The transovarial transmission in the dynamics of dengue infection: Epidemiological implications and thresholds

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ABSTRACT

The anthropophilic and peridomestic female mosquito Aedes aegypti bites humans to suck blood to mature fertilized eggs, during which dengue virus can be spread between mosquito and human populations. Besides this route of transmission, there is a possibility of dengue virus being passed directly to offspring through transovarial (or vertical) transmission. The effects of both horizontal and transovarial transmission routes on the dengue virus transmission are assessed by mathematical modeling. From the model, the reproduction number is obtained and the contribution of transovarial transmission is evaluated for different levels of horizontal transmission. Notably, the transovarial transmission plays an important role in dengue spread when the reproduction number is near one. Another threshold parameter arises, which is the product of the fractions of the susceptible populations of humans and mosquitoes. Interestingly, these two threshold parameters can be obtained from three different approaches: the spectral radius of the next generation matrix, the Routh–Hurwitz criteria and M-matrix theory.

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1. Introduction

Dengue virus is a flavivirus transmitted by arthropod of the genus Aedes. As a result of being pathogenic for humans and capable of transmission in heavily populated areas, dengue virus (an arbovirus) can cause widespread and serious epidemics, which constitute one of the major public health problems in many tropical and subtropical regions of the world where Aedes aegypti and other appropriate mosquito vectors are present [1].

The incidence of dengue is clearly dependent on abiotic factors such as temperature and precipitation, which affect directly the population dynamics of mosquitoes with serious implications for dengue transmission. By using estimated entomological parameters dependent on temperature, and including the dependency of these parameters on rainfall, the seasonally varying population size of mosquito A. aegypti was evaluated by a mathematical model [2]. This model considered only the horizontal transmission, but the transovarial (or vertical) transmission can play some role in dengue epidemics, which must be assessed.

There is evidence that transovarial (the transfer of pathogens to succeeding generations through invasion of the ovary and infection of the eggs) transmission can occur in some species of Aedes mosquitoes [3–8], but the role of transovarial transmission in the maintenance of dengue epidemics is not clearly understood [9,10]. Moreover, the transovarial transmission of dengue virus in A. aegypti has been observed at a relatively low rate [3,8].

In this paper, the transovarial transmission is included in the modeling. The effects of both horizontal and transovarial routes of dengue transmission are analyzed by obtaining the gross reproduction number, denoted by $R_0$. This is a threshold parameter encompassing model parameters related to the horizontal and transovarial transmission. The reproduction number $R_0$ is obtained by using three different methods aiming the comparison among them; evaluating the spectral radius of the next generation matrix [10], and determining the conditions that assure to Jacobian matrix eigenvalues with negative real part, which can be assessed by two methods: Routh–Hurwitz criteria and M-matrix theory [11–13].

In simple directly transmitted infection modeling, there is a well established relationship between the fraction of susceptible humans ($s$) and the basic reproduction number ($R_0$) in the endemic steady state [14,15]: $s^* = 1/R_0$. Similarly, in dengue transmission modeling considering only horizontal transmission, the inverse of $R_0$ is the product of the fractions of susceptible humans and mosquitoes, denoted by $\chi_0$. But, if transovarial transmission is included in this dengue transmission, then $\chi_0$ cannot be set as the inverse of $R_0$, and an additional threshold quantity must arise. The appearance however of two thresholds also arise for directly transmitted infections modeling. For instance, a well understood two thresholds occur in diseases with secondary infection, such as tuberculosis: a threshold and a sub-threshold [16]. But two thresholds, one for the gross reproduction number and other for the...
fraction of susceptible individuals, can occur: Driessche and Watmough [10], in their analysis of a tuberculosis transmission including treatment, did not realize the existence of these two thresholds.

The paper is structured as follows. In Section 2, model for dengue transmission encompassing transovarial transmission is presented, and in Section 3, the model is analyzed, determining the equilibrium points, and performing the stability analysis of the disease free equilibrium point. Section 4 presents the discussion about the effects of the transovarial transmission on dengue transmission and on the gross reproduction number $R_0$, and the produce of the fractions of susceptibles $X_0$, and the interpretation of these two thresholds for tuberculosis with failure in the treatment. Conclusions are given in Section 5.

2. A model for dengue transmission

Dengue virus circulates due to the interaction between human and mosquito populations in urban areas. A unique serotype of dengue virus is being considered in the modeling. A model incorporating two or more serotypes of dengue virus (currently, there are four serotypes) becomes complex. For instance, disregarding co-infection with two or more serotypes, the number of classes of infectious mosquitoes and humans are increased, besides the complexity resulting by the incorporation of the periods of time of cross-immunity in the modeling.

The model described here considers dengue virus being transmitted by both horizontal and transovarial transmission routes.

With respect to state (dynamical) variables, the human population is divided into three compartments according to the natural history of the disease: $s, i$ and $r$, which are the fractions at time $t$ of, respectively, susceptible, infectious and recovered persons, with $s + i + r = 1$. The constant total number of the human population is designated by $N$. The female adult mosquito population is divided into two compartments: $m_1$ and $m_2$, which are the numbers at time $t$ of, respectively, susceptible and infectious mosquitoes. The size of female mosquito population is given by $m = m_1 + m_2$. In both populations the latent classes are omitted.

The incorporation of the transovarial transmission of dengue virus results in more state variables. A fraction $\alpha$, with $0 \leq \alpha \leq 1$, of eggs laid by infectious mosquitoes $m_2$ is infected by virus dengue through transovarial transmission. Hence, the immature (or aquatic) phase of mosquito is split into two categories, which are denoted by $I_1$ and $I_2$ representing the numbers of, respectively, uninfected and infected immatures (comprising larvae and pupae, following Yang et al. [17]) at time $t$, where the total size is $l = l_1 + l_2$. In Yang et al. [18], $A. aegypti$ population modeling considered larva and pupa compartments. Due to the transovarial transmission being focused on, a simplified version of the model (constant human population and an aquatic phase comprising larva and pupa) is considered here (Table 1).

![Table 1](image1)

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>$l_1$</td>
<td>Density of uninfected immatures (females)</td>
</tr>
<tr>
<td>$l_2$</td>
<td>Density of infected immatures (females)</td>
</tr>
<tr>
<td>$l$</td>
<td>Total density of immatures (females)</td>
</tr>
<tr>
<td>$m_1$</td>
<td>Density of uninfected adult mosquitoes (females)</td>
</tr>
<tr>
<td>$m_2$</td>
<td>Density of infected adult mosquitoes (females)</td>
</tr>
<tr>
<td>$m$</td>
<td>Total density of mosquito population (females)</td>
</tr>
<tr>
<td>$s$</td>
<td>Fraction of susceptible humans</td>
</tr>
<tr>
<td>$i$</td>
<td>Fraction of infectious humans</td>
</tr>
<tr>
<td>$r$</td>
<td>Fraction of recovered humans</td>
</tr>
<tr>
<td>$N$</td>
<td>Total size of human population</td>
</tr>
</tbody>
</table>

![Table 2](image2)

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_h$</td>
<td>Transmission coefficient to female mosquitoes</td>
</tr>
<tr>
<td>$\beta_m$</td>
<td>Transmission coefficient to humans</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Fraction of immatures infected by vertical transmission</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Per-capita oviposition rate</td>
</tr>
<tr>
<td>$q$</td>
<td>Fraction of eggs hatching</td>
</tr>
<tr>
<td>$f$</td>
<td>Fraction of female eggs laying in larval stage</td>
</tr>
<tr>
<td>$C$</td>
<td>Total number of breeding sites</td>
</tr>
<tr>
<td>$\sigma_a$</td>
<td>Per-capita transformation rate of immatures to adults</td>
</tr>
<tr>
<td>$\mu_a$</td>
<td>Per-capita mortality rate of immatures</td>
</tr>
<tr>
<td>$\mu_f$</td>
<td>Per-capita mortality rate of humans</td>
</tr>
<tr>
<td>$\sigma_r$</td>
<td>Per-capita recovery rate of humans</td>
</tr>
</tbody>
</table>

With respect to the model parameters, the birth and mortality rates of human population are equal (constant size), both designated by $\mu_h$. The life cycle of $A. aegypti$ encompasses an aquatic phase (larva and pupa) followed by winged (adult) form. The number of eggs is determined by the oviposition rate $\psi(M) = \hat{q} \hat{M}$, where $\phi$ is the per-capita oviposition rate. As $l$ is the number at time $t$ of immatures comprised by larvae and pupae (female) that constitute the entire aquatic phase, the effective immatures production rate is given by $\hat{q} f (1 - 1/C) \hat{m}$, where $q$ and $f$ are the fractions of eggs that are hatching to larva and that will originate female mosquitoes, respectively, and $C$ is the total carrying capacity of the breeding sites (see [19] for a model including egg compartments). The number of immatures decreases according to change to adult form (or mature) and death, described, respectively, by the changing $\sigma_a$ and the mortality $\mu_a$ rates. The number of female mosquitoes increases according to the emerging of immatures ($\sigma_a$) and decreases according to the mortality rate $\mu_f$.

The horizontal transmission of dengue virus is sustained by the flows between human and mosquito compartments according to the following dengue epidemics cycle. The susceptible humans are infected during the blood meal by infectious mosquitoes, with the transmission rate being designated by $B_0$, which depends on the frequency of bites on humans by mosquitoes. A very simple way to take into account the frequency of bites is letting it to be proportional to oviposition rate $\phi$, that is, $B_0 = \beta_h \alpha \phi$, where $\beta_h$ is the transmission coefficient from mosquito to human (dimensionless). The infectious persons are removed to recovered (immune) class after an average recovery period $1/\sigma_h$, where $\sigma_h$ is the recovery rate. Neither loss of immunity nor induced mortality due to the disease (a unique serotype infection) are considered. With respect to the vector, the susceptible mosquitoes are infected at a rate $B_m = \beta_m \phi$, with $\beta_m$ being the transmission coefficient from human to mosquito (dimensionless). These infectious mosquitoes remain infective until death. To incorporate the feature that a particular human is bitten by a particular mosquito, the transmission rates $B_0$ and $B_m$ must be divided by $N$.

In the transovarial transmission route, it is assumed that a fraction $\alpha$ of eggs laid by infected mosquitoes are indeed harboring dengue virus. It is assumed that uninfected ($l_1$) and infected ($l_2$) aquatic forms have similar behavior. The infected aquatic forms that emerge as male mosquitoes are not considered here, in order to simplify the model (see [20] for a model considering the mating between male and female mosquitoes) (Table 2).

