Journal of Biological Systems, Vol. 23, No. 4 (2015) 527–554

DOI: 10.1142/S0218339015500278

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ASSESSING THE EFFECTS OF TEMPERATURE AND DENGUE VIRUS LOAD ON DENGUE TRANSMISSION

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Received 8 December 2014
Revised 29 May 2015
Accepted 30 June 2015
Published 6 November 2015

In this study, we propose a model to assess the effect of temperature on the incidence of dengue fever. For this, we take into account the dependence of the entomological and epidemiological parameters of the transmitter vector *Aedes aegypti* with respect to the temperature. The model consists of an ODE system that describes the transmission between humans and mosquitoes considering the aquatic stage of the vector population. The qualitative analysis of the model is made in terms of the parameters R_M and R_0, which represent the basic offspring of mosquitoes, and the basic reproductive number of the disease, respectively. If $R_M < 1$ mosquito population extinguishes while for $R_M > 1$ it tends asymptotically to a nonzero equilibrium. Analogously, the disease transmission is eliminated if $R_0 < 1$, and it approaches an endemic equilibrium for $R_0 > 1$. Using entomological data of mosquitoes as well as experimental data of disease transmission we evaluate R_M and R_0 at different temperatures, obtaining that around 30°C both parameters attain their maximum. Sensitivity analysis reveals that infection rates and mosquito mortality are the parameters for which R_0 is more sensitive.

Keywords: Entomological Parameters; Extrinsic Incubation Period; Basic Offspring Number; Basic Reproductive Number.

1. Introduction

Dengue fever (DF) is an endemic disease in the tropical regions of the world caused by Dengue virus of the family Flaviviridae. Four serotypes have been found, denoted by DEN-I, DEN-II, DEN-III and DEN-IV, respectively. Infection by any dengue serotype produces permanent immunity to it, but apparently only temporary cross immunity to the other serotypes. The virus is transmitted to humans by the bite of *Aedes* mosquitoes, *Acdes aegypti* being the principal transmitter. The infection in the mosquito is for life.[1]

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Dengue virus causes a variety of febrile syndromes ranging from asymptomatic infection, to a self-limiting illness, and to severe dengue characterized by increased capillary permeability and shock.[2] The mild form of the disease, Classical DF, is generally observed in older children and adults. A small proportion of cases develops dengue hemorrhagic fever (DHF) and its associated dengue shock syndrome (DSS). This manifestation is most commonly observed in children under the age of 15 years, but it can also occur in adults, and due to the acute vascular permeability syndrome, this form of the disease can be fatal.[1]

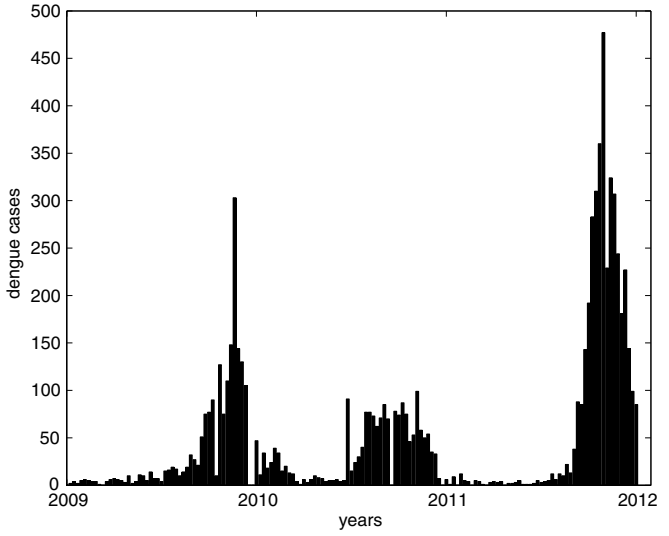
Individuals infected asymptomatically by dengue virus are believed to represent the majority of the infections although their role as a potential reservoir is not known. Seroepidemiological studies to antibodies against dengue virus conducted in different countries have shown that more than 80% of the cases could be subclinical.[3–5]

The risk factors associated with severe and fatal dengue infections are not well understood. Epidemiological studies of the outbreaks in Thailand and Cuba suggested that an important risk factor for DHF/DSS is a previous dengue infection with a different serotype.[1,6,7] These facts led to the formulation of the secondary infection or antibody enhancement hypothesis (ADE) to explain the severe form of the disease.[8] The exact mechanism behind ADE is still unclear. It may be caused by poor binding of non-neutralizing dependent antibodies and delivery into the wrong compartment of white blood cells that have ingested the virus for destruction.

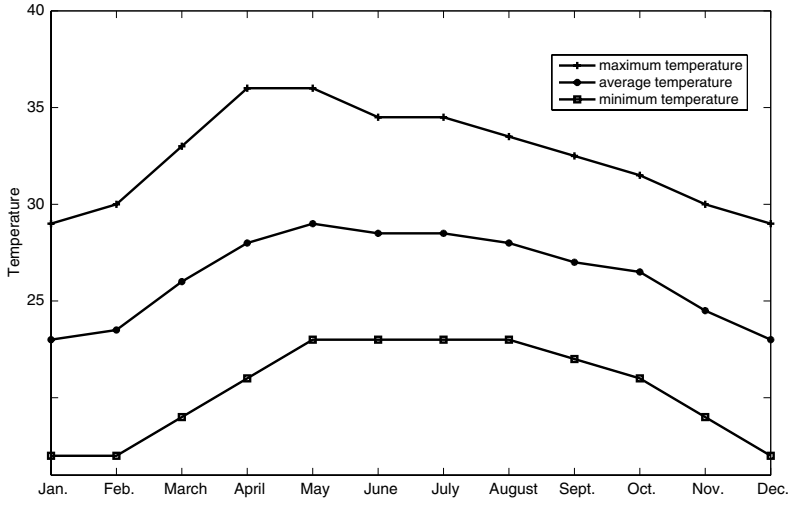
The presence of DHF in patients experiencing the first infections has suggested another hypothesis to explain the severity of the disease.[9–13] Research on dengue suggests that the pathogenesis of DHF and DSS involves virulence factors and detrimental host responses, collectively resulting in abnormal hemostasis and increased vascular permeability.[14] Several authors suggest the virulence hypothesis, which claims that certain dengue virus strains are responsible for more severe disease. The serotypes can be further classified into different genotypes on the basis of nucleotide variations. Viral genetic differences have been associated with differences in virulence.[15,16]

Some authors remark that the first outbreak of DHF in the Americas occurred in 1981 coinciding with the introduction of possibly more virulent DEN-II Southeast Asian genotype, while the less virulent indigenous DEN-II genotype was already circulating in the region.[10,17] It has also been proposed that intra epidemic evolution of the circulating dengue serotype might be responsible for increased severity of disease.[18]

Epidemiological records of dengue in endemic regions show that number of dengue cases depends on the climatic conditions. For example, in Bangkok, Thailand, dengue peaks occur during the rainy season (June to November) whilst the mean temperature ranges from 28°C to 30°C,[19] while in the Mexican Southeast, epidemics are generally at the end of the rainy season (October, November), as shown in Fig. 1(a) where we see the behavior of dengue epidemics in the State of Yucatán, México, during 2009–2011 (data taken from Ref. 20). In Fig. 1(b), we



(a)



(b)

Fig. 1. (a) Reported number of dengue cases in Yucatán State, México during 2009–2011 according to data given in Ref. 20. (b) Monthly maximum, medium and minimum temperatures in Mérida, Yucatán. *Source*: www.climate/annualClimo-Merida-MXYN

observe that maximum temperature in Mérida, Yucatán, fluctuates around 30°C during the period of year with more occurrence of dengue cases.

Temperature, rain and humidity affect the biology and ecology of vectors and in consequence the risk of disease transmission, but the relationships among climatic conditions, vector ecology and dengue transmission have not been completely

understood. However, experimental studies on vector competence of mosquitoes for several arboviruses have shown that temperature strongly influences the extrinsic incubation period of DEN II, as well as virus transmission.[21–23] Also, some evidences that temperature influenced the efficiency of *A. aegypti* for dengue transmission of DHF cases in Bangkok, Thailand, were provided in Ref. 24. The same authors found that titers of the mosquito-infecting virus dose affect the temperature range for DEN-2 virus transmission by *A. aegypti*. Also, in Ref. 19 it was reported that the extrinsic incubation period of 25 days at 30°C was reduced to 12 days for mosquitoes infected with high virus doses, which coincides with the idea that the duration of the extrinsic incubation period varies directly with the titer of the mosquito-infecting dose.[25] These evidences lead the authors to suggest that the temperature variations in the efficiency of *A. aegypti* may be an important determinant in the cyclic pattern of DHF epidemics in Bangkok.

The aim of this study is to evaluate the risk of DF outbreaks assuming that the manifestations of the disease are related to the titers of the mosquito-infecting virus which are temperature-dependent. For this purpose, we extend the classical mathematical models for dengue disease[26] by incorporating two classes of infected mosquitoes: the infectious with low and high viral loads, respectively. We assume that a proportion of humans bitten by high viral loaded mosquito should manifest severe case of dengue, and the relation between humans infected by mosquitoes with high and low viral loads provides the relation between reported and non-reported (asymptomatic) cases of dengue. Finally, we assess the effect of the variations of the entomological and epidemiological parameters with respect to the temperature on the vector efficiency of *A. aegypti* for dengue virus.

The paper is organized as follows. The model is formulated in Sec. 2. Existence and stability of equilibria of the model are investigated in Sec. 3. Numerical simulations to evaluate the effect of temperature on DF are reported in Sec. 4. Sensitivity of the basic reproduction number is done in Sec. 5, and finally, conclusions are given in Sec. 6.

2. Formulation of the Model

In the formulation of the model we will assume that the infection is produced by only one serotype of dengue virus. The dynamics of female *A. aegypti* encompasses egg phase, two successive aquatic stages: larva (L) and pupa (P); and adult female mosquitoes (M). In turn, M is divided in four compartments: susceptibles, M_s, exposed but not infectious, M_e, infectious with low viral load, M_1, and infectious with high viral load, M_2. Transmission by mosquitoes of class M_2 can trigger hemorragic dengue in humans.

