0.004318148 \)) to the high \( E_0^{\text{high}} = 5.527807, V_0^{\text{high}} = 10.99821, J_0^{\text{high}} = 0.3055878 \), or vice-versa. In Figure 3 there are two sets of simulations a) and b) illustrate that fluctuations on the transmission rates (α and β) do not cause the vector equilibria to “jump” from the low demographic equilibria to the high demographic equilibria. In c) and d) the control parameter (ε) is varied and results in the vector density to move from the low demographic equilibria \( E_0^{\text{low}} = 0.230129, V_0^{\text{low}} = 0.4099141 \) and \( J_0^{\text{low}} = 0.004318148 \) to the high
Figure 2. Moderate seasonal effects on host and vector transmission rates \((\alpha, \beta, \text{and } \epsilon)\). The parameter values are: \(\mu = 0.00004\), \(\mu_c = 0.003\), \(\mu_m = 0.03\), \(\delta = 0.09\), \(\gamma = 0.14\), \(\rho = 15\), \(\omega = 0.2\), \(\epsilon = 15\), \(\alpha = 0.5\), \(\beta = 0.5\), \(a = 0.5\) Initial conditions: \(S_0 = 9999\), \(I_0 = 1, R_0 = 0\) (host population). In this case we show the infected host class \((I(t))\) when seasonal effects take place in the transmission rates \((\alpha \text{ and } \beta)\) and control measures \((\epsilon)\). For a) and b) \(\alpha \text{ and } \beta\) are varied simultaneously; a) \(\tilde{\alpha} = 0.5 + 0.4 \sin\left(\frac{2\pi t}{180}\right)\) and \(\tilde{\beta} = 0.5 + 0.4 \sin\left(\frac{2\pi t}{180}\right)\), b) \(\tilde{\alpha} = 0.8 + 0.4 \sin\left(\frac{2\pi t}{180}\right)\) and \(\tilde{\beta} = 0.8 + 0.4 \sin\left(\frac{2\pi t}{180}\right)\). For c) and d) \(\epsilon\) is varied; c) \(\tilde{\epsilon} = 15 + 5 \sin\left(\frac{2\pi t}{180}\right)\) and d) \(\tilde{\epsilon} = 15 + 10 \sin\left(\frac{2\pi t}{180}\right)\). For a discussion see the text.

Figure 3. Moderate seasonal effects on host and vector transmission rates \((\alpha, \beta, \text{and } \epsilon)\). The parameter values are: \(\mu = 0.00004\), \(\mu_c = 0.003\), \(\mu_m = 0.03\), \(\delta = 0.09\), \(\gamma = 0.14\), \(\rho = 15\), \(\omega = 0.2\), \(\epsilon = 15\), \(\alpha = 0.5\), \(\beta = 0.5\), \(a = 0.5\) Initial conditions: \(S_0 = 9999\), \(I_0 = 1, R_0 = 0\) (host population). In this case we show the vector population \((V(t))\) when seasonal effects take place in the transmission rates \((\alpha \text{ and } \beta)\) and control measures \((\epsilon)\). For a) and b) \(\alpha \text{ and } \beta\) are varied simultaneously; a) \(\tilde{\alpha} = 0.5 + 0.4 \sin\left(\frac{2\pi t}{180}\right)\) and \(\tilde{\beta} = 0.5 + 0.4 \sin\left(\frac{2\pi t}{180}\right)\), b) \(\tilde{\alpha} = 0.8 + 0.4 \sin\left(\frac{2\pi t}{180}\right)\) and \(\tilde{\beta} = 0.8 + 0.4 \sin\left(\frac{2\pi t}{180}\right)\). For c) and d) \(\epsilon\) is varied; c) \(\tilde{\epsilon} = 15 + 5 \sin\left(\frac{2\pi t}{180}\right)\) and d) \(\tilde{\epsilon} = 15 + 10 \sin\left(\frac{2\pi t}{180}\right)\). The vector begins at the low demographic equilibrium \(E_{low}^0 = 0.230129, V_{low}^0 = 0.4099141\) and \(J_{low}^0 = 0.004318148\) and then jumps to the high equilibrium \(E_{high}^0 = 5.527807, V_{high}^0 = 10.99821, J_{high}^0 = 0.3055878\). In the absence of seasonality \(\epsilon = 15\) there is no jump. For a discussion see the text.

demographic equilibria \((E_{high}^0 = 5.527807, V_{high}^0 = 10.99821, J_{high}^0 = 0.3055878)\) for the given set of parameters.

