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ORIGINAL ARTICLE

Threshold Conditions for a Non-Autonomous Epidemic System Describing the Population Dynamics of Dengue

F.A.B. Coutinho[a], M.N. Burattini[a], L.F. Lopez[a], E. Massad[a,b,*]

[a] *School of Medicine, The University of São Paulo and LIM 01/HCFMUSP, Av. Dr. Arnaldo 455, São Paulo CEP 01246-903, SP, Brazil*
[b] *London School of Hygiene and Tropical Medicine, London University, London, UK*

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Abstract A non-autonomous dynamical system, in which the seasonal variation of a mosquito vector population is modeled, is proposed to investigate dengue overwintering. A time-dependent threshold, $R(t)$, is deduced such that when its yearly average, denoted by $\overline{R}$, is less than 1, the disease does not invade the populations and when $\overline{R}$ is greater than 1 it does. By not invading the population we mean that the number of infected individuals always decrease in subsequent seasons of transmission. Using the same threshold, all the qualitative features of the resulting epidemic can be understood. Our model suggests that trans-ovarial infection in the mosquitoes facilitates dengue overwintering. We also explain the delay between the peak in the mosquitoes population and the peak in dengue cases.

Keywords Dengue · Vector-borne · *Aedes aegypti* · *Aedes albopictus* · Overwinter · Vertical transmission · Modeling · Non-autonomous systems

1. Introduction

Dengue fever and dengue hemorrhagic fever (DF/DHF) are caused by the dengue virus, a flavivirus, and it is transmitted by mosquitoes of the genus Aedes (Stegomyia), mainly by the species *Aedes aegypti* Bancroft (1906). The infection has recently resurged in the American continent after some decades without epidemics, becoming a major public health problem (Gubler and Kuno, 1997; Luz et al., 2003).

In subtropical regions, the disease shows a resurgent pattern with yearly epidemics, which starts typically in the months characterized by heavy rains and heat, peaking some 3 or 4 months after the beginning of the rainy season. In the dry months, the number of cases drop essentially to zero due to the virtual

*Corresponding author.
E-mail address: edmassad@usp.br (E. Massad).

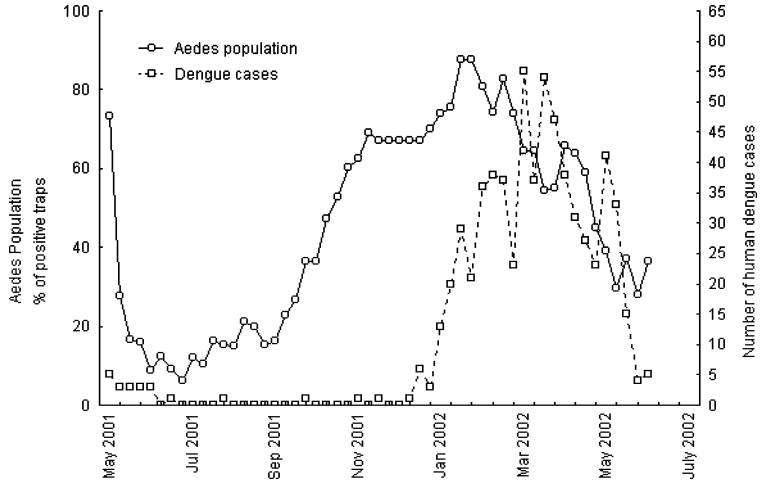

Fig. 1 Delay between the increase in the proportion of positive traps for females of aedes mosquitoes and dengue cases. We do not intend to fit this data set in any of our simulations but only to illustrate qualitatively the delay between mosquitoes and dengue outbreaks.

disappearance of the vector. Since the infection reappears for some years in the same regions, it is natural to ask how the virus survives the dry season.

Some hypotheses have been proposed to explain this 'overwintering' of dengue fever in the subtropical regions. First, the survival of some particularly long-lived infected mosquitoes females; second, the vertical transmission in the mosquito population density with a fraction of the eggs remaining infected throughout the dry season, hatching in the beginning of the rainy season (Monath and Heinz, 1996); and third, the presence of a vertebrate reservoir that could keep the infection in the wild. This last hypothesis is just a theoretical possibility, and we shall not consider it in this paper.

Another observation related to dengue transmission is that, in some subtropical areas, the density of mosquitoes peaks some months before the human epidemic, as seen in Fig. 1 (Alvaro Eiras, 2003, personal communication), which shows data from Belo Horizonte, Brazil.

It can be seen in the figure that mosquitoes start to increase in number in the beginning of the rainy season (October), whereas the cases of dengue start to increase more than 3 months later.

This paper is an attempt to test the first two hypotheses of dengue 'overwintering' (the vertical transmission and the survival of infected females throughout winter) and to explain the delay in the epidemics peak as compared to the peak in the mosquitoes population density. For this, we propose a dynamical model, which allows the testing of distinct epidemiological scenarios.