The entomological parameters of *A. aegypti* are the per capita oviposition rate, ϕ, which is the average number of eggs by female mosquito; the transition rates from larva to pupa, and pupa to adult, σ_l and σ_p, respectively; the per capita mortality rates of larvas, pupas and mosquitoes, μ_l, μ_p and μ_m, respectively. All

Table 1. Entomological parameters in the numerical simulations of dengue model (2.1) according to Ref. 30. Units are in days^{-1}.

T°C	ϕ	σ_l	μ_l	σ_p	μ_p	μ_m
16	0.697	0.044	0.014	0.088	0.088	0.036
17	1.060	0.059	0.017	0.132	0.079	0.035
18	1.508	0.074	0.023	0.183	0.072	0.036
19	2.040	0.088	0.324	0.237	0.066	0.0366
20	2.647	0.1	0.042	0.289	0.061	0.037
21	3.321	0.110	0.052	0.334	0.058	0.037
22	4.047	0.118	0.062	0.370	0.057	0.037
23	4.809	0.124	0.071	0.395	0.057	0.036
24	5.586	0.13	0.078	0.412	0.058	0.035
25	6.353	0.136	0.083	0.423	0.061	0.033
26	7.082	0.143	0.086	0.433	0.066	0.031
27	7.741	0.151	0.087	0.45	0.071	0.03
28	8.294	0.16	0.086	0.478	0.079	0.028
29	8.704	0.171	0.084	0.521	0.088	0.028
30	8.927	0.183	0.081	0.580	0.098	0.029
31	8.916	0.195	0.078	0.651	0.110	0.032
32	8.622	0.205	0.076	0.726	0.123	0.038
33	7.991	0.213	0.076	0.791	0.138	0.048
34	6.966	0.215	0.08	0.828	0.154	0.063
35	5.487	0.21	0.089	0.818	0.172	0.083
36	3.488	0.195	0.105	0.743	0.191	0.109

the above parameters vary with temperature according to Table 1. Finally, q is the proportion of eggs that result in female mosquitoes, and C is the carrying capacity of the recipients to receive larvae from hatched eggs, both parameters are assumed independent of temperature.

The human population is assumed to be constant with size equal to H, and per capita mortality rate given by μ_h. The population is divided according to the natural history of the disease in susceptibles, exposed, infectious and recovered classes, whose fractions are denoted by h_s, h_e, h_i and h_r, respectively, with $h_s + h_e + h_i + h_r = 1$. In addition, the exposed class h_e is divided into the exposed infected by mosquitoes with low viral load, h_1, and with high viral load, h_2, which evolve to the asymptomatic, and symptomatic cases, respectively (the hemorrhagic cases would be a fraction of h_2). The classes h_1 and h_2 are not transmitting the virus, only the class of infective humans, h_i. Due to the fact that humans are homeothermic, we assume that those infected with low and high viral load spend the same time in the incubation stage, and become infectious after the same period of time $1/\alpha_e$.

Since $h_r = 1 - h_s - h_1 - h_2 - h_i$, it is enough to describe the dynamics of h_s, h_1, h_2 and h_i.

Dengue transmission is sustained by the flows between humans and mosquitoes compartments. Susceptible mosquitoes are infected by humans during the blood meal with per capita transmission coefficient β_m. The transmission rates from mosquitoes of the classes M_1 and M_2 to susceptible humans are denoted by β_1

and β_2, respectively. Since the viral load is higher in mosquitoes of class M_2, then $\beta_1 \leq \beta_2$. The exposed (infected but not infectious) humans and mosquitoes become infectious at rate α_e and γ_e, respectively, where $1/\alpha_e$ and $1/\gamma_e$ are the intrinsic and extrinsic periods of virus replication in humans and mosquitoes, respectively. We assume that β_m, β_1, β_2, γ_e and γ_1 change with temperature.

By the fact that mosquitoes do not develop a full immune response against dengue virus, we assume that dengue virus load at certain temperature increases proportionally to the time elapsed since the mosquito acquires the virus. Hence, it seems plausible that in the first moment of infectiousness, elapse upon of the incubation period $1/\gamma_e$, mosquitoes become infective. However, from this time on, the load of dengue virus inside mosquitoes is continuously increasing, and after an average period of time $1/\gamma_1$, the mosquitoe-infecting virus doses are high enough for it to become an infectious class M_2, responsible for symptomatic dengue in humans. Hence, this assumption follows the nonexistence of an immune response in the mosquitoes. As was mentioned in the Sec. 1, $1/\gamma_e$ depends also on the titer of the mosquito-infecting virus doses, but since our main objective is to study the influence of temperature on disease transmission, we will only consider this factor.

Finally, the humans recover from the disease at a constant per capita rate α_i, while the mosquitoes remain infectious during their entire life.

From the above assumptions, the model is given by the following system of differential equations:

$$
\begin{aligned}
\frac{dL}{dt} &= q\phi(1 - L/C)M - (\sigma_l + \mu_l)L, \\
\frac{dP}{dt} &= \sigma_l L - (\sigma_p + \mu_p)P, \\
\frac{dM_s}{dt} &= \sigma_p P - \beta_m h_i M_s - \mu_m M_s, \\
\frac{dM_e}{dt} &= \beta_m h_i M_s - (\gamma_e + \mu_m)M_e, \\
\frac{dM_1}{dt} &= \gamma_e M_e - (\gamma_1 + \mu_m)M_1, \\
\frac{dM_2}{dt} &= \gamma_1 M_1 - \mu_m M_2, \\
\frac{dh_s}{dt} &= \mu_h - \left(\beta_1 \frac{M_1}{M} + \beta_2 \frac{M_2}{M}\right) h_s - \mu_h h_s, \\
\frac{dh_1}{dt} &= \beta_1 \frac{M_1}{M} h_s - (\alpha_e + \mu_h)h_1, \\
\frac{dh_2}{dt} &= \beta_2 \frac{M_2}{M} h_s - (\alpha_e + \mu_h)h_2, \\
\frac{dh_i}{dt} &= \alpha_e h_1 + \alpha_e h_2 - (\alpha_i + \mu_h)h_i.
\end{aligned}
\tag{2.1}
$$

Since $M = M_s + M_e + M_1 + M_2$, we see from the first six equations of (2.1) that mosquito dynamics from larva stage to adult form is given by

$$\begin{aligned} \frac{dL}{dt} &= q\phi(1 - L/C)M - (\sigma_l + \mu_l)L, \\ \frac{dP}{dt} &= \sigma_l L - (\sigma_p + \mu_p)P, \\ \frac{dM}{dt} &= \sigma_p P - \mu_m M. \end{aligned} \tag{2.2}$$

3. Analysis of the Model

In the following, we analyze models (2.1) and (2.2) assigning to the parameters constant averaged values according to the calendar year.

3.1. *Mosquito dynamics*

We analyze the mosquito population dynamics given by system (2.2). Considering constant values of the parameters, system (2.2) has two equilibria, the mosquitoe-free state, and the state characterized by the presence of mosquitoes denoted by

$$\begin{aligned} E_0 &= (0, 0, 0), \\ E_1 &= (\bar{L}, \bar{P}, \bar{M}), \end{aligned} \tag{3.1}$$

respectively, where

$$\begin{aligned} \bar{L} &= \left(\frac{R_M - 1}{R_M}\right) C \\ \bar{P} &= \frac{\sigma_l}{\sigma_p + \mu_p}\bar{L} \\ \bar{M} &= \frac{\sigma_p \sigma_l}{\mu_m(\sigma_p + \mu_p)}\bar{L}. \end{aligned} \tag{3.2}$$

In the above equations, R_M denotes the *basic offspring number* given by

$$R_M = \frac{q\phi\sigma_l\sigma_p}{\mu_m(\sigma_l + \mu_l)(\sigma_p + \mu_p)}. \tag{3.3}$$

R_M is interpreted biologically as follows: $\frac{1}{\sigma_l+\mu_l}$ is the average time of survival of a larva to the pupa stage, and $\frac{1}{\sigma_l}$ is the average time of its permanence as such, then $\frac{\sigma_l}{\sigma_l+\mu_l}$ is the probability that an egg will succeed to become a pupa. Arguing in the same way, $\frac{\sigma_p}{\sigma_p+\mu_p}$ is the probability that a pupa becomes an adult insect, therefore $\frac{q\sigma_l\sigma_p}{(\sigma_l+\mu_l)(\sigma_p+\mu_p)}$ is the probability that an egg will succeed to become a female insect, and since $\frac{\phi}{\mu_m}$ is the average number of eggs oviposited by each female during its lifetime, the product of the last two quantities, which is equal to R_M, is

the average number of secondary female insects produced by a single female insect. In demographic terms, R_M is the basic offspring number of insect population, and it is necessary the condition $R_M > 1$ is satisfied in order to have a positive number of mosquitoes.[27]

In Appendix A, it is shown that all solutions of system (2.2) approach zero when $R_M \leq 1$, while for $R_M > 1$, solutions with positive initial conditions approach $E_1 \neq 0$. This result implies that mosquito population attains extinction if $R_M \leq 1$, while for $R_M > 1$ it persists.