Based on the foregoing descriptions of model parameters and dynamical states, the dengue transmission encompassing transovarial transmission is described by the system of differential
equations

\[
\begin{align*}
\frac{d}{dt} l_1 &= q_f \phi (m_1 + (1 - \alpha) m_2) \left(1 - \frac{l_1 + l_2}{C}\right) - (\sigma_a + \mu_f) l_1 \\
\frac{d}{dt} l_2 &= q_f \phi \alpha m_2 \left(1 - \frac{l_1 + l_2}{C}\right) - (\sigma_a + \mu_f) l_2 \\
\frac{d}{dt} m_1 &= \sigma_a l_1 - (\beta_m \phi + \mu_f) m_1 \\
\frac{d}{dt} m_2 &= \sigma_a l_2 + \beta_m \phi m_1 - \mu_f m_2 \\
\frac{d}{dt} s &= \mu_h - \left(\frac{\beta_h \phi}{N} m_2 + \mu_h\right) s \\
\frac{d}{dt} i &= \beta_h \phi N m_2 S - (\sigma_h + \mu_h) i.
\end{align*}
\]

(1)

where the decoupled fraction of immune persons is given by \( r = 1 - s - i \). Notice that the vector population is described by total numbers and the human population, by fractions. However, equations describing the mosquito population can be divided by the carrying capacity \( C \), which result in densities (number of mosquitoes and larvae per carrying capacity).

3. Analysis of the model

The system of Eq. (1) is dealt with determining the equilibrium points, and assessing the stability of these points.

3.1. Equilibrium points

There are three equilibrium points. The first is the absence of mosquitoes, that is, the equilibrium 

\[ P^{o0} = (l_1 = 0, l_2 = 0, m_1 = 0, m_2 = 0, s = 1, i = 0), \]

which corresponds to the eradication of mosquito population.

The second equilibrium is the trivial equilibrium \( P^0 \), or disease free equilibrium (DFE), given by 

\[ P^0 = (l_1 = 1, l_2 = 0, m_1 = m^*, m_2 = 0, s = 1, i = 0), \]

with \( P^+ \) and \( m^+ \) being given by

\[
\begin{align*}
P^+ & = C \left(1 - \frac{1}{Q_0}\right) \\
m^+ & = \frac{\sigma_a}{\mu_f} C \left(1 - \frac{1}{Q_0}\right),
\end{align*}
\]

(2)

where

\[ Q_0 = \frac{\sigma_a q_f \phi}{\sigma_a + \mu_a \mu_f} \]

(3)

is the basic offspring number considering entire aquatic form as one compartment. Clearly the mosquito population exists if \( Q_0 > 1 \). This equilibrium describes a mosquito population well established in a region without dengue transmission.

The basic offspring number \( Q_0 \) is interpreted as follows. One female mosquito lays on average \( \sigma_a / \sigma_a + \mu_a \) eggs (female) during her entire lifespan. These eggs must hatch \( q \) and survive the aquatic phase (with probability \( \sigma_a / (\sigma_a + \mu_a) \)), and then emerge as adults. Hence \( Q_0 \), given by Eq. (3), is the average number of female mosquitoes generated by a single female mosquito.

Finally, the non-trivial equilibrium \( P^* \), or endemic equilibrium (see Appendix A for details), which corresponds to the dengue infection occurring in human and mosquito populations, is given by 

\[ P^* = (l_1 = l_1^*, l_2 = l_2^*, m_1 = m_1^*, m_2 = m_2^*, s = s^*, i = i^*), \]

with the coordinates being given by

\[
\begin{align*}
l_1^* &= (1 - \alpha) \frac{\beta_m \phi + \mu_f}{\beta_m \phi (1 - \alpha) + \mu_f} C \left(1 - \frac{1}{Q_0}\right) \\
l_2^* &= \alpha \frac{\beta_m \phi + \mu_f}{\beta_m \phi (1 - \alpha) + \mu_f} C \left(1 - \frac{1}{Q_0}\right) \\
m_1^* &= (1 - \alpha) \frac{\beta_m \phi + \mu_f}{\beta_m \phi (1 - \alpha) + \mu_f} \frac{\sigma_a}{\mu_f} C \left(1 - \frac{1}{Q_0}\right) \\
m_2^* &= \alpha \frac{\beta_m \phi + \mu_f}{\beta_m \phi (1 - \alpha) + \mu_f} \frac{\sigma_a}{\mu_f} C \left(1 - \frac{1}{Q_0}\right) \\
\phi = m^* &= \frac{\beta_m \phi (\mu_h + \mu_f) (\sigma_a + \mu_a)}{\mu_h \mu_f (R_0 - 1)} \]

(4)

resulting in \( R_0 = R_0^0 R_0^1 \). Notice that \( [(\beta_m \phi) N] / \mu_f \) is the average number of humans (in a susceptible population of size \( N \)) infected by one infectious mosquito during her entire lifespan; hence \( R_0^0 \) is the average number of infectious humans produced by one infectious mosquito introduced in a community free of dengue. Now, \( [(\beta_m \phi) N] m^* / (\sigma_a + \mu_a) \) is the average number of mosquitoes (in a susceptible population of size \( m^* \)) infected by one infectious human during his/her infectious period; hence \( R_0^1 \) is the average number of infectious mosquitoes produced by one infectious human introduced in a community free of dengue.

The gross reproduction number \( R_g \) is interpreted as follows. \( R_0 \) is the average number of secondary infectious humans (or mosquitoes) produced by one primary infectious human (or mosquito) introduced in a completely susceptible populations of humans and mosquitoes. That is, \( R_g \) gives the average number of secondary infectious mosquitoes due to horizontal transmission. The term \( R_0 \) is the contribution of the transovarial transmission, which is not the average number of infectious mosquitoes (daughters) generated by a single infectious mosquito by transovarial transmission. Hence \( R_g \), given by Eq. (5), is the overall number of infectious mosquitoes generated by a single infectious mosquito due to horizontal plus a contribution due to transovarial transmissions (see below for the role played by \( R_0 \) and \( R_0^1 \) in the dynamics of dengue transmission).

The combination of \( \phi^* \) and \( m^* \) in the endemic steady state, given by Eqs. (2) and (4), results in

\[
\phi^* \frac{m^*}{m_f} = X_0 = 1 - \frac{\alpha}{R_0} - \frac{1 - R_0}{R_0}. \]

(8)

where \( X_0 \) is the product of the fractions in the steady state of susceptible humans and mosquitoes encompassing the transovarial
transmission. If $R_v = 1$, then $m_t^* = 0$ and $s^*m_t^*/m^* = 0$. Notice that it is not equal to the inverse of the gross reproduction number $R_g$ given by Eq. (5). But, if the transovarially transmitted dengue virus is neglected ($R_v = 0$), then we retrieve the well known relationship $\chi_0 = 1/R_0$.

However, $\chi_0$ brings implicitly the idea of the gross reproduction number, as expected. The equation relating susceptible fractions, given by Eq. (8), has clearly a biological interpretation. The term $1/R_0$ is the decreasing in the fractions of susceptible populations due to the horizontal transmission, while the term $R_v/R_0$ is the additional decreasing due to transovarial transmission. The appearance of $R_0$ in latter term shows that the transovarial transmission is a consequence of horizontal transmission, in other words, it is necessary that $R_0 > 0$. Additionally, this latter term is such that the sum of denominator ($R_0$) and numerator ($R_v$) results in the gross reproduction number, hence $\chi_0$ brings indirectly the concept of $R_g$. Further, as $R_v$, $\chi_0$ must also be a threshold parameter. In this particular modeling, the transovarial reproduction number $R_v$ does not depend on the horizontal transmission coefficients $\beta_h$ and $\beta_m$, neither on entomological parameters.

There are two routes of transmission. One is the horizontal transmission, where dengue transmission occurs according to the random encounter between densities of sub-populations (mass action law). This route is assessed by the horizontal reproduction number ($R_0$). The transovarial transmission route, however, is not a random event: whenever infectious mosquitoes exist, a fraction $\alpha$ is certainly infected offsprings constituting of infections promoted by feedback of infectious mosquitoes. Hence, the gross reproduction number $R_0$ is a sum of random event ($R_0$) and a certain event ($R_v$). For this reason, the horizontal reproduction number $R_0$ is also the well known basic reproduction number. This is corroborated by Eq. (8): the denominator is $R_0$.

Let the existence of the equilibrium points be summarized:

1. The human population free of mosquitoes is described by the equilibrium $p^0$, which always exists.

2. The mosquito population well established in a region without dengue transmission is described by the trivial equilibrium $p^0$, which exists if $Q_0 > 1$.

3. The dengue transmission occurring in human and mosquito populations is described by the non-trivial equilibrium $p^*$, which exists if $Q_0 > 1$ and $R_0 > 1$.

3.2. Stability analysis of DF

The stability analysis is restricted to the DF by applying the spectral radius theory. For this reason, the order of equations in dynamical system (1) is reorganized according to vector

$$x = (m_2, i, l_2, l_1, m_1, s)^T,$$

with $T$ standing for the transposition of a matrix, and Eq. (1) can be written in matrix form as

$$\frac{dx}{dt} = f_p(x) - \nu_p(x), \quad p = 1, \ldots, 6,$$  \hspace{1cm} (10)

where the coordinates of $f_p$ and $\nu_p$ are zeros or terms of the right hand side of system (1). The partial derivatives of $f = (f_1, \ldots, f_6)^T$ and $\nu = (\nu_1, \ldots, \nu_6)^T$ with respect to the state variables are evaluated at the DFE.

Preliminarily, the Jacobian matrix corresponding to Eq. (10) evaluated at DFE, named $J = J(p^0)$, results in

$$J = \begin{bmatrix} F & 0 \\ J_1 & J_2 \end{bmatrix},$$

where the matrices $F$ and $J_2$ are

$$F = \begin{bmatrix} -\mu_f & \beta_m \phi m^* \\ \beta_h \phi \frac{m^*}{m} & -\sigma_a + \mu_h \\ \alpha q f \phi \frac{1}{\phi} & 0 & -(\sigma_a + \mu_a) \end{bmatrix}$$

and

$$J_2 = \begin{bmatrix} M & 0 \\ 0 & H \end{bmatrix},$$

with the matrices $M$ and $H$ being given by

$$M = \begin{bmatrix} -q f \phi \frac{m^*}{\phi} - (\sigma_a + \mu_a) & q f \phi \frac{m^*}{\phi} \\ \sigma_a & -\mu_f \end{bmatrix}, \quad H = [-\mu_h].$$

Finally, the matrix $J_1$ is

$$J_1 = \begin{bmatrix} (1 - \alpha) q f \phi \frac{1}{\phi} & 0 & q f \phi \frac{m^*}{\phi} \\ 0 & -\beta_m \phi m^* & 0 \\ -\beta_h \phi \frac{m^*}{\phi} & 0 & 0 \end{bmatrix}.$$  \hspace{1cm} (11)

Notice that the stability of the DFE is assessed by the eigenvalues of $J$ (it is enough to evaluate eigenvalues of $F$ and $J_2$). In Appendix B, Routh–Hurwitz criteria and M-matrix theory are applied to matrix $J$ in order to establish the stability of DFE.

In the next generation matrix method [10,21], the matrix $F$ given by Eq. (11) is divided into two matrices $F_1$ and $V$ and the next generation matrix $F_1V^{-1}$ is calculated, where $F = F_1 - V$ (see below). The spectral radius corresponding to matrix $F_1V^{-1}$, denoted by $\rho(F_1V^{-1})$, is evaluated, which is accepted as the basic reproduction number.