Vector density is started at the low demographic equilibria for all simulations with seasonality to illustrate the effect of the parameters on the vector density.

It is important to re-state that vector density levels may shift from low to high levels and vice versa from the impact of strong fluctuations in control efforts \((\epsilon)\), however, simulations suggest that either level of vector density (high or low) leads to approximately the same level of dengue prevalence in human infections (see Figure 2).
5. Conclusions

A model for the transmission dynamics of dengue that includes the egg/larva stage of the vector and control efforts directed towards the adult vector population is considered. The model couples, in a simple way, a modified version of the classical SIR model for the host with a vector model that includes vector life stages (from egg to adult). Sharp conditions for local stability of disease-free and endemic equilibria are computed in the absence and presence of control measures. It is shown that, under the right conditions, the disease-free equilibrium is globally stable provided that $R_0 < 1$ and $R_d(0) > 1$ (that is, when a critical mass of vectors exists). Selective control measures geared towards the “elimination” of the adult population ($R_0 > 1$) can give rise to a landscape that supports multiple stable vector levels. In fact, under some control scenarios, it is possible to establish the local stability of endemic states having $R_0 > 1$ and $R_d(g_c^{-1}(\phi)) < 1$.

The possibility of “eliminating” a vector population over sustained periods of time, using drastic policies directed to the adult vectors, seems virtually impossible since reducing vector densities (even significantly) may not seriously impact host-dengue prevalence levels in humans (see example). Control methods that include “attacks” on additional vector-life stages must be implemented. Such efforts should include, for example, dramatic reductions on the numbers and sizes of breeding sites. Currently, in the tradition of Ross, most theoretical work has focused on the use of control efforts aimed at adult vector populations. This is unfortunate. In fact, Ross was clearly aware of the importance of incorporating our knowledge of the ecology and life history of vectors in the development of disease control policies. Ross did not pursue detailed mathematical studies of vector control strategies because he lacked access to modern computational tools. Frameworks that include vector’s life-history dynamics are needed to test control measures that focus on “vulnerabilities” in non-adult vector populations. The introduction of seasonal variation in control measures in a rather artificial setting has helped (we hope) illustrate the view that low vector densities lead to equivalent disease host prevalence levels than large vector densities. Methods that focus only on controlling adult mosquito populations are simply inadequate. Those that focus (simultaneously) on vector’s life-history stages (integrated management approaches) need to be developed, tested and implemented.

6. Acknowledgments

We would like to thank Karl Hader, Juan Aparicio and Gus Engman for their advice and support during the preparation of this paper. All three authors acknowledge the support of the Mathematical and Theoretical Biology Institute, Cornell University. The first author acknowledges the support of the Alfred P. Sloan Foundation. The second author acknowledges the support of the NSF grant Model Institute of Excellence, Universidad Metropolitana.

7. Appendix

7.1. Dengue situation in Singapore. Included is a time series plot with confirmed dengue fever (DF+DHF) cases from 2001 – 2005 (up to date). Note that the number of cases appears to have a seasonal pattern probably climate related, wet and dry season and probably more important temperature since vector feeding
habits are temperature dependent. However, the number of cases has gradually increased from 2001-2003 and there was a big change starting in 2004 and continuing in 2005 up week 42 (16 Oct. - 22 Oct.). Singapore has a tremendous public health system (http://www.moh.gov.sg) and their control efforts seem (from the published data) to have had little to no effect on the number of cumulative cases of dengue over the past four years. Here are some of their preventive measures:

**Figure 4.** Time series of confirmed dengue cases in Singapore from 2001-present.

- Intensified control actions are implemented in these cluster areas
- Surveillance control programs
  - Vector control
  - Larval source reduction (search-and-destroy)
- Health education
  - House to house visits by health officers
  - Dengue prevention Volunteer Groups (National Environment Agency)
- Law enforcement
  - Large fines for repeat offenders

### 7.2. Proof of Result 4.2.

**RESULT 4.2.** Let \( \bar{x}_\infty(DF) = (E_\infty, V_\infty, N, 0, 0, 0) \) be a positive disease free equilibrium of (1) then \( \bar{x}_\infty(DF) \) is locally asymptotically stable if \( R_0 < 1 \) and \( R_d(g_c^{-1}(\phi)) < 1 \). If one of \( R_0 \) or \( R_d(g_c^{-1}(\phi)) \) is greater than one then the equilibrium is unstable.

**PROOF.** The characteristic polynomial for the Jacobian at \( \bar{x}_\infty(DF) \) contains the quadratic factor
\[
\lambda^2 + (\mu_m + \mu_e + \delta)\lambda + \left(\mu_m(\mu_e + \delta) - \delta f'(g_c^{-1}(\phi))\right)
\]
so that the negativity of the real parts of its roots requires, that
\[
(\mu_m(\mu_e + \delta) - \delta f'(g_c^{-1}(\phi))) > 0,
\]
but this is equivalent, by definition, to \( R_d(g_c^{-1}(\phi)) < 1 \). The characteristic polynomial at the disease-free equilibrium contains a factor
\[
\lambda^2 + (\mu + \mu_m + \gamma)\lambda + [\mu_m(\mu + \gamma) - \alpha\beta],
\]
so that these roots have negative real part if and only if \( \mu_m(\mu + \gamma) - \alpha\beta > 0 \), which is equivalent to \( R_0 < 1 \).

### 7.3. Proof of Result 4.3.

**RESULT 4.3.** Let \( \bar{x}_\infty = (E_\infty, V_\infty, S_\infty, R_\infty, J_\infty, I_\infty) \) be an endemic equilibrium of (1) then \( V_\infty + J_\infty \in \{g_c^{-1}(\phi)\} \), \( R_0 > 1 \), and \( \bar{x}_\infty \) is locally asymptotically stable if \( R_d(g_c^{-1}(\phi)) < 1 \) and unstable if \( R_d(g_c^{-1}(\phi)) > 1 \).
\textbf{Proof.} $V_\infty + J_\infty \in \{ g^{-1}_c(\phi) \}$ follows immediately from the sum of equations $V_\infty$ and $J_\infty$. From $I_\infty$ we see that endemicity requires $R_0 > 1$. Now, the roots of the quadratic factor of equation all have negative real part if and only if

$$(\mu_m(\mu_e + \delta) - \delta f'(g_c^{-1}(\phi))) > 0$$

but, by definition, this is equivalent to $R_d(g_c^{-1}(\phi)) < 1$. It remains only to verify that all the zeros of the cubic factor of,

\begin{equation}
\lambda^3 + \left[ (\mu + \gamma) + \frac{\mu_m(\mu R_0^2 + \beta)}{\beta + \mu} + \frac{\mu(\mu + \beta)R_0^2}{\beta + \mu R_0^2} \right] \lambda^2
+ \left[ \mu_mR_0^2(\mu + \gamma) \left( \frac{\mu_m(\mu R_0^2 - 1)}{\mu + \beta} + \frac{\mu(\mu + \beta)R_0^2}{\beta + \mu R_0^2} \right) \right] \lambda + \mu(\mu + \gamma)\mu_m(R_0^2 - 1),
\end{equation}

have, under these conditions, negative real parts. For this we use the Routh-Hurwitz criteria. With $a_1, a_2, a_3$ defined as the coefficients of the second, first and zeroth degree terms respectively, we clearly have $a_1 > 0$, and $a_3 > 0$ when $R_0 > 1$. We now multiply the first terms of $a_1$ and $a_2$ and observe that the products of all the other terms are positive since $R_0 > 1$. Therefore

$$a_1a_2 - a_3 = \mu_m(\mu + \gamma)R_0^2 + \text{positive terms} - \mu_m(\mu + \gamma)(R_0^2 - 1)$$

and hence $a_1a_2 - a_3 > 0$. So the Routh-Hurwitz criteria are satisfied and the result is proved. \hfill \square