3.2. *The basic reproductive number*

To analyze the dengue dynamics, in the following we will assume $R_M > 1$, since otherwise the mosquito population is zero, and therefore there is no disease for obvious reasons. For $R_M > 1$, solutions approach asymptotically the equilibrium E_1, and therefore we can assume that the mosquito population has already reached its equilibrium, and hence the total population of adult mosquitos is constant and equal to $\bar{M}$. We take proportions $m_s = M_s/\bar{M}$, $m_e = M_e/\bar{M}$, $m_1 = M_1/\bar{M}$, $m_2 = M_2/\bar{M}$, and since $m_s = 1 - m_e - m_1 - m_2$, model (2.1) is equivalent to the system of differential equations for the proportions:

$$\begin{aligned}
\frac{dm_e}{dt} &= \beta_m h_i(1 - m_e - m_1 - m_2) - (\gamma_e + \mu_m)m_e,\\
\frac{dm_1}{dt} &= \gamma_e m_e - (\gamma_1 + \mu_m)m_1,\\
\frac{dm_2}{dt} &= \gamma_1 m_1 - \mu_m m_2,\\
\frac{dh_s}{dt} &= \mu_h - (\beta_1 m_1 + \beta_2 m_2)h_s - \mu_h h_s,\\
\frac{dh_1}{dt} &= \beta_1 m_1 h_s - (\alpha_e + \mu_h)h_1,\\
\frac{dh_2}{dt} &= \beta_2 m_2 h_s - (\alpha_e + \mu_h)h_2,\\
\frac{dh_i}{dt} &= \alpha_e h_1 + \alpha_e h_2 - (\alpha_i + \mu_h)h_i.
\end{aligned} \tag{3.4}$$

Next, we will analyze model (3.4) in terms of the *basic reproductive number* of the disease, R_0, which represents the average number of secondary cases that one case can produce if introduced into a susceptible population of humans and mosquitoes. If $R_0 < 1$, less than one secondary case will arise from a primary case and the disease will fade out. On the contrary, if $R_0 > 1$ an outbreak will start. Following the *next generation operator* approach given in Ref. 28, R_0 is equal to the spectral radius of KF^{-1}, where K is the non-negative matrix of the

infection terms,

$$K = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \beta_m \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_1 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and F is the non-singular M-matrix of the transition terms,

$$F = \begin{pmatrix} \gamma_e + \mu_m & 0 & 0 & 0 & 0 & 0 \\ -\gamma_e & \gamma_1 + \mu_m & 0 & 0 & 0 & 0 \\ 0 & -\gamma_1 & \mu_m & 0 & 0 & 0 \\ 0 & 0 & 0 & \alpha_e + \mu_h & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha_e + \mu_h & 0 \\ 0 & 0 & 0 & -\alpha_e & -\alpha_e & \alpha_i + \mu_h \end{pmatrix},$$

respectively.

Then, the operator of the next generator, KF^{-1}, is equal to

$$\begin{pmatrix} 0 & 0 & 0 & -\frac{\beta_m \alpha_e}{(\alpha_e+\mu_h)(\alpha_i+\mu_h)} & -\frac{\beta_m \alpha_e}{(\alpha_e+\mu_h)(\alpha_i+\mu_h)} & -\frac{\beta_m}{(\alpha_i+\mu_h)} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ -\frac{\beta_1 \gamma_e}{(\gamma_e+\mu_m)(\gamma_1+\mu_m)} & -\frac{\beta_1 \gamma_e}{(\gamma_1+\mu_m)} & 0 & 0 & 0 & 0 \\ -\frac{\beta_2 \gamma_e \gamma_1}{(\gamma_e+\mu_m)(\gamma_1+\mu_m)\mu_m} & -\frac{\beta_2 \gamma_1}{(\gamma_1+\mu_m)\mu_m} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and its eigenvalues are zero of multiplicity four, and

$$\pm\sqrt{R_1^2 + R_2^2},$$

where

$$\begin{aligned} R_1 &= \sqrt{\frac{\beta_1 \beta_m \gamma_e \alpha_e}{(\gamma_e + \mu_m)(\gamma_1 + \mu_m)(\alpha_e + \mu_h)(\alpha_i + \mu_h)}}, \\ R_2 &= \sqrt{\frac{\beta_2 \beta_m \gamma_e \gamma_1 \alpha_e}{(\gamma_e + \mu_m)(\gamma_1 + \mu_m)(\alpha_e + \mu_h)(\alpha_i + \mu_h)\mu_m}}. \end{aligned} \tag{3.5}$$

Therefore, the basic reproductive number is $R_0 = \sqrt{R_1^2 + R_2^2}$. Theorem 2 in Ref. 29 assures that the disease-free equilibrium

$$P_0 = (0, 0, 0, 1, 0, 0, 0)$$

is locally asymptotically stable (LAS) if $R_0 < 1$, and unstable if $R_0 > 1$. To ensure the elimination of disease regardless of initial population sizes, a global stability

proof for the disease-free equilibrium is needed. This is done using a comparison theorem (see Appendix B).

The epidemiological implication of the above result is that the disease will be eliminated from the community if $R_0 < 1$, regardless of the initial number of infected individuals. Note that R_1 and R_2 defined in (3.5) can be interpreted as the number of secondary infections produced by an infectious mosquito of class m_1 and m_2, respectively. Then, the probability of dengue hemorrhagic fever depends on the interplay between these quantities.

3.3. *Endemic equilibrium*

The endemic equilibria of system (3.4) are the non-trivial solutions of the algebraic system

$$\begin{aligned}
\beta_m \bar{h}_i(1 - \bar{m}_e - \bar{m}_1 - \bar{m}_2) - (\gamma_e + \mu_m)\bar{m}_e &= 0,\\
\gamma_e \bar{m}_e - (\gamma_1 + \mu_m)\bar{m}_1 &= 0,\\
\gamma_1 \bar{m}_1 - \mu_m \bar{m}_2 &= 0,\\
\mu_h - (\beta_1 \bar{m}_1 + \beta_2 \bar{m}_2)\bar{h}_s - \mu_h \bar{h}_s &= 0,\\
\beta_1 \bar{m}_1 \bar{h}_s - (\alpha_e + \mu_h)\bar{h}_1 &= 0,\\
\beta_2 \bar{m}_2 \bar{h}_s - (\alpha_e + \mu_h)\bar{h}_2 &= 0,\\
\alpha_e \bar{h}_1 + \alpha_e \bar{h}_2 - (\alpha_i + \mu_h)\bar{h}_i &= 0.
\end{aligned} \tag{3.6}$$

Solving (3.6) in terms of $\bar{m}_e$ we obtain

$$\begin{aligned}
\bar{m}_1 &= \frac{\gamma_e}{\gamma_1 + \mu_m}\bar{m}_e,\\
\bar{m}_2 &= \frac{\gamma_e \gamma_1}{(\gamma_1 + \mu_m)\mu_m}\bar{m}_e,\\
\bar{h}_s &= \frac{\mu_h(\gamma_1 + \mu_m)}{\mu_h(\gamma_1 + \mu_m) + \gamma_e(\beta_1 + (\gamma_1/\mu_m)\beta_2)\bar{m}_e},\\
\bar{h}_1 &= \frac{\beta_1 \gamma_e \mu_h \bar{m}_e}{(\alpha_e + \mu_h)(\mu_h(\gamma_1 + \mu_m) + \gamma_e(\beta_1 + (\gamma_1/\mu_m)\beta_2)\bar{m}_e)},\\
\bar{h}_2 &= \frac{\beta_2 \gamma_e (\gamma_1/\mu_m)\mu_h \bar{m}_e}{(\alpha_e + \mu_h)(\mu_h(\gamma_1 + \mu_m) + \gamma_e(\beta_1 + (\gamma_1/\mu_m)\beta_2)\bar{m}_e)}\\
\bar{h}_i &= \frac{\alpha_e \gamma_e (\beta_1 + \beta_2(\gamma_1/\mu_m)\mu_h \bar{m}_e}{(\alpha_i + \mu_i)(\alpha_e + \mu_h)(\mu_h(\gamma_1 + \mu_m) + \gamma_e(\beta_1 + (\gamma_1/\mu_m)\beta_2)\bar{m}_e)}.
\end{aligned} \tag{3.7}$$

Substituting $\bar{m}_1$, $\bar{m}_2$ and $\bar{h}_i$ in the first equation of (3.6), we then obtain some tedious calculations that $\bar{m}_e$ is given by

$$\bar{m}_e = \frac{\beta_m \alpha_e \mu_h \mu_m}{(\gamma_e + \mu_h)(\beta_m \alpha_e \mu_h + (\alpha_e + \mu_h)(\alpha_i + \mu_h)\mu_m)} \times \frac{R_0^2 - 1}{R_0^2}. \tag{3.8}$$

It follows that $\bar{m}_e > 0$ if and only if $R_0 > 1$. Then, a unique endemic state $P_1 = (\bar{m}_e, \bar{m}_1, \bar{m}_1, \bar{h}_s, \bar{h}_1, \bar{h}_2, \bar{h}_i)$ emerges when $R_0 > 1$. In Appendix B, we show that positive initial conditions evolve to P_1.

4. Assessing the Effect of Temperature on Dengue Outbreaks

The risk of Dengue is strongly associated with the presence of *A. aegypti* mosquitoes, and for this reason it is important to estimate this population for different temperatures. In Ref. 30, the authors designed temperature-controlled experiments and mathematical models to estimate the entomological parameters of the mosquito's life cycle at different temperatures (see Table 1). They found that the basic offspring R_M given by (3.3) is less than one for temperatures below 13.60°C and above 36.55°C. Then, according to the results given in Sec. 3, the mosquito population cannot be maintained at those temperature ranges which obviously implies no dengue transmission. Based on the values of the parameters given in Table 1, and taking $q = 0.8$, we obtain the curve of R_M for the temperature interval $[16°, 36°]$ illustrated in Fig. 2. We observe that the maximum value of R_M, and consequently of the size of the mosquito population is obtained at 30°C.