In the analysis of the stability of DFE by evaluating the spectral radius, eigenvalues of matrix $J_2$, or eigenvalues of matrices $M$ and $H$ given by Eq. (12), are assumed to have negative real part. As shown in Appendix B, three eigenvalues $\lambda_{1,2,3}$ corresponding to matrix $J_2$ have negative real part if $Q_0 > 1$.

The next generation matrix is constructed as a subsystem of (10) taking into account the state-at-infection ($l_2$) and the states of infectiousness ($m_2, i$) [22]. Two cases are presented. Remember that exposed compartments of humans and mosquitoes were not considered, which are states-at-infection.

3.2.1. Case I

Here, the procedure is given with some details. Eq. (1) reordered according to Eq. (9) has vectors $f$ and $\nu$ given by

$$f = \left( \beta_m \phi m_1, \beta_h \phi N^{-1}m_2s, 0, 0, 0, 0 \right)^T,$$

and

$$\nu = \begin{bmatrix} -\sigma_d_2 + \mu_f m_2 \\ (\sigma_a + \mu_h)i \\ -q f \phi a m_2 (1 - \frac{h}{1 + h}) + (\sigma_a + \mu_a)i_2 \\ -q f \phi (m_1 + (1 - \alpha)m_2)(1 - \frac{h}{1 + h}) + (\sigma_a + \mu_a)l_1 \\ -\sigma_d_1 + (\beta_m \phi i + \mu_f)m_1 \\ -\mu_h + (\beta_h \phi m^* + \mu_h)s \end{bmatrix}.$$  \hspace{1cm} (12)

Notice that the vector $f$ comprises only horizontal transmission terms.

The partial derivatives of $f$ and $\nu$ evaluated at the DFE are partitioned as

$$DF = \frac{\partial f_p}{\partial x_n} = \begin{bmatrix} F_1 & 0 \\ 0 & 0 \end{bmatrix}, \quad D\nu = \frac{\partial \nu_p}{\partial x_n} = \begin{bmatrix} V \\ -J_1 & -J_2 \end{bmatrix}, \quad 1 \leq p, n \leq 6.$$
where $F_{1}$ and $V$, which are the partial derivatives with respect to $m_{2}$, $i$ and $l_{2}$, are

$$F_{1} = \begin{bmatrix} 0 & \beta_{m_{1}} \phi m^{*} & 0 \\ \frac{\beta_{c}}{N} & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} \mu_{f} & 0 & -\sigma_{a} \\ 0 & \sigma_{h} + \mu_{h} & 0 \\ -ja_{f} \phi \frac{1}{\sigma_{c}} & 0 & \sigma_{a} + \mu_{a} \end{bmatrix},$$

and $J_{2}$ and $J_{1}$ are given by Eqs. (11) and (13). The eigenvalues $\lambda_{1,2,3}$ of matrix $J_{2}$, $\det (J_{2} - \lambda I) \equiv \det (M - \lambda I)$ $\det (H - \lambda I) = 0$, with matrices $M$ and $H$ given by Eq. (11), were discussed above.

First, the case $\alpha < 1$ is studied. The inverse of the matrix $V$ exists and is

$$V^{-1} = \begin{bmatrix} \frac{1}{(1-\sigma_{c})\sigma_{h}} & 0 & \frac{\sigma_{a}}{(1-\sigma_{c})\sigma_{h}(\sigma_{c} + \mu_{a})} \\ \frac{1}{\sigma_{h} + \mu_{h}} & 0 & 0 \\ 0 & \frac{1}{(1-\sigma_{c})\sigma_{h}(\sigma_{c} + \mu_{a})} & 0 \end{bmatrix},$$

and the next generation matrix $F_{1}V^{-1}$ is

$$F_{1}V^{-1} = \begin{bmatrix} 0 & \frac{1}{\sigma_{c}} R_{0}^{h} & 0 \\ \frac{1}{1-\sigma} \frac{1}{\sigma_{c}} R_{0}^{h} & 0 & \frac{1}{\sigma_{c}} R_{0}^{h} \end{bmatrix}.$$ 

In this case, the next generation matrix $F_{1}V^{-1}$ is

$$F_{1}V^{-1} = \begin{bmatrix} 0 & \frac{1}{\sigma_{c}} R_{0}^{h} \sigma_{g} & 0 \\ \alpha \sigma_{g} + \mu_{a} & 0 & 0 \end{bmatrix}.$$

and the corresponding characteristic equation is

$$\lambda^{2} - R_{g}\lambda = 0,$$

with the eigenvalues being $\lambda_{4} = 0$ and $\lambda_{5,6} = \pm \sqrt{R_{g}}$, where $\chi_{0}$ is given by (8), and the spectral radius is $\rho(F_{1}V^{-1}) = \sqrt{R_{g}}$. If $\rho(F_{1}V^{-1}) < 1$, then all eigenvalues corresponding to matrix $F_{1} - V$ have negative real part, and DFE is locally asymptotically stable [10], assuming that all eigenvalues corresponding to $J_{2}$ have negative real part (in fact, this is true whenever $Q_{0} > 1$). Hence, the reproduction number, denoted by $R_{0}^{h}$, is

$$R_{0}^{h} = \frac{\rho(F_{1}V^{-1})}{\sqrt{R_{g}}} = \sqrt{\chi_{0}}.$$

For $\alpha = 1$, $\det(V) = 0$ and $V$ is not invertible. Hence, the next generation matrix is not defined.

For $R_{0}^{h} < 1$, DFE is locally asymptotically stable, and unstable for $R_{0}^{h} > 1$. Therefore, the threshold occurs at $\chi_{0} = 1$, and DFE is unstable for $\chi_{0} < 1$. 

3.2.2. Case 2

The vector $f$, given by Eq. (14), can be constructed in a different way. From vector $v$, the terms corresponding to the emerging of infectious mosquitoes from infectious aquatic phase ($\sigma d_{2}$) and the increasing in the infected aquatic phase due to eggs laid by infectious mosquitoes ($q_{f} \phi a m_{2}(1 - (l_{1} + l_{2})/C)$) are transferred to vector $f$. Hence, the vector $f$ is constructed as

$$f = \begin{bmatrix} \beta_{m} \phi m_{1} + \sigma_{d_{2}} \frac{\beta_{c}}{N} m_{3_{S}} & q_{f} \phi a m_{2} \left(1 - \frac{l_{1} + l_{2}}{C}\right), 0, 0, 0 \end{bmatrix}^{T},$$

in which case, matrix $V$ is diagonal. 

In the mosquito population, the dependency of the non-trivial equilibrium point $P_{0}$ on the transovarial transmission parameter $\alpha$ shows two features. One is the practically linear dependency of susceptible and infectious classes of aquatic and adult mosquitoes, and the other is the displacement of the susceptible mosquitoes by the infectious mosquitoes.

When $\alpha = 0$, there is dengue transmission due only to the horizontal transmission. All results can be obtained from the model presented in [2] dropping out the latent classes of mosquito and human populations. As $\alpha$ increases, susceptible aquatic and adult forms practically decrease linearly, while the infectious forms increase linearly.

When $\alpha = 1$ (and, necessarily, $R_{0}^{h} > 0$), the infectious forms displace completely the susceptible forms of the vector, that is, susceptible subpopulations are zero ($l_{1}^{*} = m_{1}^{*} = 0$), while infectious subpopulations reach $l_{2}^{*} = l^{*}$ and $m_{2}^{*} = m^{*}$, where $l^{*}$ and $m^{*}$ are given by equation (2). For this reason, the fractions of susceptible aquatic forms and mosquitoes are zero ($l_{1}^{*}/l^{*} = 0$ and $m_{1}^{*}/m^{*} = 0$).

In this situation, dengue virus can be maintained indefinitely by the transovarial transmission even when $R_{0}^{h} < 1$.

By analyzing the equilibrium values, the transovarial transmission is really important if the fraction of infected eggs $\alpha$ tends to one. Moreover, if the transmission of dengue among mosquitoes is intense, then the transovarial transmission is irrelevant in the
overall dengue transmission (a higher number of mosquitoes become infectious due to intense horizontal transmission; and all mosquitoes are infectious if $\beta_m \to \infty$). However, the infectious humans reach the highest value asymptotically.

Next, the effects of transovarial transmission are assessed by considering susceptible and infectious humans.

### 4.2. Assessing the contributions of the transovarial transmission

Let the effects of transovarial transmission be analyzed through $s^*$ and $i^*$ (Eq. (4)), remembering that the biologically feasible conditions for $s^*$ and $i^*$ are satisfied for $R_0 \geq 1$.

The fraction of infectious humans $i^*$, rewritten as

$$i^* = \begin{cases} 0; & R_0 \leq 1 \\ \frac{\mu_f(R_0 - 1)}{\beta_m \mu + \mu_f(\sigma_h + \mu_h)/R_0}; & R_0 > 1, \end{cases}$$

increases from $i_0^*$ to $i_1^*$ when $\alpha$ goes from 0 to 1, where

$$i_0^* = \begin{cases} 0; & R_0 \leq 1 \\ \frac{\mu_h \mu_f(R_0 - 1)}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & R_0 > 1, \end{cases}$$

$$i_1^* = \begin{cases} 0; & R_0 \leq 1 \\ \frac{\mu_h \mu_f + \mu_f(\sigma_h + \mu_h)/R_0}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & R_0 > 1. \end{cases}$$

Notice that $i_1^*$ is Hill function of order 1 [24]. The fraction of susceptible humans $s^*$, rewritten as

$$s^* = \begin{cases} 0; & R_0 \leq 1 \\ \frac{\beta_m \mu_h \mu_f + \mu_f(\sigma_h + \mu_h)(1 - \alpha)}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & R_0 > 1, \end{cases}$$

decreases from $s_0^*$ to $s_1^*$ when $\alpha$ goes from 0 to 1, where

$$s_0^* = \begin{cases} 0; & R_0 \leq 1 \\ \frac{\beta_m \mu_h \mu_f + \mu_f(\sigma_h + \mu_h)}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & R_0 > 1, \end{cases}$$

$$s_1^* = \begin{cases} 0; & R_0 \leq 1 \\ \frac{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & \forall R_0. \end{cases}$$

The difference and quotient between $i^*_\alpha$ and $i^*_0$ and also $s^*_\alpha$ and $s^*_0$ are determined.