7.4. \textbf{Proof of Result 4.5.}

\textbf{Result 4.5.} Assume that $c(L) = 0$, that is, $f(L) = Lg_0(L)$ where $g_0(L)$ is strictly decreasing. If $R_d(0) > 1$ and $R_0 < 1$ then the unique positive disease-free equilibrium, $\bar{x}_\infty$, given by (4), is globally asymptotically stable in the domain $\Omega = \{ (E, V, S, R, J, I) | E > 0, V > 0, S + I + R = N \} \subset \mathbb{R}_+^6$.

\textbf{Proof.} The condition $R_d(0) > 1$ together with the fact that $g_0(L)$ is strictly decreasing implies $g_0(L) = \phi$ has a unique positive solution proving the existence and, in this case, uniqueness of the equilibrium.

Now, let $(E(t), V(t), S(t), R(t), J(t), I(t))$ be any solution of the system (1) with initial condition $(E_0, V_0, S_0, R_0, J_0, I_0) \in \Omega$. The sum of the differential equations $V'$ and $J'$ together with $E'$ gives the reduced, two dimensional system in $E$ and $L = V + J$

\begin{align*}
\frac{dE}{dt} &= f(L) - (\mu_e + \delta)E = F(E, L) \\
\frac{dL}{dt} &= \delta E - \mu_m L = G(E, L)
\end{align*}

on $\mathbb{R}_+^2$.

Both $(0, 0)$ and $(E_\infty, L_\infty) = \left( \frac{\mu_m}{\delta} g_0^{-1}(\phi), g_0^{-1}(\phi) \right)$ are equilibria of (9), (10), but a short calculation shows that the condition $R_d(0) > 1$ implies that $(0, 0)$ is a saddle point whose stable manifold does not intersect $\mathbb{R}_+^2 \setminus \{ (0, 0) \}$. It is also easy to see that $\mathbb{R}_+^2 \setminus \{ (0, 0) \}$ is positively invariant. As a result, no positive semi-orbits starting in $\mathbb{R}_+^2 \setminus \{ (0, 0) \}$ can converge to $(0, 0)$. On the other hand $(E_\infty, L_\infty)$ is locally asymptotically stable by Result 4.2 since $g_0$ strictly decreasing implies
\[ R_c(g_0^{-1}(\phi)) \leq 1. \] The divergence of the vector field defining the flow for (9), (10) is negative on all of \( \mathbb{R}^2_+. \) Hence, by Bendixson’s theorem there is no periodic orbit.

Integration of (9) yields
\[
E(t) \leq e^{-(\mu_e + \delta)t}E_0 + \frac{M}{(\mu_e + \delta)}(1 - e^{-(\mu_e + \delta)t})
\]
where \( M \) is the upper bound for \( f(L) \) and, therefore, \( E(t) \) is bounded for \( t > 0. \) A similar argument, together with the boundedness of \( E(t) \), proves that \( L(t) \) is bounded for \( t > 0. \)

The Poincaré-Bendixson theorem now applies as follows: Since \( (E(t), L(t)) \) is a bounded semi-orbit in a region which contains no periodic orbit and only one, asymptotically stable equilibrium, then the limit set of the semi-orbit must contain nothing but the equilibrium \( (E_\infty, L_\infty) \). In other words, all semi-orbits of the full system must enter the invariant set
\[
\{(E, V, S, R, J, I) \mid E > 0, V > 0, E = E_\infty, V + J = L_\infty, S + I + R = N\}.
\]