Dengue epidemics not only depend upon the size of the mosquito population, but also on the competence of *A. aegypti* to transmit the disease. Both the extrinsic incubation period and the transmission probability play an important role in the spread of the disease. Data showing that length of the extrinsic incubation period decreases with temperature have been documented for several virus-mosquito vector systems.[19,21,22,31] Based on empirical data it is assumed in Refs. 32 and 33 that the length of time required for the development of the malaria parasite within a

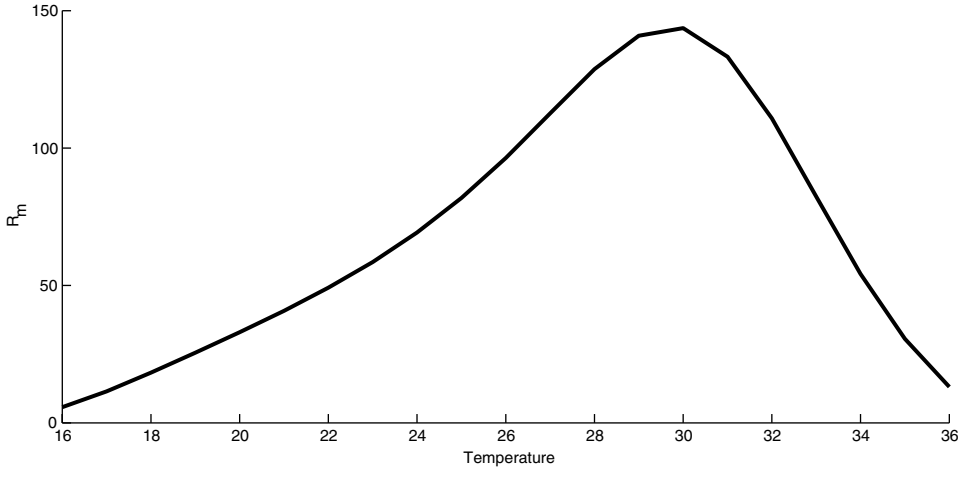


Fig. 2. Variation of the basic offspring of mosquito population with respect to the temperature according data of Table 1. In all the simulations we assume $q = 0.8$.

mosquito, $1/\gamma_e$, with increasing temperature is given by

$$\frac{1}{\gamma_e} = \frac{f}{T-g}, \tag{4.1}$$

where f is the thermal sum, measured in degree-days, representing the accumulation of temperature units over time to complete the parasite development required to become infective in the vector; g is a threshold below which development ceases, and T is the ambient temperature. Here, we assume the same relation for dengue virus with $g = 16°\text{C}$. It is reported in Ref. 19 that $1/\gamma_e \approx 7.5$ days when the temperature $T = 32°\text{C}$. Substituting these values in (4.1) we obtain $f = 120°\text{C}\times\text{day}$. The extrinsic period reduces less than half when the temperature ranges from 22°C to 32°C, the ideal temperature of the mosquitoes to reproduce.

Virus transmission from mosquito to human (human to mosquito) depends on the mosquito biting rate, denoted by b, and the transmission probability from vector to human (human to vector), denoted by p_{vh} (p_{hv}). The biting rate is the average number of bites per mosquito per day. It is driven by the time it takes to complete a gonotrophic cycle since female mosquito needs blood meal for each batch of eggs it produces. This time depends on a number of factors, in particular climatic ones, but in general, the interval of time between the blood supply and gonotrophic cycle is 48 h in tropics under optimal temperature conditions,[34,35] which implies that female mosquito bites every 2 days, and therefore the biting rate should be $1/2$ days^{-1}, although changes in temperature could make a large difference in this value. Due to the relation between the interval between mosquito blood meals and the gonotrophic period, it is reasonable to assume that biting rate b is proportional to oviposition rate ϕ, that is $b = a\phi$, where the constant a is taken such that the maximum oviposition rate corresponds to the maximum biting rate. According to Table 1, the maximum value of ϕ is 8.927 eggs per day per female, and this should correspond to 0.5 bites per day per female, which implies $a = 0.056$ bites/eggs. Therefore, the proportion of bites that a human receives per unit of time is $b = 0.056\phi$.

The transmission probability is the probability that an infectious bite gives rise to a new case in a susceptible member of the other species, and it depends on the efficiency of vectors and humans to transmit the disease. Laboratory studies suggest that the required temperature to attain efficient vector transmission depends on the particular arbovirus-mosquito vector system.[36] For instance, observations reported for western equine encephalitis virus and *Culex tarsalis* mosquitoes showed that maximum vector efficiency was attained for temperatures below 25°C, and transmission rates decreased with high temperatures.[36] In contrast, laboratory results described in Ref. 19 indicated that the maximum efficiency for the transmission of DEN-2 virus by *A. aegypti* was attained between 32°C and 35°C, with no evidence that elevated temperature interfered with virus replication and transmission.

From Fig. 2, it follows that there are no mosquitoes at 16°C, which implies that at this temperature $R_0 < 1$. On the other side, the results in Ref. 19 indicate that the probability of transmission from vector to host increases from $p_{vh} = 0.72$ at

26° to $p_{vh} = 0.95$ at 36°C, and from these results we assume for simplicity that p_{vh} increase according to the linear function:

$$p_{vh}(T) = 0.023\,T + 0.122. \tag{4.2}$$

Now, taking $\beta_1 = bp_{vh}$, we obtain that β_1 increases with temperature according to

$$\beta_1(T) = 0.056\phi(T)p_{vh}(T). \tag{4.3}$$

We recall that β_2 is the transmission rate from mosquitoes with high virus load to humans. In this case, we will assume that the probability of an effective infection is 0.95, therefore the transmission of mosquitoes with high virus load is

$$\beta_2(T) = 0.056\phi(T)0.95 = 0.053\phi(T). \tag{4.4}$$

Experimental results reported in Ref. 19 for mosquitoes infected with a high dose of DEN-2 virus indicate that the percentage of infected mosquitos ranged from 0.25% maintained at 20°C to 58% at 30°C. Assuming also a linear relation for p_{hv}, we obtain

$$p_{hv}(T) = 0.033\,T - 0.41,$$

with $T > 12.5$°C, which implies

$$\beta_m(T) = 0.056\phi(T)(0.033T - 0.41). \tag{4.5}$$

It has been reported that virus transmission by *A. aegypti* varies directly with virus titers associated to salivary glands of the mosquito. Also, there is evidence (at least for other species of mosquitoes) that viral load in salivary glands increases with incubation temperature.[19] This suggests $\gamma_1 = k\gamma_e$. In order to determine k, we observe that from the 1.6 million cases of dengue reported in the Americas in 2010, 49,000 cases were severe dengue,[2] i.e., at most 0.03 of the reported cases were severe. In Singapore, in 2004, 0.04 of the reported cases were severe (of 3186 cases, there were 130 severe cases).[18] Then, according to these numbers, the estimation of $k \approx 0.01$ seems to be plausible. However, it is important to note that this estimation of k is an upper bound since the percentage is taken from the number of reported cases which is a fraction of the total cases.

The latent and infectious periods for dengue disease last around seven days,[1] so we assume $1/\alpha_e = 1/\alpha_i = 7$ days, and therefore $\alpha_e = \alpha_i = 0.1174$ days^{-1}.

The dependence of the basic reproductive number with respect to the temperature is illustrated in Fig. 3. We notice that the graph of R_0 versus temperature is very similar to that of R_M despite the fact that both extrinsic incubation rate and probability of transmission increase with temperature. Further, the maximum number of secondary cases occurs at the same temperature for which the maximum of the basic offspring number is reached (30°C). The same figure shows that $R_0 < 1$ for temperatures below 22°C, and above 36°C because at those temperatures mosquito life expectancy is less than the period of time required to be infectious. The above

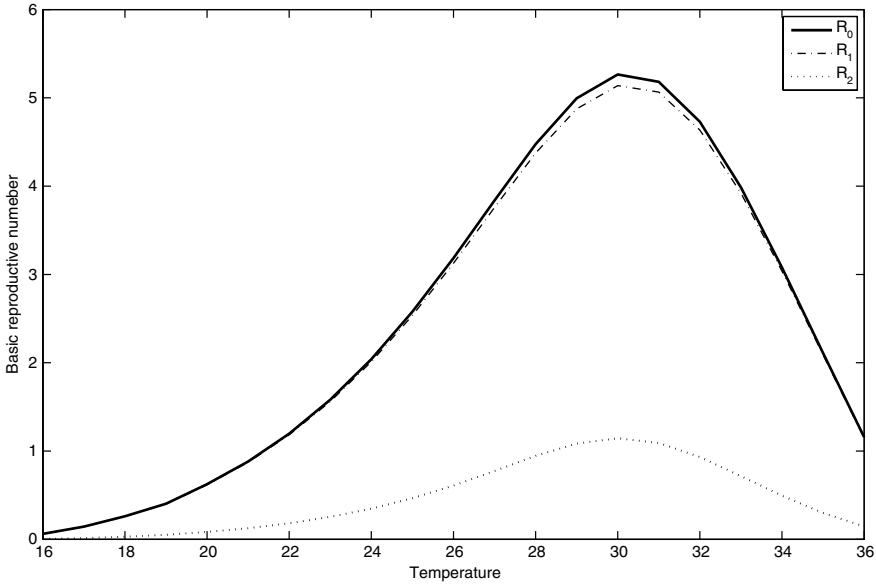


Fig. 3. Variation of the basic reproductive number R_0 with respect temperature T for $\gamma_e(T) = \frac{T-15}{120}$ days,$^{-1}$, $\gamma_1 = 0.01 \times \gamma_e$ days^{-1}, $\alpha_e = \alpha_i = 0.1174$ days^{-1} and $\mu_h = 0.0000431$ days^{-1}. The transmission probabilities $\beta_1(T)$ and $\beta_2(T)$ are given by (4.3), (4.4), and $\beta_m(T)$ by (4.5).

observations suggest that variations of the vector entomological parameters with respect to the temperature is crucial for the occurrence of dengue epidemics, and magnitude of the outbreaks.