The fractions of infectious humans with (index $\alpha$) and without (index 0) transovarial transmission are compared considering the difference ($d_\alpha$) and the relative contribution, or quotient ($q_\alpha$), between them. From Eqs. (21) and (22), $d_\alpha = i^*_\alpha - i^*_0$ and $q_\alpha = i^*_\alpha/i^*_0$ are given by

$$d_\alpha = \begin{cases} 0; & R_0 \leq 1 \\ \frac{\mu_h \mu_f(R_0 - (1 - \alpha))}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & 1 - R_0 < R_0 \leq 1 \\ \frac{\mu_h \mu_f + \mu_f(\sigma_h + \mu_h)/R_0}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & R_0 > 1, \end{cases}$$

which is continuous for all $R_0$, and

$$q_\alpha = \begin{cases} 0; & R_0 \leq 1 - R_v \\ \frac{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & 1 - R_v < R_0 \leq 1 \\ \frac{1 + \frac{\alpha}{R_v - 1}}{1 + \frac{\alpha}{R_v - 1}}; & R_0 > 1, \end{cases}$$

which is continuous for $R_0 > 1$. The difference $d_\alpha$ increases monotonically from 0 (at $R_0 = 1 - R_v$) to $A_\alpha$ (at $R_0 = 1$), where $A_\alpha$ is

$$A_\alpha = \frac{\mu_h \mu_f}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)},$$

and, then, decreases monotonically to 0 (for $R_0 \to \infty$). In its turn, the quotient $q_\alpha$ is undefined for $R_0 = 1 - R_v$ ($i_0^* = i_1^* = 0$), infinity for $1 - R_v < R_0 \leq 1$ ($i_0^* > 0$ and $i_1^* = 0$), and decreases from infinity to asymptote $q_\alpha = 1$, when $R_0$ goes from 1 to $\infty$.

The difference ($d_\alpha$) and the quotient ($q_\alpha$) between the fractions of infectious humans show two major features:

(i) Higher values of $d_\alpha$ and $q_\alpha$ situate around $R_0$ near 1 (the maximum at $R_0 = 1$, given by $A_\alpha$), showing that the contribution of transovarial transmission is measurable and important near bifurcation value. However, for higher $R_0$, the contribution of transovarial transmission is negligible.

(ii) Higher the transovarial transmission parameter $R_\alpha$, higher the value of $A_\alpha$, and the effects of transovarial transmission is strongly enhanced, that is, there is an increase in the number of infectious individuals in comparison with the number of infectious individuals resulted by considering only the horizontal transmission of dengue.

Therefore, when horizontal transmission is higher, the transovarial transmission does not matter. However, for lower horizontal transmission, or even below the threshold value, the contribution of the transovarial transmission surpasses the horizontal transmission, and the relative contribution ($q_\alpha$) can approach infinity for $|R_0 - 1| < \varepsilon$, for small $\varepsilon$. In temperate regions, the transovarial transmission can be neglected in favorable (summer) seasons, but in unfavorable (winter) seasons, the contribution of transovarial transmission could be important in order to maintain the dengue transmission even for $R_0 < 1$.

The fractions of susceptible humans with (index $\alpha$) and without (index 0) transovarial transmission are compared considering the difference ($d_\alpha$) and the relative contribution, or quotient ($q_\alpha$), between them. From Eqs. (23) and (24), $d_\alpha = s_\alpha^* - s_0^* = -\frac{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}$ and $q_\alpha = s_\alpha^*/s_0^*$ are given by

$$d_\alpha = \begin{cases} 0; & R_0 \leq 1 - R_v \\ \frac{\sigma_h + \mu_h}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & 1 - R_v < R_0 \leq 1 \\ \frac{\sigma_h + \mu_h}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & R_0 > 1, \end{cases}$$

showing that $s_\alpha^* \leq s_0^*$, which is continuous for all $R_0$, and

$$q_\alpha = \begin{cases} 0; & R_0 \leq 1 - R_v \\ \frac{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & 1 - R_v < R_0 \leq 1 \\ \frac{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}; & R_0 > 1, \end{cases}$$

which is continuous for all $R_0$, and clearly $C_\alpha \leq 1$. The difference $d_\alpha$ decreases monotonically from 0 (at $R_0 = 1 - R_v$) to $-B_v$ (at $R_0 = 1$), where $B_v$ is

$$B_v = \frac{\sigma_h + \mu_h}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0},$$

and, then, increases monotonically to 0 (for $R_0 \to \infty$). In its turn, the quotient $q_\alpha$ is unity for $R_0 \leq 1 - R_v$ ($s_\alpha^* = s_0^*$), decreases from 1 (at $R_0 = 1 - R_v$) to $C_\alpha = 1 - B_v$ (at $R_0 = 1$), and assumes fixed value $C_\alpha$, when $R_0$ goes from 1 to $\infty$.

The difference ($d_\alpha$) and the quotient ($q_\alpha$) between the fractions of susceptible humans show practically the same features presented in the above analysis regarded to infectious individuals: maximum at $R_0$ near 1. However, the quotient $q_\alpha$ assumes finite value at $R_0 = 1$. differently of $q_\alpha$. Notice that, for $R_0 \geq 1$, the relation

$$s_\alpha^* = C_\alpha s_0^* = \frac{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0}{\beta_m \mu_h + \mu_f(\sigma_h + \mu_h)/R_0} s_0^*,$$

with $C_\alpha \leq 1$, shows that the transovarial transmission decreases the fraction of susceptible individuals in comparison with the case where only horizontal transmission is occurring ($d_\alpha < 0$), and the
highest decreasing occurs at $\alpha = 1$. Remember that, in this case, $s_1^* > 0$ but $m_1^* = m^*$, resulting in $m_1^*/m^* = 0$. hence $X_0 = 0$.

Summarizing, the transovarial transmission increases the fractions of infectious humans and mosquitoes, but decreases the susceptible populations. Additionally, for higher values of the transmission coefficients, the corresponding values of $d_i$, $q_i$, and $q_f$ show that the transovarial transmission is irrelevant. However, from $d_i > 0$ and $d_{ii} < 0$, the epidemics occurring with transovarial transmission is more severe than epidemics occurring with horizontal transmission only, especially in the range $|R_0 - 1| < R_0$. In a seasonal environment, the effective reproduction number will at some point always be in this range (see [2]), showing the importance of transovarial transmission in dengue epidemics.

Finally, the product of the fractions of susceptible populations of humans and mosquitoes enhances the above discussion. The equation for the fraction of infectious humans $I^*$ was written in terms of the gross reproduction number $R_0$, according to Eq. (4). However, this fraction can be written in terms of the product of fractions of susceptible populations $X_0$ as, for $\alpha \neq 1$,

$$I^* = \frac{\mu_h \mu_f (1 - \alpha)(X_0^{-1} - 1)}{\beta_h \phi \mu_h + \mu_f (\sigma_h + \mu_h) R_0},$$

where $X_0$ is given by Eq. (8), that is, $X_0 = 1/R_0 - R_0/R_0$. The term $R_i/R_0$ is negligible for higher $R_0$, but considerable for lower $R_0$, hence the decrease in the product of fractions of susceptible populations $X_0$ is very sensitive for lower $R_0$.

Fig. 1 illustrates the dependency of $X_0^{-1}$ (a) and $I^*$ (b) as a function of $\alpha$, using values of parameters given in Table 3, except $\beta_m = 0.06$ and $\beta_h = 0.09$ for low temperature 17°C. High temperature is labeled by 1, and for low temperature, the label is 2. For high temperature ($R_0 = 3.57$), $X_0^{-1}$ varies broadly, and $I^*$ varies little as $\alpha$ increases. For lower temperature ($R_0 = 0.98$), $I^*$ varies broadly as $\alpha$ increases.

![Fig. 1. $X_0^{-1}$ (a) and $I^*$ (b) varying $\alpha$, using values given in Table 3: Curves labeled by 1 correspond to summer season, and 2, to winter season, except $\beta_m = 0.06$ and $\beta_h = 0.09$.](image)

**Table 3**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (28°C)</th>
<th>Value (17°C)</th>
<th>Unit</th>
</tr>
</thead>
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<tr>
<td>$\beta_m$</td>
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<td>0.006</td>
<td>–</td>
</tr>
<tr>
<td>$\beta_h$</td>
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<td>0.009</td>
<td>–</td>
</tr>
<tr>
<td>$\mu_s$</td>
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</tr>
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<td>$\mu_f$</td>
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</tr>
<tr>
<td>$\mu_i$</td>
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<td>0.035859</td>
<td>days$^{-1}$</td>
</tr>
<tr>
<td>$\phi$</td>
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<td>1.060327</td>
<td>days$^{-1}$</td>
</tr>
<tr>
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<td>0.5</td>
<td>–</td>
</tr>
<tr>
<td>$f$</td>
<td>0.5</td>
<td>0.5</td>
<td>–</td>
</tr>
<tr>
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<td>$(70 \times 365)^{-1}$</td>
<td>days$^{-1}$</td>
</tr>
<tr>
<td>$\sigma_h$</td>
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<td>$(7)^{-1}$</td>
<td>days$^{-1}$</td>
</tr>
<tr>
<td>$c$</td>
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<td>1</td>
<td>–</td>
</tr>
<tr>
<td>$N$</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

4.3. Dynamical trajectories

When $\alpha = 1$, dynamical system (1) does not clearly show the displacement of the susceptible by infectious mosquitoes, while the asymptotic values of the equilibrium point $P^*$ given by Eq. (4) clearly do. But, inspecting Eq. (1), infectious mosquitoes $m_i$ generate always infectious mosquitoes, which number is increased by the flow of newly infected mosquitoes. Horizontal transmission is well understood, hence the focus is on the transovarial transmission (parameter $\alpha$ is varied broadly), and the relative influence of the transovarial transmission is evaluated numerically. Numerical solutions of the system of ordinary differential equations (1) are obtained by the 4th order Runge–Kutta method [25].

The initial conditions supplied to the system of Eq. (1) are

$$\begin{align*}
I_1(0) &= I^*, I_2(0) = 0, m_1(0) = m^*, m_2(0) = 0, s(0) \\
&= 1 - i_0, i(0) = i_0,
\end{align*}$$

where $i_0$ is the fraction of infectious individual introduced in a community free of dengue, hence $I^*$ and $m^*$ are given by Eq. (2). The initial introduction of infectious individuals is $i_0 = 1 \times 10^{-5}$, which describes, for instance, 1 infectious individual in a population of size $10^5$. According to foregoing results, the equilibrium point before the introduction of infectious case is given by $P^0$. Depending on the value of the gross reproduction number, the dengue disease fades out after a small epidemics ($R_s < 1$), or attains an endemic level ($R_s > 1$).

The model parameters used in numerical simulations are given in Table 3, considering two temperatures aiming to portrait two extreme conditions: 28°C (summer season) and 17°C (winter season). The entomological parameters values are those obtained by Yang et al. [18], $\alpha$ is allowed to vary, $\beta_m$ and $\beta_h$ are arbitrary values being equal in both seasons (in winter, they must be smaller), and $C = 1$ and $N = 1$. For real world, however, the values of $C$ and $N$ must be multiplied by the corresponding size of population.

Using values given in Table 3, the steady state equilibrium values of aquatic forms $I^*$, adult mosquitoes $m^*$, the basic offspring number $Q_0$ and the basic (or horizontal) reproduction number $R_0$ are given in Table 4. In winter, $Q_0$ is decreased in 8.8-fold and $R_0$, in 364-fold in comparison with summer season.

The dynamical trajectories corresponding to summer season are shown in Fig. 2: short term (a) and long term (b) for $\alpha = 0$; and short term (c) and long term (d) for $\alpha = 1$. At $\alpha = 1$, there is only the first peak of epidemics, and the subsequent damped oscillations disappear, see Fig. 2(c). Indeed, as $\alpha$ increases damped oscillations is weakened due to the increasing in the number of infectious mosquitoes (figure not shown), resulting in decreased fra-
The dynamical trajectories corresponding to summer season: short term (a) and long term (b) for $\alpha = 0$; and short term (c) and long term (d) for $\alpha = 1$. 