Now, we need only compute the limits for \( S, R, J \) and \( I \), and the limit of \( V \) will follow from the constraint \( V + J = L_\infty. \) To this end, we integrate equations \( J'(t) \) and \( I'(t) \) to obtain:
\[
J(t) = e^{-(\mu + \gamma)t}J_0 + \frac{\beta}{e^{(\mu + \gamma)t}} \int_0^t e^{(\mu + \gamma)\tau} \frac{S(\tau)J(\tau)}{L(\tau)} d\tau
\]
and
\[
I(t) = e^{-\mu_m t}I_0 + \frac{\alpha}{Ne^{\mu_m t}} \int_0^t e^{\mu_m \tau} I(\tau) V(\tau) d\tau.
\]

Clearly,
\[
S(t) \leq N, I(t) \leq N, \quad \frac{J(t)}{L(t)} \leq 1, \quad \text{and} \quad V(t) \leq L(t)
\]
and now that we have proved that \( L(t) \) approaches a finite limit, by (13), all of \( V(t), I(t), S(t), \) and \( J(t) \) must also be bounded. Computing \( \limsup \) of both (11) and (12) and using L'Hôpital’s rule, we have
\[
\limsup_{t \to \infty} I(t) \leq \frac{\beta}{\mu + \gamma} \limsup_{t \to \infty} \frac{J(t)}{L(t)} \limsup_{t \to \infty} S(t)
\]
and
\[
\limsup_{t \to \infty} J(t) \leq \frac{\alpha}{\mu_m N} \limsup_{t \to \infty} I(t) \limsup_{t \to \infty} V(t)
\]
We now claim that
\[
\limsup_{t \to \infty} J(t) = \lim_{t \to \infty} J(t) = 0.
\]
If \( \limsup_{t \to \infty} V(t) = 0 \) then by (15) \( \limsup_{t \to \infty} J(t) = \lim_{t \to \infty} J(t) = 0 \) and the claim is established. Now assume \( \limsup_{t \to \infty} V(t) > 0 \) and suppose \( \limsup_{t \to \infty} J(t) > 0 \) for the purpose of proving the claim by contradiction. Since \( \limsup_{t \to \infty} L(t) = \lim_{t \to \infty} L(t) = L_\infty > 0 \) exists
\[
\limsup_{t \to \infty} \frac{J(t)}{L(t)} = \frac{1}{L_\infty} \limsup_{t \to \infty} J(t)
\]
but also \( V(t) \leq L(t) \) for all \( t \) so that

\[
\limsup_{t \to \infty} \frac{1}{V(t)} \geq \frac{1}{L_{\infty}}.
\]

Combining (16) and (17) gives

\[
\limsup_{t \to \infty} \frac{J(t)}{L(t)} \leq \limsup_{t \to \infty} \frac{J(t)}{V(t)}
\]

Substituting (18) into (14) gives us

\[
\limsup_{t \to \infty} I(t) \leq \beta \limsup_{t \to \infty} J(t) \mu + \gamma \limsup_{t \to \infty} V(t) \limsup_{t \to \infty} S(t)
\]

And then, finally substituting (19) into (15) and using the definition for \( R_0 \) we arrive at

\[
\limsup_{t \to \infty} J(t) \leq \frac{R_0^2}{N} \limsup_{t \to \infty} J(t) \limsup_{t \to \infty} S(t)
\]

but since \( \limsup_{t \to \infty} S(t) \leq N \) this leads to the contradiction \( R_0 \geq 1 \). Hence we must have

\[
\lim_{t \to \infty} J(t) = 0.
\]

Now from (14) and (16) it follows that \( I(t) \to 0 \). Since \( L = V + J \) and \( J(t) \to 0 \) we must have \( V(t) \to L_{\infty} = g_0^{-1}(\phi) \). Finally, by integrating \( R(t) \) and using the fact that \( I(t) \to 0 \) we get \( R(t) \to 0 \) and since \( S + I + R = N \), \( S(t) \to N \).

This completes the proof. □

References


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