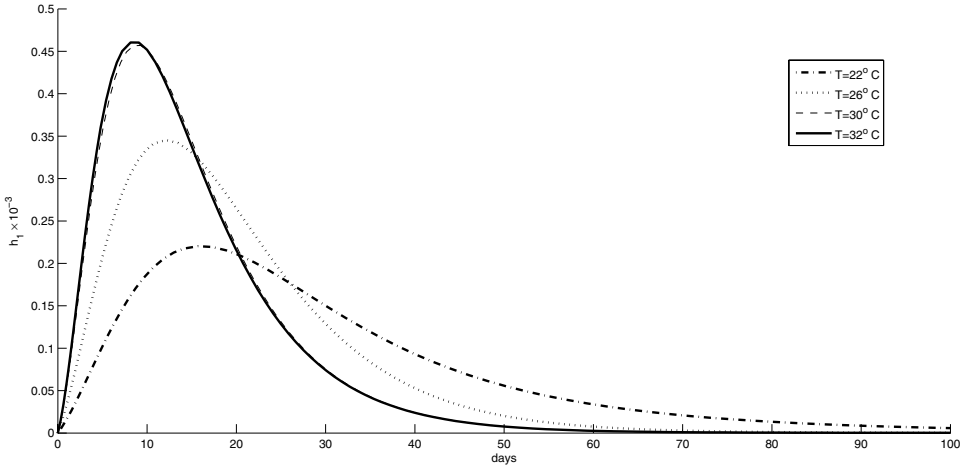
It is interesting to observe that the value of R_0 obtained from data of a dengue epidemic occurred in Salvador, Brazil, with an average temperature of 26°C, was around 2.85,[37] which is very close to the value shown in Fig. 3 for the same temperature.

On the other side, Fig. 4 illustrates the influence of temperature on the temporal course of infective humans. The graphs show the first epidemic peak, and from them it is noticed that maximum prevalence increases with temperature, and also that mild and severe human infections increase at the same velocity since there is no delay in the emergence of the severe cases.

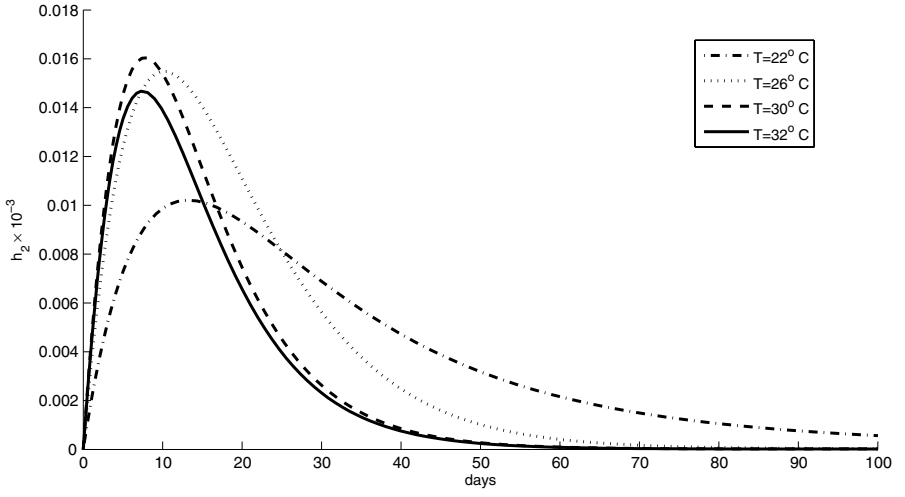
The ratios between severe and non-severe cases for human and mosquito infected populations at equilibrium P_1 are given by

$$r_h = \frac{h_2}{h_1} = \frac{R_2^2}{R_1^2} = \frac{\beta_2}{\beta_1} \times \frac{\gamma_1}{\mu_m}$$
$$r_m = \frac{m_2}{m_1} = \frac{\gamma_1}{\mu_m}, \tag{4.6}$$

respectively. The ratio between m_2 and m_1 depends directly on γ_1, and inversely on μ_m. As temperature increases, γ_1 increases (extrinsic incubation diminishes)



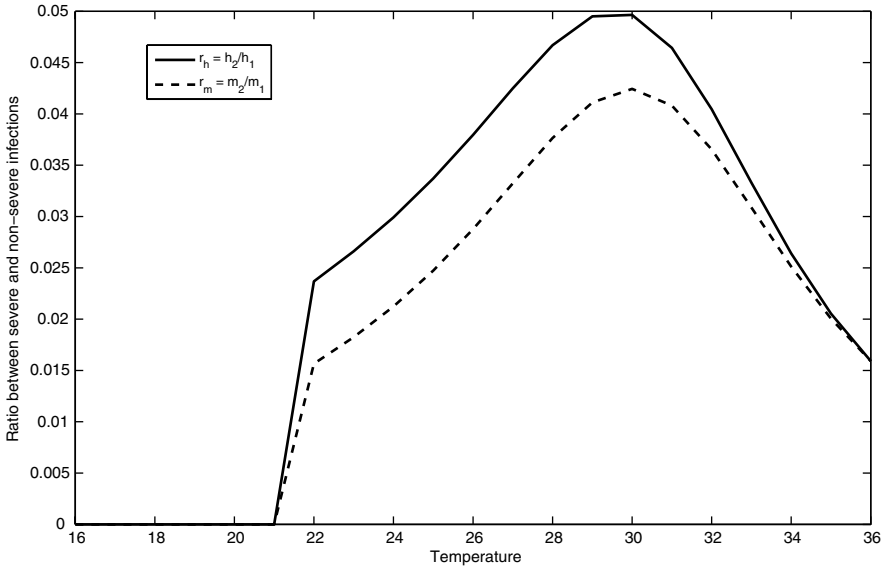
(a)



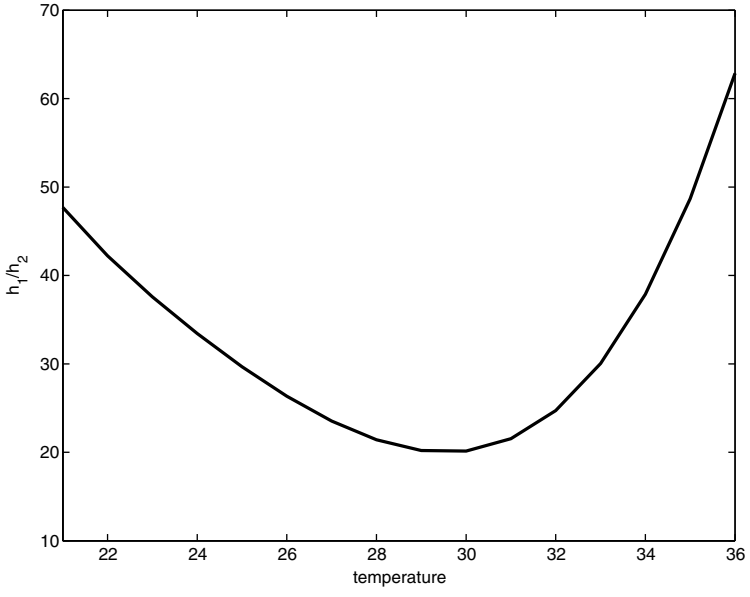
(b)

Fig. 4. Simulations of the temporal course of the infected humans for different temperatures using system (3.4). The parameters are as in Fig. 3, and the initial conditions are $m_e = 0$, $m_1 = m_2 = 0.1$, $s_h = 0.9$, $h_1 = h_2 = 0$, $h_i = 0.1$. (a) h_1 and (b) h_2.

and μ_m decreases (average life span of mosquitoes increases), which leads to an increase of the proportion of heavily infected mosquitoes. For humans, besides $\frac{\gamma_1}{\mu_m}$, $\frac{\beta_2}{\beta_1}$ is another factor that influences the ratio of persons infected by heavily infected mosquitoes. If heavily infected mosquitoes are more competent in transmitting dengue, that is, $\beta_2 > \beta_1$, then, increasing temperature increases the number of severe cases of dengue (see Fig. 5).



(a)



(b)

Fig. 5. (a) Ratios $r_h = h_2/h_1$, and $r_m = m_2/m_1$ between infectives of class 2 and 1 in human and mosquito populations at equilibrium P_1, respectively. (b) Ratio between non-severe and severe dengue cases h_2/h_1 at equilibrium P_1. The parameters are the same of Fig. 3.

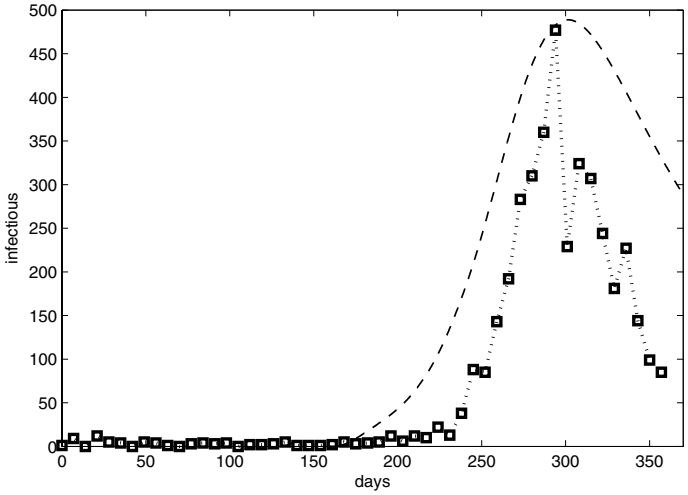


Fig. 6. Numerical simulations of the number of reported dengue cases during 2011 in Yucatán, México using model (3.4), and assuming that temperature varies according (4.7).

Figure 5(b) shows the relation h_1/h_2 which roughly gives the proportion of unreported cases of dengue with respect to the reported ones. The minimum relation obtained is around 20, and from this value the proportion increases rapidly.

We use model (3.4) to simulate the effect of temperature on the number of cases over one year. For this end we simulate the annual average temperature variation given in Fig. 1(b) with a periodic function given by

$$T(t) = 30 + 4(\sin(\pi t/365 - 0.018)). \tag{4.7}$$

where t is measured in days. We substitute this expression in the equations that define the parameters β_1, β_2, β_m, γ_e and γ_1 given in Sec. 4, and we fit the data of entomological parameters given in Table 1 versus T.