The dynamical trajectories corresponding to winter season are shown in Fig. 3: short term (a) and long term (b) for $\alpha = 0$; and short term (c) and long term (d) for $\alpha = 1$. In Fig. 3(a) and (b) the disease fades out, but in Fig. 3(c) and (d), the disease is maintained at endemic level ($R_g = 1.0099$) due to transovarial transmission. When $\alpha = 1$, the behavior is the same that observed in summer season. 

The displacement of the susceptible by infectious mosquitoes for $\alpha = 1$ occurs for all values of the horizontal reproduction number $R_g$. This behavior is shown in Fig. 4: (a) for summer season ($R_g = 3.57$), and (b) for winter season ($R_g = 0.0099$). 

To illustrate the epidemiological situation corresponding to quasi endemicity, the model parameters are those given in Table 3 corresponding to winter season, but the transmission coefficients $\beta_m$ and $\beta_h$ are 10-fold higher: $\beta_m = 0.06$ and $\beta_h = 0.09$. (10-fold higher $\beta_m$ and $\beta_h$ correspond to a region where there are 10-fold higher number of humans and mosquitoes.) The corresponding horizontal reproduction number is $R_g = 0.9849448$. The dynamical behavior for $\alpha = 0$ is similar to that shown in Fig. 3 (in this case, $R_g = R_h < 1$, and for $\alpha = 1$, similar to Fig. 2. Fig. 5 shows the behavior when $\alpha = 0.02$ (remember that transovarial transmission has been observed at a relatively low rate [3,8]): short term (a) and long term (b). This is epidemiological situation in which dengue is endemic due to the transovarial transmission ($R_g = R_h = 1.0049448$). 

Suppose that $\alpha = 0$, but $R_g = R_h = 1.0049448$. This is possible if $\beta_m = 0.06077249$ and $\beta_h = 0.09077249$, and other parameters are those given in Table 3 (winter season). The dynamical behaviour is similar than that observed in Fig. 5. However, after initial 11.1 × 10^3 days, the infectious humans and mosquitoes are higher when transovarial transmission occurs. The highest relative differences between infectious humans ($((t_{\alpha=0.02} - t_{\alpha=0})/t_{\alpha=0})$ and mosquitoes ($((m_{\alpha=0.02} - m_{\alpha=0})/m_{\alpha=0})$) with and without transovarial transmission are 12.95% and 13.88%, respectively. These highest differences occur at the peak of the first epidemics (24.6 × 10^3 days). The increase in almost 13% in the cases of dengue due to the transovarial transmission of low intensity (2%) among humans is not negligible. Asymptotically, they reach 2.02% and 2.86%, respectively.

In last two examples, the gross reproduction number $R_g$ encompassing transovarial transmission ($R_h = 0.9849448$ and $R_g = 0.02$) is equal to the basic reproduction number $R_g$ without transovarial transmission ($R_g = 1.0049448$ and $R_h = 0$). As pointed out, after $t = 11.1 \times 10^3$ days transovarial transmission influences dynamics, resulting in $t_{\alpha=0.02} > t_{\alpha=0}$ and $m_{\alpha=0.02} > m_{\alpha=0}$. But, from the beginning of the epidemics up to $t = 11.1 \times 10^3$ days the influence.
Fig. 3. The dynamical trajectories corresponding to winter season: short term (a) and long term (b) for $\alpha = 0$; and short term (c) and long term (d) for $\alpha = 1$.

Fig. 4. The displacement of the susceptible by infectious mosquitoes for $\alpha = 1$: (a) for summer season, and (b) for winter season.

Fig. 5. The dynamical trajectories corresponding to winter season using values of parameters given in Table 3, but with higher transmission coefficients $\beta_m$ and $\beta_h$: short term (a) and long term (b) for $\alpha = 0.02$. 
of transovarial transmission in the dynamical trajectories is negligible, and dengue infection is higher for higher basic reproduction number, that is, $k_{e}=0.02<k_{e}=0$ and $m_{2}=0.02<m_{2}=0$. Hence, two main features are stated: (1) the horizontal transmission dictates the course of the epidemics in the initial phase, and (2) the effects of transovarial transmission become detectable after some periods of time. In other words, transovarial transmission can be characterized as a slow dynamics (see Fig. 4). This is another reason why $R_{0}=\alpha$ (very small contribution in the beginning of epidemics), instead of higher value $\alpha \times Q_{0} \times R_{0}$, which is $R_{0}$ secondary mosquitos producing $Q_{0}$ offsprings from which a fraction $\alpha$ is infected.

Now, consider winter season ($R_{0}=0.0099$), but $\alpha = 0.99$, resulting in $R_{0} = 0.9999$. Dynamical trajectories are similar to those shown in Fig. 3(a) and (b) which describe the case $R_{0} = 0.0099$ and $\alpha = 0$, except that infectious mosquitos ($m_{2}$) are reduced to zero in approximately 102 days. In Fig. 3(b), infectious mosquitos ($m_{2}$) are reduced to zero in approximately 102 days.

Dynamical trajectories of dengue transmission presented here come from a model taking into account a unique serotype of dengue virus. If this restriction is eliminated by incorporating infections by other serotypes, the transovarial transmission will change the dynamics of the interactions between serotypes, especially in seasonal environments.

4.4. The thresholds $R_{0}$ and $\chi_{0}$

Many authors identified the spectral radius as the basic reproduction number [10,21,22], which is a unique threshold parameter for simple directly transmitted infections or vector-borne diseases both restricted to horizontal transmission (here denoted by $R_{0}$, the contribution of the horizontal transmission). However, due to the transovarial transmission in dengue infection, another threshold appeared, which is the product of the fractions of susceptible populations $\chi_{0}$.

Let spectral radius given by Eqs. (17) and (20) be discussed. The spectral radius (Eq. (17)) obtained using only horizontal transmission terms in the vector $f$ resulted as the square root of the inverse of product of the fractions of susceptible mosquitos and humans $\chi_{0}$, given by Eq. (8). However, including transovarial transmission terms and the flow from exposed to infectious class in the vector $f$, the spectral radius (Eq. (20)) was obtained as the square root of the gross reproduction number $R_{0}$, given by Eq. (5).

Hence, the calculation of the spectral radius of the next generation matrix depends on the construction of vector $f$. In two further ways of construction of $f$, the same spectral radius was found, given by Eq. (C2) from Appendix C. However, in these cases, and the case considered in Section 3.2.2, the reproduction number is the same, given by $R_{0} = R_{0} + R_{v}$, with $R_{v} = \alpha$, if conjecture presented in [26] and proved in [27] (a brief explanation is presented in Appendix D) is applied in Eqs. (19), (C1), and (C4). Applying the same conjecture to Eq. (16), the product of the fractions of susceptible populations is $\chi_{0} = 1/R_{0} - R_{0}/R_{0}$. Hence, the forms of the construction of the vectors $f$ and $v$ do not matter. In Appendix C an example of misconstruction of the next generation matrix is given.

The appearance of the square root in the spectral radius deserves some explanations (see [26] for details). Let the spectral radius be written as the square root of two parameters (in dengue transmission encompassing only horizontal transmission, the parameters are the partial reproduction numbers, given by Eq. (7)). Then, the spectral radius is the geometric mean of two parameters [28]. Instead of accepting the geometric mean or the spectral radius as the reproduction number, it is possible to define the product of two parameters as the reproduction number. In other words, the reproduction number is the square of the spectral radius. By accepting the latter definition, the above results show that $\chi_{0}^{-1} = \rho((1-V^{-1})^{2}$ and $\beta = \beta((1-V^{-1})$ are the spectral radii given by Eqs. (17) and (20), respectively. Therefore, all three approaches (Routh–Hurwitz criteria, $M$-matrix and the next generation matrix) provide the same expressions for the thresholds $R_{0}$ and $\chi_{0}$.

Summarizing, two distinct thresholds appear when two routes of flow occur in an infection: the infection of susceptibles by infectious by random encounter (parameter $\beta$, the horizontal transmission), and the influx to infectious class originated directly from infectious individuals (parameter $\alpha$, the transovarial transmission).

In this case, a second reproduction number arises, the transovarial reproduction number $R_{0}$, playing the following role: (1) it is summed in the net reproduction number ($R_{0} = R_{0} + R_{0}$), and (2) it is subtracted in the product of the susceptible populations ($\chi_{0} = 1/R_{0} - R_{0}/R_{0}$).

To test results summarized above, a directly transmitted infection is considered. Driessche and Watmough [10] analyzed a tuberculosis transmission including treatment and concluded that the basic reproduction number must be

$$R_{0} = \frac{v_{1}\beta_{1}}{(d+v+r_{1})(d+r_{2})-pv_{2}}$$

which is $R_{1}$ given by Eq. (E.1) in Appendix E. They also found other ways of writing the basic reproduction number, listed in Eq. (E.4) except the last equation, but argued that they are wrong forms.

The thresholds $R_{1}$ and $R_{1}$ are discussed following the same reasoning evoked to interpret and to understand the transovarial transmission in dengue transmission.

With respect to $R_{1}$, Eq. (E.1), or Eq. (E.7), can be rewritten as

$$s^{*} = 1 = \frac{R_{1}}{R_{1}} = \frac{R_{1}}{R_{1}}$$

where the basic reproduction number $R_{0}$ is

$$R_{0} = \frac{v_{1}\beta_{1}}{(d+v+r_{1})(d+r_{2})}$$

and the contribution due to the failure of treatment is

$$R_{1} = \frac{pv_{2}}{(d+v+r_{1})(d+r_{2})}$$

which is called failure reproduction number. The interpretation follows next.

The term $v/(d+v+r_{1})$ is the probability of a infected person surviving exposed class and entering into infectious class, and $1/(d+r_{2})$ is the average number of secondary infections produced during the infectious period $1/(d+r_{2})$. Hence, $R_{0}$ is the average number of secondary cases produced by one infectious individuals introduced in a completely susceptible population in the absence of any constraints. However, when $p > 0$, a constraint given by failure of treatment arises. A fraction $p$ of infectious individuals under treatment fails, and returns to exposed class by $p_{2}/(d+r_{2})$, with $r_{2}/(d+r_{2})$ being the probability of surviving the infectious class and returning to exposed class. Surviving the exposed class with probability $p/(d+v+r_{1})$, these previously infected but treatment failed individuals return again to infectious class. Then $R_{0}$ accounts for the number of not newly infected but by “feedback” of infectious individuals originated from a failure of treatment.

The failure reproduction number $R_{1}$ plays a similar role played by the transovarial reproduction number $R_{0}$ in dengue transmission. In both cases, $R_{1}$ and $R_{1}$ account for the increase in the number of infectious individuals due to “internal infection”, new not new infection. For this reason, there is a diminishing in the fraction of susceptible individuals, which is proportional to the infection produced by “feedback” of infectious individuals due to the failure of treatment.
Now, $R_1^t$ given by Eq. (E.1) is discussed. This threshold is written as
\[
R_1^t = R_g = R_0 + R_f,
\]
where the basic reproduction number $R_0$ and the failure reproduction number $R_f$ are given by Eqs. (25) and (26), respectively. Notice that $R_f < 1$. Similarly to the dengue infection with transovarial transmission, the gross reproduction number is sum of infections promoted by the random encounter between susceptible and infectious individuals ($R_0$) and by the infectious individuals who failed to the treatment and ‘infect’ again ($R_f$).

It is worth stressing the fact that there is a particular form of constructing the vector $f$ in order to result the product of the fractions of susceptible populations $x_0$ or the fraction of the susceptible population $s^*$: taking the infection by random encounter terms and also all other flows from exposed class to infectious class (hence $V^{-1}$ is obtained easily). In all other constructions of $f$, the reproduction number is retrieved if the conjecture in [26] is applied. But, the construction of $f$ taking only the terms of the infection by random encounter that results in a non-diagonal matrix $V$ (becoming the evaluation of $V^{-1}$ hard) yields the square root of the gross reproduction number. However, this could not be valid for complex routes of transmission, such as vector transmission together with direct infection.

5. Conclusions

Dengue transmission modeling incorporating transovarial transmission was analyzed. Qualitative analysis showed that the horizontal (or basic) reproduction number $R_0$ plays the major role in the dynamics of dengue propagation. However, when this number is small, especially near 1, the transovarial transmission (assessed by the transovarial reproduction number $R_v = \alpha$) enhances strongly the dynamics of dengue infection.

One of the effects is the outbreak of dengue epidemics even for $R_0 < 1$, if the gross reproduction number $R_0$ is higher than 1. The other is the increasing in the fraction of infectious humans due to transovarial transmission near 1: the difference $d_i$ may be small, but the relative contribution $q_i$ is very high, due to the fact that the horizontal transmission produces very lower number of infectious individuals.

The gross reproduction number is compounded by two routes of transmission. The horizontal transmission accounted for the random encounter between densities of sub-populations (mass action law), while the transovarial transmission accounted for the absolutely certain infection of a fraction $\alpha$ of offsprings from infected mosquitoes. Numerical simulations of the dynamical system showed that the horizontal transmission prevails during the initial phase of epidemics, while the transovarial transmission affects on its long run.

Besides the gross reproduction number $R_g$, another threshold parameter appeared due to the transovarial transmission. The product of the fractions of susceptible human and mosquito populations is given by $x_0$, which is not $1/R_g$ as found in vector-borne infections where only horizontal transmission occurs. Notably, when $R_0 = 1$, all the mosquitoes are infectious, and $x_0$ must be zero, which is true (see Eq. (8)). However, $R_g = R_0 + 1$ (see Eq. (5)), with $R_0 > 0$ to have dengue transmission, and dengue disease never can be eliminated ($R_g > 1$) due to the displacement of susceptible by infectious mosquitoes. This behavior corroborates the arising of two thresholds $R_g$ and $x_0$.

DFE was analyzed by three different approaches. These methods, the spectral radius of the next generation matrix, Routh–Hurwitz criteria and $M$-matrix theory, provided two threshold parameters: the gross reproduction number $R_g = R_0 + R_v$, with $R_v = \alpha$, and the product of the fractions of susceptible populations $x_0 = 1/R_0 - R_v/R_0$. Especially in the next generation matrix method, a third threshold was obtained. However, if the conjecture proved in [27] is applied, then only two thresholds $R_v$ and $x_0$ are retrieved. These arguments had been applied to the model analyzed by Driessche and Watmough [10], and a misinterpretation of $R_1$ given by Eq. (E.1) as the basic reproduction was pointed out. Indeed, $R_1$ is the inverse of the fraction of susceptible individuals, while the actual basic (gross) reproduction number is $R_1^t$ given by Eq. (E.1).

Summarizing above results, a procedure can be stated – among several ways of constructing vector $f$, there are two special constructions: (1) choosing $f$ such that matrix $V$ is diagonal (Eq. (18) and $f_1$ in Eq. (E.2)), resulting in $R_1^t$; and (2) choosing $f$ taking into account only infection terms by random encounter such that matrix $V$ is non-diagonal (Eq. (14) and $f_1$ in Eq. (E.2)), resulting in $x_0^{-1}$. If both constructions of $f$ result in the same expression (applying the conjecture in [27]), then there is only one threshold parameter ($R_0 = x_0^{-1}$).

From the epidemiologic point of view, according to Fig. 5 in [18], the basic reproduction number due to horizontal transmission $R_0$ is very high at elevated temperatures, and very low for lower temperatures (see Table 4). Let the influence of transovarial transmission be assessed along the years in subtropical and temperate regions. In these regions, summer seasons are characterized by high temperatures, while winter seasons present low temperatures. In hot seasons, the basic reproduction number $R_0$ is high, and the contribution of the transovarial transmission is really negligible in the course of dengue epidemics. However, at cold seasons, when $R_0$ is even lower than 1, dengue must fade out in the next summer if horizontal transmission is the only route of transmission. Notwithstanding, this is not what happens, and a possible reason behind it is the additional transovarial transmission route. During winter seasons the additional transovarial transmission can sustain the dengue infection (the gross reproduction number $R_g$ could be slightly above the threshold), and as soon as summer seasons begin, the horizontal transmission prevails and maintains the epidemics at high level. In tropical regions, the outbreak of dengue epidemics as soon as the first rainfalls occur in the beginning of rainy season after dry season could also be explained by the transovarial transmission.

Another important aspect of dengue transmission not considered here is the capacity of stored eggs assuming quiescence stage: eggs stored around four months showed increased capacity of fitness, that is, the basic offspring number $Q_0$ is the highest [19]. Hence, the existence of four serotypes, transovarial transmission, quiescence stage of eggs and variation in temperature and precipitation [2] become quite unpredictable the occurrence of dengue epidemics. In a future work, evaluation of transovarial transmission can be done in a real world, instead of illustrative examples given in Section 4.3.

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Appendix A. Non-trivial equilibrium point

Letting the derivatives with respect to time equal to zero in Eq. (1), the coordinates of the non-trivial equilibrium point are given by the positive and non-zero solution of the algebraic system of
equations
\[
\begin{align*}
0 &= qf_2\phi (m_1 + (1 - \alpha)m_2)(1 - \frac{l_1 + l_2}{C}) - (\sigma_a + \mu_a)l_1 \\
0 &= qf_2\phi m_2(1 - \frac{l_1 + l_2}{C}) - (\sigma_a + \mu_a)m_2 \\
0 &= \sigma_a l_1 - (\beta_m \phi f + \mu_f)m_1 \\
0 &= \sigma_a l_2 + \beta_m \phi m_1 - \mu_f m_2 \\
0 &= \mu_b - (\frac{\beta_f}{\mu_f}m_2 + \mu_b)S \\
0 &= \frac{\beta_f}{\mu_f}m_2 S - (\sigma_a + \mu_a)i.
\end{align*}
\]

The sum of (a) and (b) results in
\[
qf_2\phi (m_1 + m_2)(1 - \frac{l_1 + l_2}{C}) - (\sigma_a + \mu_a)(l_1 + l_2) = 0,
\]

and the sum of (c) and (d) results in
\[
\sigma_a (l_1 + l_2) - \mu_f (m_1 + m_2) = 0.
\]

and the solution for both equations is \(\tilde{l}_1 + \tilde{l}_2 = l^*\) and \(\tilde{m}_1 + \tilde{m}_2 = m^*\), with \(l^*\) and \(m^*\) being given by Eq. (2).

From (b), \(\tilde{l}_2\) is
\[
\tilde{l}_2 = \frac{qf_2\phi}{\sigma_a + \mu_a}(1 - \frac{l_1}{C})\tilde{m}_2.
\]

and substituting in (d), and using the fact that \((1 - l^*/C) = 1/Q_0\), \(\tilde{m}_2\) is
\[
\tilde{m}_2 = \frac{\beta_m \phi m^*}{\sigma_a + \mu_a} \left(1 - \frac{l_1^*}{C}\right).
\]

Substituting \(\tilde{m}_2\) back to \(\tilde{l}_2\), and using \(m^* = \sigma_a C(1 - 1/Q_0)/\mu_f\), the compartments of mosquito population \(\tilde{l}_1 = l^* - \tilde{l}_2, \tilde{l}_2, \tilde{m}_1 = m^* - \tilde{m}_2\) and \(\tilde{m}_2\) are obtained as a function of \(l^*\) and they correspond to first four equations of Eq. (4). Clearly, if \(\beta_m = 0\), then \(\tilde{m}_2 = 0\), and the non-trivial equilibrium is possible if \(\beta_m > 0\).

From (e), \(\tilde{S}\) is
\[
\tilde{S} = \frac{\mu_b}{\frac{\beta_f}{\mu_f}m_2 + \mu_b}.
\]

and substituting in (f), \(\tilde{i}\) is
\[
\tilde{i} = \frac{\beta_f \mu_b \tilde{m}_2}{(\sigma_a + \mu_b)(\frac{\beta_f}{\mu_f}m_2 + \mu_b)}.
\]

Clearly, if \(\beta_b = 0\), then \(\tilde{i} = 0\), and the non-trivial equilibrium is possible if \(\beta_b > 0\). Finally substituting \(\tilde{m}_2\), and solving for \(l^*\), the last two compartments of human population in Eq. (4) are obtained.

Appendix B. Jacobian matrix

There are well known techniques to assess the stability of equilibrium points. One is the application of Routh–Hurwitz criteria, and other, the M-matrix theory. The results are presented briefly.

B1. Routh–Hurwitz criteria

The local stability of DFE is assessed by the eigenvalues of the characteristic equation \(\det (J - \lambda I) = 0\), which can be written as
\[
\det (J - \lambda I) \equiv \det (F - \lambda I) \det (M - \lambda I) = 0,
\]

where matrix \(F\) is given by Eq. (11), and matrices \(M\) and \(H\), by Eq. (12).

The eigenvalue corresponding to vital dynamics matrix of humans \(H\) is \(\lambda_1 = -\mu_h\).

The characteristic equation corresponding to vital dynamics matrix of mosquitoes \(M\) is \(\lambda^2 + \left[qf_2\phi m/C + \sigma_a + \mu_a + \mu_f\right] \lambda + \left[(\sigma_a + \mu_a)\mu_f (Q_0 - 1)\right] = 0\), with \(Q_0\) being given by Eq. (3). The eigenvalues \(\lambda_{2,3}\) have negative real part since all the Routh–Hurwitz criteria [29] are satisfied when \(Q_0 > 1\).