Figure 6 shows the numerical simulations of dengue cases, $i_h(t)$ up to a constant multiplicative factor. We use a periodic function of the temperature to reproduce the average annual variation of temperature in the state of Yucatan [Fig. 1(b)]. We found a relative good fit of the number of cases reported in this state each month from January to December 2011 [Fig. 1(a)] in the sense that the curve obtained by the numerical simulation of the model reproduces qualitatively the shape of the data curve.

We note that DF outbreaks of 2009 and 2011 are similar, and therefore model predictions are qualitatively good fit for these years, but not of data of 2010.

5. Sensitivity Analysis of R_0

It is illustrative to investigate the sensitivity of R_0 to changes in the parameters that vary with temperature. For this end we calculate the differential of the expression

Table 2. Total variation ΔR_0 at temperatures 22°C, 30°C and 35°C, when the relative variation of the corresponding parameter is equal to 0.1, and the other parameters are kept fixed.

Parameter	22°C	30°C	35°C
β_m	0.1	0.59	0.15
β_1	0.9	0.56	0.15
β_2	0.0023	0.02	0.003
γ_e	0.037	0.11	0.05
γ_1	0.001	0.004	0.001
μ_m	−0.13	−1.25	−0.32
μ_h	0	−0.0005	−0.0001
α_e	0.0001	0.0004	0.0001
α_i	−0.09	−0.56	−0.14

of R_0 given in (3.5) to approximate its total variation with respect the variations of the parameters p_i, $i = 1, \ldots, 10$, of model (3.4):

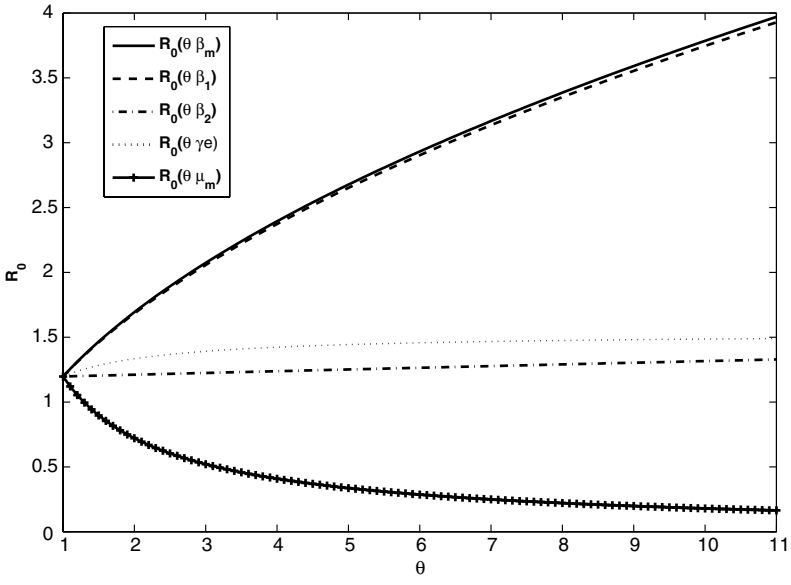
$$\Delta R_0 \approx dR_0 = \sum_{i=1}^{10} \frac{\partial R_0}{\partial p_i} \Delta p_i. \tag{5.1}$$

We take the same relative variation of the parameter p_i, $\frac{\Delta p_i}{p_i} = 0.1$, and we rank the parameters according their partial contribution to the total variation of R_0. The results are shown in Table 2 for temperatures 22°C, 30°C and 35°C, respectively. The parameters μ_m, μ_h and α_i decrement the value of R_0, while the rest increases it.

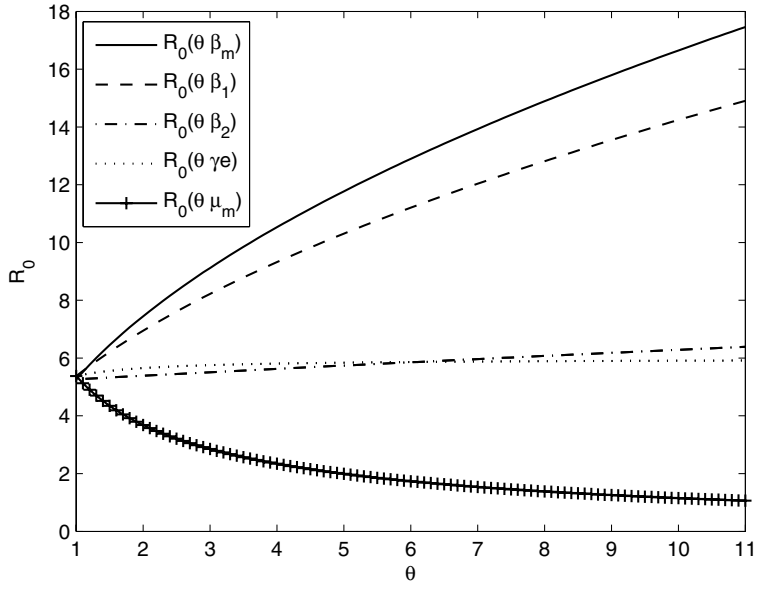
From Table 2, we observe that sensitivity to parameters of R_0 depends on the temperature, thus for $T = 22$°C, β_1 is the larger contributers to the variation of R_0, while at 30°C and 35°C, μ_m is the one that contributes more in a negative way. In general, for the three temperatures, β_1, β_m and μ_m are the parameters for which R_0 is more sensitive, suggesting that variations of these parameters are fundamental for the occurrence and severity of dengue epidemics. The relative increment of R_0 with respect to the inverse of the extrinsic period, γ_e, has a maximum at 22°C, coinciding with the fact that this parameter increases rapidly at lower temperatures (around 16°C) according to (4.1).

For low temperatures (e.g., 22°C), there are little changes in R_0, and changes due to the increment of human infection β_1 are practically twice the ones due to the other parameters. At elevated temperatures (e.g., 30°C and 35°C), mosquito mortality is the parameter that contributes to the highest change in R_0 (in absolute value). Parameters related to mosquito population are the ones that contribute with higher values, while the infectious period in humans contributes reasonably to R_0. Extrinsic incubation period and infection rate β_2 contribute moderately at intermediate temperatures (e.g., 30°C). By the fact that at temperature around 30°C, both β_2 and γ_e present higher variations in comparison to other temperatures, we can assert that variations in the incidence of DHF are higher at intermediate temperatures.

Figures 7(a)–7(c) illustrate, for temperatures 22°C, 30°C and 35°C, the dependence of the basic reproductive number R_0 obtained as a function of θp, p being a

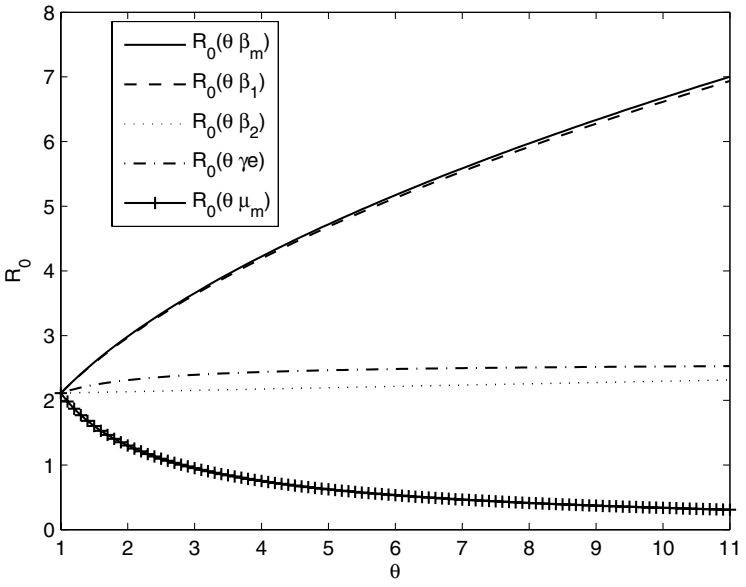


(a)



(b)

Fig. 7. Evolution of the basic reproductive number R_0 as a function of θp for p a parameter of model (3.4) and θ a factor increasing from 1 to 10 at a fixed temperature. In the simulations (a) $T = 22, \beta_m = 0.07, \beta_1 = 0.14, \beta_2 = 0.21, \gamma_e = 0.06, \mu_m = 0.04$, (b) $T = 30, \beta_m = 0.3, \beta_1 = 0.4, \beta_2 = 0.47, \gamma_e = 0.12, \mu_m = 0.03$. (c) $T = 35, \beta_m = 0.23, \beta_1 = 0.28, \beta_2 = 0.3, \gamma_e = 0.17, \mu_m = 0.08$.



(c)

Fig. 7. (*Continued*)

parameter of model (3.4), and θ a factor increasing from 1 to 10. In the three figures we see that the mosquito infecting rate β_m is the parameter that most contributes to the increase of the basic reproductive in the long run, especially at 30°C where R_0 increases more than four times. We also notice that at 22°C and 35°C, β_1 has the same effect on R_0 that β_m, but at 30^o the increment of R_0 due to this parameter is lower. On the contrary, mortality of the mosquito, μ_m, is the parameter for which R_0 decreases more. Extrinsic incubation period γ_e and infection rate β_2 do not have a noticeable impact over R_0 at a large scale. Therefore, we conclude that Fig. 7 corroborates the results obtained from the sensitivity analysis.

6. Conclusions

Transmission of dengue in endemic tropical regions occurs year round, however cyclical patterns have been found to be associated with climatic variability due to rain, humidity and temperature.[38] In particular, temperature has an important influence on dengue and DHF incidences. Temperatures between 27°C and 32°C allow the vectors to grow faster and to have better survival.[30] Further, some studies have shown that mosquitoes *Aedes* exposed to higher temperatures after ingestion of virus become infectious more rapidly than mosquitoes exposed to lower temperatures[19] suggesting that temperature has a considerable effect on the extrinsic incubation period of the mosquito *Aedes*.

In this work, we explored the influence of temperature on dengue transmission through a mathematical model incorporating temperature-dependent parameters. We assessed the severity of dengue disease by assuming that heavily infected mosquitoes are responsible for DHF. Although the results of the model depend on parameters obtained from laboratory experiments, epidemiological data clearly show that temperature variations are determinant on the incidence of dengue and DHF.

We estimated the basic reproductive number, R_0, for a range of temperatures using the entomological parameters given in Ref. 30, and the experimental and theoretical results in Refs. 19 and 33 for the transmission parameters. We found that variations of R_0 with respect to the temperature follow the same pattern of the basic offspring of mosquitoes with maximum values fluctuating between 30°C and 32°C. The numerical results also show that dengue and DHF cases are bigger for the same range of temperatures. These results suggest that variations in dengue transmission are more influenced by factors associated with mosquito life cycle, such as oviposition, maturation and longevity, rather than factors related with intrinsic viral dynamics, such as extrinsic period or virulence, however our results also indicate that intensity of the outbreaks are affected by the length of the extrinsic period, and the mosquitoes infection period.

The numerical results obtained from the model agree qualitatively with epidemiological data observed in Yucatán, México and Bangkok, Thailand, in the sense that the most severe dengue epidemic peaks occur when temperature oscillates between 28°C and 32°C. The same pattern has been observed in the Gulf of Thailand region,[38] where the maximal dengue incidence was obtained in Yala with temperatures between 27°C and 32°C; in the region of Los Tuxtlas, Gulf of Mexico[39] with temperatures oscillating between 28°C and 30°C, and in other regions of the mexican southeast.

From the model results we also obtained that number of severe cases (h_2) in relation to the asymptomatic dengue cases (h_1) showed an optimal temperature, which is situated at elevated temperatures. At this optimal temperature, the number of reported cases increases more than the asymptomatic cases, and the relation between them is the highest. The highest is also the number of potentially severe cases of dengue. In Fig. 5(b), we showed the relation h_1/h_2, which is roughly the relation between the unreported and reported cases of dengue.

Sensitivity analysis reveals that sensitivity of R_0 to parameters depends on the temperature, and β_1, μ_m and β_m are the parameters for which R_0 is more sensitive, suggesting that severity of epidemics are related with variations of these parameters.

To conclude, we want to state that, besides the environmental conditions, there are biological factors such as host susceptibility to a particular strain, or cross reaction between different serotypes (secondary infection hypothesis) which also modulate the severity of dengue epidemics. Because of this, we are conscious of the necessity of more empirical studies and theoretical models to assess the role of environmental and immunological factors on the transmission of dengue and DHF.

Acknowledgments

This work was supported by grant from FAPESP (Projeto Temático 09/150980). L. Esteva was supported by grant IN112713 from PAPIIT-UNAM.

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Appendix A. Stability of the Equilibria E_0 and E_1

In this Appendix, we prove the stability properties of the equilibria E_0 and E_1.

We recall the definition of R_M given by (3.3), then for $R_M \leq 1$ the mosquito-free equilibrium E_0 of system (2.2) is globally asymptotically stable (GAS), and for $R_M > 1$ it is unstable.

Local stability of E_0 is governed by the eigenvalues of the Jacobian matrix of system (2.2) around E_0,

$$\begin{pmatrix} -(\sigma_l + \mu_l) & 0 & q\phi \\ \sigma_l & -(\sigma_p + \mu_p) & 0 \\ 0 & \sigma_p & -\mu_m \end{pmatrix}.$$

The eigenvalues are given by the roots of the polynomial

$$p(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3,$$

where

$$\begin{aligned} a_1 &= \sigma_l + \mu_l + \sigma_p + \mu_p + \mu_m \\ a_2 &= (\sigma_l + \mu_l)(\sigma_p + \mu_p + \mu_m) + (\sigma_p + \mu_p)\mu_m \\ a_3 &= (\sigma_l + \mu_l)(\sigma_p + \mu_p)\mu_m(1 - R_M). \end{aligned}$$

The condition that the eigenvalues have negative real part is equivalent to the coefficients of p satisfying the Routh–Hurwitz criteria for a polynomial of degree 3, namely, $a_i > 0$, $i = 1, \ldots, 3$, and $a_1 a_2 > a_3$.[40] It is immediate to see that these conditions are fulfilled for $R_M < 1$. Hence, the equilibrium E_0 is LAS if $R_M < 1$. When $R_M > 1$, $a_3 < 0$, which implies that E_0 is unstable in this case.

Global stability of E_0 is shown by the Lyapunov function $\mathcal{V} : R_+^3 \to R$ given by

$$\mathcal{V} = L + \frac{\sigma_l + \mu_l}{\sigma_l} P + \frac{(\sigma_l + \mu_l)(\sigma_p + \mu_p)}{\sigma_l \sigma_p} M, \tag{A.1}$$

with orbital derivative

$$\dot{\mathcal{V}} = q\phi(1 - L/C)M - \mu_m \left(\frac{(\sigma_l + \mu_l)(\sigma_p + \mu_p)}{\sigma_l \sigma_p} \right) M$$
$$= -q\phi LM/C - \mu_m \left(\frac{(\sigma_l + \mu_l)(\sigma_p + \mu_p)}{\sigma_l \sigma_p} \right) M(1 - R_M) \leq 0$$

for $R_M \leq 1$. The Lyapunov–Lasalle Theorem[41] implies that all positive solutions of (2.1) approach the largest positively invariant set contained in $\dot{\mathcal{V}} = 0$. By inspection, it can be seen easily that this set is equal to $\{E_0\}$ proving global stability of E_0 when $R_M \leq 1$.

Assume $R_M > 1$, then the equilibrium E_1 emerges in the region of biological interest. To prove that all trajectories with initial conditions bigger than zero approach it, we use the Lyapunov function given in Ref. 42 for ecological models,

$$\mathcal{U} = b_1 \left(L - \bar{L} - \bar{L} \ln \frac{L}{\bar{L}} \right) + b_2 \left(P - \bar{P} - \bar{P} \ln \frac{P}{\bar{P}} \right) + b_3 \left(M - \bar{M} - \bar{M} \ln \frac{M}{\bar{M}} \right), \tag{A.2}$$

where $b_1 = 1$, $b_2 = q\phi(1 - \bar{L}/C)\frac{\bar{M}}{\sigma_l \bar{L}}$, and $b_3 = q\phi(1 - \bar{L}/C)\frac{\bar{M}}{\sigma_p \bar{P}}$.

The orbital derivative of $\mathcal{U}$ is given by

$$\dot{\mathcal{U}} = b_1 \left(1 - \frac{\bar{L}}{L} \right) (q\phi(1 - L/C)M - (\sigma_l + \mu_l)L)$$
$$+ b_2 \left(1 - \frac{\bar{P}}{P} \right) (\sigma_l L - (\sigma_p + \mu_p))$$
$$+ b_3 \left(1 - \frac{\bar{M}}{M} \right) (\sigma_p P - \mu_m M). \tag{A.3}$$

From system (2.2) we obtain the following relations

$$\sigma_l + \mu_p = q\phi(1 - \bar{L}/C)\frac{\bar{M}}{\bar{L}}$$
$$\sigma_p + \mu_p = \frac{\sigma_l \bar{L}}{\bar{P}} \tag{A.4}$$
$$\mu_m = \frac{\sigma_p \bar{P}}{\bar{M}}.$$

Substituting the constants b_i, and the parameters $\sigma_l + \mu_p$ up to μ_m in the Lyapunov derivative (A.3), we obtain after several calculations and simplifications

$$\dot{\mathcal{U}} = q\phi(1 - \bar{L}/C)\bar{M} \left[3 - \frac{\bar{P}}{P}\frac{L}{\bar{L}} - \frac{\bar{M}}{M}\frac{P}{\bar{P}} - \frac{M}{\bar{M}} + \frac{M}{\bar{M}}\frac{(C - L)}{(C - \bar{L})} \left(1 - \frac{\bar{L}}{L} \right) \right].$$

Adding and subtracting $\frac{M}{\bar{M}}\frac{\bar{L}}{L}$, and after more simplifications we obtain

$$\dot{\mathcal{U}} = q\phi(1 - \bar{L}/C)\bar{M} \left[\left(3 - \frac{\bar{P}}{P}\frac{L}{\bar{L}} - \frac{\bar{M}}{M}\frac{P}{\bar{P}} - \frac{M}{\bar{M}}\frac{\bar{L}}{L} \right) - \frac{M}{\bar{M}}\frac{(L - \bar{L})^2}{L(C - \bar{L})} \right].$$

The last summand inside the brackets is negative since $\bar{L} < C$. On the other hand, defining $x_1 = \frac{L}{\bar{L}}$, $x_2 = \frac{P}{\bar{P}}$ and $x_3 = \frac{M}{\bar{M}}$, the expression inside the parenthesis can be written as

$$f(x_1, x_2, x_3) = 3 - \frac{x_1}{x_2} - \frac{x_2}{x_3} - \frac{x_3}{x_1}.$$

Using the fact that the geometric mean is less or equal than the arithmetic mean, it is straightforward to see that $f(x_1, x_2, x_3) \leq 0$, for x_j in R_+, $i = 1, \ldots, 3$, and $f(x_1, x_2, x_3) = 0$ only when $x_j = 1$. Hence, it follows that $\dot{\mathcal{U}} \leq 0$ and $\dot{\mathcal{U}} = 0$ if and only if $L = \bar{L}$, $P = \bar{P}$, $M = \bar{M}$. This implies that all trajectories with initial conditions bigger than zero approach E_1 as $t \to \infty$, which proves the global stability of E_1.

Appendix B. Stability of the Disease-Free Equilibrium P_0 and the Endemic Equilibrium P_1

Proposition. The disease-free equilibrium, P_0, of model (3.4) is GAS whenever $R_0 < 1$.