The characteristic equation corresponding to dengue transmission matrix \(F\) is \(\lambda^3 + b_2 \lambda^2 + b_1 \lambda + b_0 = 0\), where \(b_2 > 0, b_1 > 0\) for \(R_0 < 1\), and
\[
b_0 = (\sigma_h + \mu_h)(\sigma_a + \mu_a)\mu_f (1 - R_0) > 0,
\]

for \(R_0 < 1\), with \(R_0\) and \(R_0\) \(R_0\geq \), being given by Eqs. (5) and (6), respectively. By the fact that \(b_2b_1 - b_0 > 0\) for \(R_0 < 1\), the eigenvalues \(\lambda_{4,5,6}\) have negative real part since all the Routh–Hurwitz criteria are satisfied, and DFE is locally asymptotically stable. For \(\alpha = 1\), \(b_0 = -(\sigma_a + \mu_a)\mu_f < 0\) and DFE is always unstable for all \(R_0 > 0\).

Notice that the independent term in Eq. (B.1), which is \(b_0 = \det (F)\), satisfies the procedure proposed in [26]: (1) write a positive \(K_0\) in terms of the model parameters, excluding all transmission parameters, in order to write \(b_0\) in the form \(K_0 (1 - R_0/K_1)\); and (2) define the ratio \(K_2/K_1\) as the gross reproduction number \(R_0\).

The parameter \(\chi_0\) can also be obtained from the independent term \(b_0\) following the procedure proposed in [26]: (1) write a positive \(K_0\) in terms of the model parameters, including transvarial transmission parameters, in order to write \(b_0\) in the form \(K_0 (1 - R_0/K_4)\); and (2) define the ratio \(R_0/K_4\) as the inverse of the product of fractions \(\chi_0^{-1}\). Hence,
\[
b_0 = (\sigma_h + \mu_h)(\sigma_a + \mu_a)\mu_f (1 - \alpha) (1 - \chi_0^{-1}),
\]

where \(\chi_0^{-1} = R_0/(1 - \alpha)\), with \(\chi_0\) being given by Eq. (8). \(K_3 > 0\) implies that \(\alpha < 1\), and for \(\alpha = 1\). \(\chi_0 = 0\). Notice that DFE is stable if \(\chi_0^{-1} < 1\) and bifurcates at \(\chi_0^{-1} = 1\), and above this value a unique non-trivial (endemic) equilibrium appears \((\chi_0^{-1} < 1\) is equivalent to \(R_0 < 1\).


Matrices \(F\) and \(M\), given by Eqs. (11) and (12), respectively, multiplied by \(-1\) could be \(M\) -matrix under certain conditions [12,13,30,31].

Definition. An \(n \times n\) matrix \(A = [a_{ij}]\) is a non-singular \(M\)-matrix if \(a_{ij} \leq 0, i \neq j\), and there exists a matrix \(B \geq 0\) and a real number \(u > 0\) such that \(A = ul - B\) and \(u > \rho(B)\), where \(I\) is the identity matrix and \(\rho\) is the spectral radius [30].

Or, equivalently:

**Proposition 1.** A is a non-singular \(M\)-matrix if and only if the real part of its eigenvalues is greater than zero.

**Proposition 2.** A (elements \(a_{ij}\) is a non-singular \(M\)-matrix if and only if the diagonal entries are positive, and there exists a positive diagonal matrix \(D\) (diagonal elements \(d_i > 0\), such that \(AD\) is strictly diagonal dominant, that is, \(a_{ij}d_i > \sum_j \mid a_{ij}\mid d_j,\) for \(i = 1, 2, \ldots, n\).

Matrix \(-M\) given by Eq. (12) has positive diagonal elements in accordance with the first part of Proposition 2. The second part of Proposition 2, by defining \(d_1 = 1\) and \(d_2 = \xi + \sigma_a/\mu_f\), is satisfied if \(\xi > 0\). After some calculations, the result is
\[
0 < \xi < m^* Q_0 = \frac{\sigma_a}{\mu_f} C (Q_0 - 1),
\]

using Eq. (2) for \(m^*\). Hence, whenever \(Q_0 > 1\) there exists a positive number \(\xi\), and \(-M\) is a non-singular \(M\)-matrix.

Matrix \(-F\) given by Eq. (11) has positive diagonal elements in accordance with the first part of Proposition 2. The second part of Proposition 2, by defining \(d_1 = 1\), \(d_2 = \xi + \beta_b \phi [N(\sigma_h + \mu_b)]\) and
\[ d_2 = \xi + \alpha q f \phi / [Q_0 (\alpha_u + \mu_a)] \] is satisfied if \( \xi > 0 \). After some calculations, the results is
\[ 0 < \xi < \frac{\mu f}{\rho_m \phi m^* + \sigma_a} (1 - R_0), \]
where \( R_0 = R_0 + \alpha \), according to Eq. (5). Hence, whenever \( R_0 < 1 \) there exists a positive number \( \xi \), and \(-F\) is a non-singular matrix.

For \( \alpha < 1 \), the last inequality can also be written as
\[ 0 < \xi < \frac{\mu f}{\rho_m \phi m^* + \sigma_a} (1 - \alpha \xi^1), \]
where \( \xi^1 \) is given by Eq. (8). If \( \xi^1 < 1 \) there exists a positive number \( \xi \), and matrix \(-F\) has the real part of its eigenvalues lower than zero.

**Appendix C. Spectral radius theory**

As pointed out in the main text, there are other two ways in constructing the vector \( f \), given by Eq. (18): (a) transfer the term \( q f \phi \alpha m_2 (1 - (l_1 + l_2)/C) \) from vector \( f \) to \( v \); and (b) transfer the term \( \alpha \lambda_2 \) from vector \( f \) to \( v \).

**C1. Case a**

The vector \( f \) is constructed as
\[ f = \left( \frac{\beta_m \phi m_1 + \sigma_d}{N}, \frac{\beta_0 \phi}{N} m_5, 0, 0, 0 \right)^T, \]
with \( T \) standing for the transposition of a matrix. In this case, the next generation matrix \( F_1 V^{-1} \) is
\[ F_1 V^{-1} = \begin{bmatrix} \alpha & NR_m^m & 0 & \sigma_a \frac{m}{\alpha + \mu_a} \\ \frac{1}{N} R_0^m & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \]
and the corresponding characteristic equation is
\[ \lambda^3 - R_0 \lambda^2 - R_0 \lambda = 0. \]

The eigenvalues are \( \lambda_4 = 0 \) and \( \lambda_{5,6} = \left( R_0 + \sqrt{R_0^2 + 4R_0} \right)/2 \), where \( R_0 \) is given by (6). Then, the spectral radius is \( \hat{\rho}(F_1 V^{-1}) = \left( R_0 + \sqrt{R_0^2 + 4R_0} \right)/2 \) and the reproduction number \( R_{\text{eq}} \) is
\[ R_{\text{eq}} = \hat{\rho}(F_1 V^{-1}) = \left( R_0 + \sqrt{R_0^2 + 4R_0} \right)/2. \]

For \( R_{\text{eq}} < 1 \), DFE is locally asymptotically stable, and unstable for \( R_{\text{eq}} > 1 \). Therefore, the threshold occurs at \( R_0 + R_0 = 1 \), and DFE is unstable for \( R_0 + R_0 > 1 \).

**C2. Case b**

The vector \( f \) is constructed as
\[ f = \left( \frac{\beta_m \phi m_1 + \beta_0 \phi}{N} m_5, \frac{q f \phi \alpha m_2}{C} \left( 1 - \frac{l_1 + l_2}{C} \right), 0, 0, 0 \right)^T. \]
In this case, the next generation matrix \( F_1 V^{-1} \) is
\[ F_1 V^{-1} = \begin{bmatrix} 0 & NR_m^m & 0 & 0 \\ \frac{1}{N} R_0^m & 0 & \frac{1}{N} R_0^m \frac{\sigma_a}{\alpha + \mu_a} \alpha & 0 \\ \frac{\sigma_a + \mu_a}{\alpha} & 0 & \frac{\sigma_a + \mu_a}{\alpha} & 0 \end{bmatrix}, \]
and the corresponding characteristic equation is
\[ \lambda^3 - R_0 \lambda^2 - R_0 \lambda = 0. \]

which is equal to Eq. (C1) obtained in the previous case. Next, a special construction of \( f \) is presented.

**C3. Considering only states-of-infectiousness**

The next generation matrix is constructed taking into account only the states-of-infectiousness \((m_2, i)\). In this case, vector \( f \) is given by
\[ f = \left( \beta_m \phi m_1, \frac{\beta_0 \phi}{N} m_5, 0, 0, 0 \right)^T, \]
which is equal to Eq. (14), and vector \( v \) is given by Eq. (15). The partial derivatives of \( f \) and \( v \) with respect to \( m_2 \) and \( i \) evaluated at the DFE are
\[ F_1 = \begin{bmatrix} 0 & \beta_m \phi m^* \\ \sigma_a & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \mu f & 0 \\ 0 & \sigma_h + \mu_h \end{bmatrix}. \]
and the next generation matrix \( F_1 V^{-1} \) is
\[ F_1 V^{-1} = \begin{bmatrix} 0 & NR_0^m \\ \frac{1}{N} R_0^m & 0 \end{bmatrix}, \]
where the partial reproduction numbers \( R_0^m \) and \( R_0^m \) are given by Eq. (7).

The characteristic equation corresponding to \( F_1 V^{-1} \) is
\[ \lambda^2 - R_0 = 0, \]
with the eigenvalues being \( \lambda_{4,5} = \sqrt{R_0} \), where \( R_0 \) is given by (6), and the spectral radius is
\[ \hat{\rho}(F_1 V^{-1}) = \sqrt{R_0}. \]
In this case, the transversal transmission does not appear in the threshold parameter, hence the gross reproduction number \( R_0 \), given by Eq. (5), is not retrieved.

To understand this mistake, let the partial derivatives of \( f \) and \( v \) be evaluated at the DFE. They are partitioned as
\[ Df = \frac{\partial f}{\partial a_n} = \begin{bmatrix} F_1 & 0_{2 \times 4} \\ 0_{4 \times 2} & 0_{4 \times 4} \end{bmatrix}, \]
\[ Dv = \frac{\partial v}{\partial a_n} = \begin{bmatrix} V & -F_1 \\
-2F_1 & -F_1 \end{bmatrix}, \quad 1 \leq p, n \leq 6, \]
where \( F_1 \) and \( V \) are the partial derivatives with respect to \( m_2 \) and \( i \), given by Eq. (C3). The other matrices are
\[ J_1 = \begin{bmatrix} \alpha q f \phi \frac{1}{\sigma_a} & 0 \\ 0 & 0 \end{bmatrix}, \quad J_2 = \begin{bmatrix} \alpha q f \phi \frac{1}{\sigma_a} & 0 \\ 0 & \sigma_a \end{bmatrix}, \quad J_3 = \begin{bmatrix} \sigma_a + \mu_a & 0 \\ 0 & -\beta_m \phi m^* \end{bmatrix}, \]
and
\[ -\left( \sigma_a + \mu_a \right) & 0 & 0 \\ -q f \phi \frac{\mu_m}{C} & -\left( \sigma_a + \mu_a \right) & q f \phi \frac{\mu_m}{C} \\ 0 & \sigma_a & -\mu_f \\ 0 & 0 & -\mu_h \end{bmatrix}. \]
Notice that matrix \( J_1 \) is not a null matrix. Hence, \( F_1 V^{-1} \) is not a next generation matrix.