Proof. The equations for the variables $m_e, m_1, m_2, h_1, h_2, h_i$ of system (3.4) satisfy the following linear differential inequality

$$\begin{pmatrix} m_e'(t) \\ m_1'(t) \\ m_2'(t) \\ h_1'(t) \\ h_2'(t) \\ h_i'(t) \end{pmatrix} \leq (K - F) \begin{pmatrix} m_e(t) \\ m_1(t) \\ m_2(t) \\ h_1(t) \\ h_2(t) \\ h_i(t) \end{pmatrix}, \tag{B.1}$$

where the matrices K and F are as defined in the main text and $' = d/dt$. If $R_0 < 1$, then $\rho(KF^{-1}) < 1$ which is equivalent to $K - F$ having all its eigenvalues in the left-half plane.[28,29] It follows that the linear ODE system

$$\bar{y}' = (K - F)\bar{y} \tag{B.2}$$

is stable whenever $R_0 < 1$. Therefore, the solutions $\bar{y}$ approach $(0, 0, 0, 0, 0, 0)$ as $t \to \infty$. Then, using a standard comparison theorem (Ref. 43, p. 31),

$$[m_e(t), m_1(t), m_2(t), h_1(t), h_2(t), h_i(t)] \to (0, 0, 0, 0, 0, 0)$$

for $R_0 < 1$. As a consequence, $dh_s(t)/dt \to \mu_h - \mu_h h_s(t)$, which implies $h_s(t) \to 1$. This proves that

$$[m_e(t), m_1(t), m_2(t), h_s(t), h_1(t), h_2(t), h_i(t)] \to (0, 0, 0, 1, 0, 0, 0),$$

and hence the disease-free equilibrium, P_0, is GAS whenever $R_0 < 1$.

P_0 becomes an unstable hyperbolic point for $R_0 > 1$, and the endemic equilibrium P_1 emerges. Global stability of P_1 can be proved using the following Lyapunov function of the variables $m_s, m_e, m_1, m_2, h_s, h_1, h_2, h_i$,[42]

$$\begin{aligned}\mathcal{W} = {} & c_1\left(m_s - \bar{m}_s - \bar{m}_s \ln\frac{m_s}{\bar{m}_s}\right) + c_2\left(m_e - \bar{m}_e - \bar{m}_e \ln\frac{m_e}{\bar{m}_e}\right) \\ & + c_3\left(m_1 - \bar{m}_1 - \bar{m}_1 \ln\frac{m_1}{\bar{m}_1}\right) + c_4\left(m_2 - \bar{m}_2 - \bar{m}_2 \ln\frac{m_2}{\bar{m}_2}\right) \\ & + c_5\left(h_s - \bar{h}_s - \bar{h}_s \ln\frac{h_s}{\bar{h}_s}\right) + c_6\left(h_1 - \bar{h}_1 - \bar{h}_1 \ln\frac{h_1}{\bar{h}_1}\right) \\ & + c_7\left(h_2 - \bar{h}_2 - \bar{h}_2 \ln\frac{h_2}{\bar{h}_2}\right) + c_8\left(h_i - \bar{h}_i - \bar{h}_i \ln\frac{h_i}{\bar{h}_i}\right), \end{aligned} \tag{B.3}$$

where $\bar{m}_s = 1 - \bar{m}_e - \bar{m}_1 - \bar{m}_2$, and

$$\begin{aligned} c_1 = c_2 &= \beta_1 \bar{m}_1 \bar{h}_s \alpha_e \bar{h}_1 + \beta_2 \bar{m}_2 \bar{h}_s \alpha_e \bar{h}_2, \\ c_3 &= \frac{c_1 \beta_m \bar{h}_i \bar{m}_s}{\gamma_e \bar{m}_e}, \\ c_4 &= \frac{\beta_2 \bar{m}_2 \bar{h}_s \alpha_e \bar{h}_2 \beta_m \bar{h}_i \bar{m}_s}{\gamma_1 \bar{m}_1} \\ c_5 &= \frac{c_1 \beta_m \bar{h}_i \bar{m}_s}{\beta_1 \bar{m}_1 \bar{h}_s + \beta_2 \bar{m}_2 \bar{h}_s} \\ c_6 &= \beta_m \bar{h}_i \bar{m}_s \alpha_e \bar{h}_1 \\ c_7 &= \beta_m \bar{h}_i \bar{m}_s \alpha_e \bar{h}_2 \\ c_8 &= \frac{c_1 \beta_m \bar{h}_i \bar{m}_s}{\alpha_e(\bar{h}_1 + \bar{h}_2)}. \end{aligned} \tag{B.4}$$

The orbital derivative of $\mathcal{W}$ is given by

$$\begin{aligned}\dot{\mathcal{W}} = {} & c_1\left(1 - \frac{\bar{m}_s}{m_s}\right)(\mu_m - \beta_m h_i m_s - \mu_m m_s) \\ & + c_2\left(1 - \frac{\bar{m}_e}{m_e}\right)(\beta_m h_i m_s - (\gamma_e + \mu_m) m_e) \\ & + c_3\left(1 - \frac{\bar{m}_1}{m_1}\right)(\gamma_e m_e - (\gamma_1 + \mu_m) m_1) \\ & + c_4\left(1 - \frac{\bar{m}_2}{m_2}\right)(\gamma_1 m_1 - \mu_m m_2) \\ & + c_5\left(1 - \frac{\bar{h}_s}{h_s}\right)(\mu_h - (\beta_1 m_1 + \beta_2 m_2) h_s - \mu_h h_s) \end{aligned}$$

$$+ c_6\left(1 - \frac{\bar{h}_1}{h_1}\right)(\beta_1 m_1 h_s - (\alpha_e + \mu_h)h_1)$$
$$+ c_7\left(1 - \frac{\bar{h}_2}{h_2}\right)(\beta_2 m_2 h_s - (\alpha_e + \mu_h)h_2)$$
$$+ c_8\left(1 - \frac{\bar{h}_i}{h_i}\right)(\alpha_e h_1 + \alpha_e h_2 - (\alpha_i + \mu_h)h_i). \tag{B.5}$$

From system (3.4) at equilibrium we obtain the following relations

$$\begin{aligned}
\mu_m &= \beta_m \bar{h}_i \bar{m}_s + \mu_m \bar{m}_s \\
\gamma_e + \mu_m &= \frac{\beta_m \bar{h}_i \bar{m}_s}{\bar{m}_e} \\
\gamma_1 + \mu_m &= \frac{\gamma_e \bar{m}_e}{\bar{m}_1} \\
\mu_m &= \frac{\gamma_1 \bar{m}_1}{\bar{m}_2} \\
\mu_h &= (\beta_1 \bar{m}_1 + \beta_2 \bar{m}_2)\bar{h}_s + \mu_h \bar{h}_s \\
\alpha_e + \mu_h &= \frac{\beta_1 \bar{m}_1 \bar{h}_s}{\bar{h}_1} = \frac{\beta_2 \bar{m}_2 \bar{h}_s}{\bar{h}_2} \\
\alpha_i + \mu_h &= \frac{\alpha_e(\bar{h}_1 + \bar{h}_2)}{\bar{h}_i}.
\end{aligned} \tag{B.6}$$

Substituting the constants c_i, and the parameters μ_m up to $\alpha_i + \mu_h$ in the Lyapunov derivative (B.5), we obtain after several calculations and simplifications

$$\begin{aligned}
\dot{\mathcal{W}} = &-c_1\mu_m \frac{(m_s - \bar{m}_s)^2}{m_s} - c_5\mu_h \frac{(h_s - \bar{h}_s)^2}{h_s} \\
&- A_1\left[\frac{\bar{m}_s}{m_s} + \frac{\bar{h}_s}{h_s} + \frac{\bar{m}_e h_i m_s}{m_e \bar{h}_i \bar{m}_s} + \frac{h_1 \bar{h}_i}{\bar{h}_1 h_i} + \frac{m_1 \bar{h}_1 h_s}{\bar{m}_1 h_1 \bar{h}_s} + \frac{\bar{m}_1 m_e}{m_1 \bar{m}_e} - 6\right] \\
&- A_2\left[\frac{\bar{m}_s}{m_s} + \frac{\bar{h}_s}{h_s} + \frac{\bar{m}_e h_i m_s}{m_e \bar{h}_i \bar{m}_s} + \frac{m_2 \bar{h}_2 h_s}{\bar{m}_2 h_2 \bar{h}_s} + \frac{h_2 \bar{h}_i}{\bar{h}_2 h_i} + \frac{\bar{m}_1 m_e}{m_1 \bar{m}_e} + \frac{m_1 \bar{m}_2}{\bar{m}_1 m_2} - 7\right],
\end{aligned} \tag{B.7}$$

where $A_1 = \beta_m \bar{h}_i \bar{m}_s \bar{h}_s \alpha_e \beta_1 \bar{M} \bar{m}_1 \bar{h}_1$, and $A_2 = \beta_m \bar{h}_i \bar{m}_s \bar{h}_s \alpha_e \beta_2 \bar{M} \bar{m}_2 \bar{h}_2$.

Proceeding as in the case of Lyapunov function $\mathcal{U}$ given by (A.3), it is straightforward to see that the expressions inside the square parenthesis in (B.7) are less or equal to zero, and they are zero if and only if $m_s = \bar{m}_s$, $m_e = \bar{m}_e$, $m_1 = \bar{m}_1$, $m_2 = \bar{m}_2$, $h_s = \bar{h}_s$, $h_1 = \bar{h}_1$, $h_2 = \bar{h}_2$ and $h_i = \bar{h}_i$. Therefore, $\dot{\mathcal{W}} \leq 0$, and $\dot{\mathcal{W}} = 0$ only for $(\bar{m}_s, \bar{m}_e, \bar{m}_1, \bar{m}_2, \bar{h}_s, \bar{h}_1, \bar{h}_2, \bar{h}_i)$. This implies that all trajectories $(m_e(t), m_1(t), m_2(t), h_s(t), h_1(t), h_2(t), h_i(t))$ in the interior of Ω approach P_1 as $t \to \infty$.