**Appendix D. Conjecture**

Two conjectures were presented in [26], one dealing with single infection, and other, with coinfections. The idea behind these conjectures is obtaining a threshold from the characteristic equation corresponding to the next generation matrix \( F_1 V^{-1} \), instead of
calculating the spectral radius $\rho(F_tV^{-1})$; the absolute sum of the negative coefficients is the threshold. Here, conjecture relates to single infection is stated.

**Conjecture 1.** Let the characteristic polynomial of order $n$ corresponding to the next generation matrix $F_tV^{-1}$ be written as

$$
\Lambda(\lambda) = \lambda^n - a_{n-1}\lambda^{n-1} - \cdots - a_1\lambda - a_0,
$$

with $a_i \geq 0$, for $i = 0, 1, 2, \ldots, n - 1$. Let $R_0$ denote the spectral radius of the next generation matrix, that is, $R_0 = \rho(F_tV^{-1})$, and $R_0^\infty = a_{n-1} + \cdots + a_1 + a_0$.

Then $R_0^\infty$ is a threshold value for the disease to take off or die out in the sense that:

(i) $R_0^\infty > 1$ if and only if $R_0 > 1$

(ii) $R_0^\infty = 1$ if and only if $R_0 = 1$

(iii) $R_0^\infty < 1$ if and only if $R_0 < 1$.

**Proof.** If all $a_i = 0$, the result is obvious. Otherwise the elements of the next generation matrix $F_tV^{-1}$ are non-negative as they correspond to expected numbers of different types of infected individuals. Hence, by the Perron Frobenius Theorem it has a non-negative right eigenvector whose eigenvalue is $R_0$, and $R_0$ is the largest real eigenvalue. Additionally, the characteristic polynomial is such that the number of sign differences between consecutive nonzero coefficients is one. Hence, according to Descartes rule of signs, there is exactly one positive root. However, writing

$$
\Lambda(\infty) = \lim_{\lambda \to \infty} \Lambda(\lambda),
$$

(i) if $R_0^\infty > 1$, then $\Lambda(1) < 0$ and $\Lambda(\infty) = \infty$, so $\Lambda(\lambda)$ has a root in $(1, \infty)$. Hence, the largest real eigenvalue $R_0$ corresponding to the characteristic polynomial is $R_0 > 1$.

(ii) if $R_0^\infty = 1$, then $\Lambda(0) < 0$, $\Lambda(1) = 0$ and $\Lambda(\infty) = \infty$, so the unique positive root of $\Lambda(\lambda) = 0$ is $\lambda = 1$, and $R_0 = 1$.

(iii) if $R_0^\infty < 1$, then $\Lambda(0) < 0$ and $\Lambda(1) > 0$, so $\Lambda(\lambda)$ has a root in $(0, 1)$. Hence, the largest real eigenvalue $R_0$ corresponding to the characteristic polynomial is $R_0 < 1$.

Therefore $R_0^\infty$ is a valid threshold parameter that crosses the value one exactly when $R_0$ does and determines the disease behavior in the same way that $R_0$ does. □

**Appendix E. Tuberculosis model with treatment**

Driessche and Watmough [10] proposed and analyzed a tuberculosis transmission including treatment aiming to exemplify the use of the next generation matrix method. The model is

$$
\begin{align*}
\frac{d}{dt}s &= d - ds - \beta_1is \\
\frac{d}{dt}e &= \beta_1is + \beta_2it + pr_2i - (d + v + r_1)e \\
\frac{d}{dt}i &= ve - (d + r_2)i \\
\frac{d}{dt}t &= r_te + (1 - p)r_2i - \beta_2it - dt,
\end{align*}
$$

where are $s$, $e$, $i$, and $t$ the fractions of, respectively, susceptible, exposed, infectious, and treated individuals at time $t$. Susceptible and treated individuals are infected at rates $\beta_1$ and $\beta_2$, respectively. All newborns are susceptible, with birth rate equal to mortality rate $d$; the treatment rates for exposed and infectious individuals are $r_1$ and $r_2$, respectively, with a fraction $1 - p$ of infectious individuals being successful; and $v$ is the incubation rate.

The disease free equilibrium (DFE) $P_0$ has the coordinates given by

$$
P_0 = (\bar{s} = 1, \bar{e} = 0, \bar{i} = 0, \bar{t} = 0).
$$

The eigenvalues of Jacobian, evaluated at DFE, are $\lambda_1 = \lambda_2 = -d$, and $\lambda_3, 4$ are given by the roots of

$$
\lambda^2 + (2d + v + r_1 + r_2)\lambda + (d + v + r_1)(d + r_2) - v(\beta_1 + pr_2) = 0.
$$

This equation will have negative real part if the independent term $a_0$ is positive, which can be written in two different forms

$$
\begin{align*}
\begin{cases}
0 = [(d + v + r_1)(d + r_2) - \nu pr_2] - (1 - R_1) \\
0 = (d + v + r_1)(d + r_2)[1 - R_1] \\
\end{cases}
\end{align*}
$$

where the thresholds $R_1$ and $R_1^\infty$ are

$$
\begin{align*}
R_1 &= \frac{\nu \bar{p}_1}{(d + v + r_1)(d + r_2) - \nu pr_2} \\
R_1^\infty &= \frac{\nu \bar{p}_1 + pr_2}{(d + v + r_1)(d + r_2) - \nu pr_2}. \tag{E.1}
\end{align*}
$$

Therefore, DFE is locally asymptotically stable if $R_1 < 1$ or $R_1^\infty < 1$. Above two different forms of writing $a_0$ followed the procedures presented in [26].

Now, the next generation method is considered taking into account the state-at-infection ($e$) and the states-of-infectiousness ($i$) [22]. There are four ways to construct the vector $f$, which are

$$
\begin{align*}
f_1 &= (\beta_1i, \beta_2i, 0, 0, 0)^T \\
f_2 &= (\beta_1i, \beta_2i + pr_2i, 0, 0, 0)^T \\
f_3 &= (\beta_1i + \beta_2i + pr_2i, ve, 0, 0, 0)^T \\
f_4 &= (\beta_1i + \beta_2i, ve, 0, 0)^T,
\end{align*}
$$

with $T$ standing for the transposition of a matrix. Notice that vector $f_1$ has only horizontal transmissions (infection $\beta_1$ and secondary infection $\beta_2$), and matrix $V$ for $f_3$ is diagonal. From each choice of $f$, the next generation matrix $F_tV^{-1}$ is calculated, and the corresponding characteristic equation is obtained. The characteristic equation for $f_j$, $j = 1$ to 4, are, respectively,

$$
\begin{align*}
\lambda^2 - R_1\lambda &= 0 \\
\lambda^2 - R_1^\infty\lambda &= 0 \\
\lambda^2 - R_1^\infty\lambda &= 0 \\
\lambda^2 - a\lambda - b &= 0,
\end{align*}
$$

where $R_1$ and $R_1^\infty$ are given by Eq. (E.1), and $a = \nu pr_2/[(d + v + r_1)(d + r_2)]$ and $b = \nu \bar{p}_1/[(d + v + r_1)(d + r_2)]$. Notice that the spectral radius corresponding to above equations are

$$
\begin{align*}
\rho_1(F_tV^{-1}) &= R_1 \\
\rho_2(F_tV^{-1}) &= R_1^\infty \\
\rho_3(F_tV^{-1}) &= \sqrt{R_1^\infty} \\
\rho_4(F_tV^{-1}) &= \frac{1}{2}(a + \sqrt{a^2 + 4ab}).
\end{align*}
$$

Hence, there are four thresholds.

However, if the conjecture presented in [26] and proved in [27] is applied to characteristic equation given in Eq. (E.3), then there are only two thresholds $R_1$ and $R_1^\infty$ given by Eq. (E.1), because $a + b = R_1^\infty$. Especially, the threshold $R_1$ can be understood by determining the steady state fraction of susceptible individuals $s^*$.

The endemic equilibrium $P^*$ has the coordinates given by

$$
P^* = (\bar{s} = s^*, \bar{e} = e^*, \bar{i} = i^*, \bar{t} = t^*),
$$

where

$$
\begin{align*}
s^* &= \frac{1}{1 + \frac{a}{e^*}} \\
e^* &= \frac{d + r_2}{i^*} \\
t^* &= \frac{r_2(d + r_2) + (1 - p)r_2}{\nu (d + r_2)}.
\end{align*}
$$
with \( r^* \) being the positive solution of second degree equation

\[
A^2 + Bl + C = 0,
\]

(E.6)

where the coefficients are

\[
A = d(d + v + r_1)\beta_1 \beta_2
\]

\[
B = d^2(d + v + r_1)(d + r_2) - pv r_2(1 - R_1) \beta_1
\]

\[
C = d^2[(d + v + r_1)(d + r_2) - pv r_2(1 - R_1)],
\]

with \( R_1 \) being given by Eq. (E.1), and \( R_2 \) is obtained by substituting \( \beta_1 \) in \( R_1 \) by \( \beta_2 \), that is,

\[
R_2 = \frac{v \beta_2}{(d + v + r_1)(d + r_2) - pv r_2}.
\]

Eq. (E.6) does not have a simple expression for positive root, because the discriminant \( \Delta = \sqrt{B^2 - 4AC} \) is given by

\[
\Delta = d^4(d + v + r_1)^2 \beta_2^2
\]

\[
+ d^2[(d + v + r_1)(d + r_2) - pv r_2]^2(1 - R_1)^2 \beta_1^2
\]

\[
- 2d^2(d + v + r_1)(d + v + r_1)(d + r_2) - pv r_2]
\]

\[
\times (1 + 2R_1 - R_2)\beta_1 \beta_2,
\]

which cannot be simplified. Depending on the values let to \( \beta_1 \) in \( \beta_2 \), there is a possibility of two positive roots (see [16] for backward bifurcation).

Let the special case \( \beta_2 = 0 \) (absence of secondary infections) be studied. In this situation, \( R_2 = 0 \) and the source for the appearance of backward bifurcation is eliminated. In this case, \( A = 0 \) and other coefficients are

\[
B = d[(d + v + r_1)(d + r_2) - pv r_2] \beta_1
\]

\[
C = d^2[(d + v + r_1)(d + r_2) - pv r_2](1 - R_1),
\]

with another way of writing the coefficient \( C \),

\[
C = d^2(d + v + r_1)(d + r_2)(1 - R_1).
\]

The fraction of infectious individuals is

\[
i^* = \frac{d}{\beta_1}(R_1 - 1).
\]

Substituting in Eq. (E.5), the fraction of susceptible individuals, independently of the form assumed by \( C \), is

\[
s^* = \frac{1}{R_1} = \frac{d + v + r_1)(d + r_2) - pv r_2}{v \beta_1},
\]

(E.7)

and, clearly, \( s^* \) cannot be written as \( s^* = 1/R_1 \). Notably, the thresholds \( R_1 \) and \( R_1^* \) given by Eq. (E.1) are not changed by letting \( \beta_2 = 0 \).

References