This paper is organized as follows. In Section 2.1, we present the biological assumptions that guided the model's structure. In Section 2.2, we present the model's equations and definition of the variables and parameters. In Section 2.3, we study the variation of the mosquitoes and eggs populations densities without the disease during the year. In Section 3, we deduce an approximate threshold, which can be

used to predict all the possible behaviors of the system. We should stress that we present no mathematical proof that supports this threshold. Instead, we present an intuition for it and we have tested it numerically. In any case, this threshold allows us to test the two overwintering hypotheses and explain the observed delay between the peak in mosquitoes density and the initial rising in the number of dengue cases. This is done in Section 4. In Section 5, we summarize and discuss our findings and finally, in the appendix we present a simplified model, in which we can show analytically that there is a time-dependent threshold, $R(t)$, such that when its yearly average, denoted $\overline{R}$, is less than 1, the disease does not invade the populations and when $\overline{R}$ is greater than 1 it does. By not invading the population, we mean that the number of infected individuals always decrease in subsequent seasons of transmission.

2. The model

2.1. Biological assumptions

Before describing the model proposed, we introduce the main assumptions related to the mosquito life cycle and the seasonality considered.

The mosquito goes through four separate and distinct stages during its life cycle: egg, larva, pupa, and adult. Each of these stages can be easily recognized by its appearance. How long each stage lasts depends on both temperature and species' characteristics. For instance, *Culex tarsalis*, a common California (USA) mosquito, might go through its life cycle in 14 days at 70 °F and take only 10 days at 80 °F. On the other hand, some species have naturally adapted to go through their entire life cycle in as little as 4 days or as long as 1 month.[1] In this paper, we assumed that the immature stages between eggs and adults (larvae and pupae) are clumped in a single state, hereafter called as 'eggs'.

In temperate and sub-tropical regions, the aedes population density present marked variations along the year, peaking in the summer and dropping to very low in the winter. Seasonal and climatic effects on mosquitoes influence transmission. Temperature and humidity affect mosquitoes longevity and activity, gonadotrophic cycle length, oviposition rates, eggs survival rates, and eggs hatching rates. Also, as a water-breeding species, aedes requires standing water to reproduce, thus cold winters and/or dry summers substantially reduce mosquitoes breeding and feeding (Beaty and Marquardt, 1996).

Therefore, seasonality can be driven by the several biological and environmental mechanisms described earlier. As discussed in the next section, we choose to model seasonality by forcing the rate at which eggs mature into adults to change periodically along the year. This assumption can be better understood by the fact that adults of the northern univoltine aedes species usually emerge in the spring. The reproductive season extends from spring until the end of autumn. The eggs laid in the end of autumn do not hatch until the beginning of the next spring, diapausing along the winter (Beauty and Marquardt, 1996, p. 89). Of course, in

[1] http://www.mosquito.org/info.php.

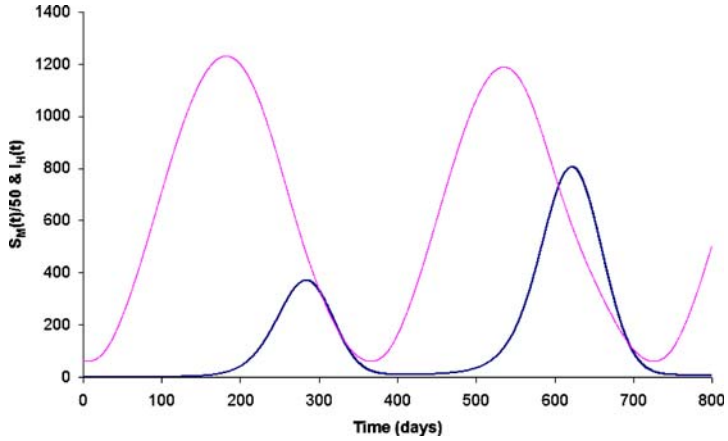

Fig. 2 Simulation of the delay between mosquitoes peak and dengue outbreak. The average daily men-biting rate, i.e., the average per capita biting rate at $t = 0$, MBR $= [\{S_M(0)\}/\{N_H\}]a$, was set as 0.065 bites per day and the initial conditions were such that the densities of susceptible mosquitoes ($S_M(0)$) and eggs ($S_E(0)$), and the hatching rate were at their minimum. The fine line represents susceptible mosquitoes density and gross line the infected humans density. Note the delay of about 100 days.

tropical regions, diapausing of multivoltine species is less extreme and the rate of eggs hatching in the dry season significantly diminishes, but does not go to zero.

As we shall see in Section 2.3 and Fig. 2, the seasonality mechanism chosen has the effect of forcing the adults and eggs population densities to oscillate in phase with a period of 1 year, thus mimicking in a schematic way the seasonality in the density of mosquitoes populations.

Another assumption of our model is that the density of aedes adults is checked by the availability of breeding places. We, therefore, assumed that the oviposition rate is dependent on the total eggs density. This is a consequence of competition for limited breeding places in the dry season.

Finally, we assumed that some infected female aedes lay infected eggs that hatch into infected females. This vertical transmission has already been suggested by field studies, in which this effect was considered to be important for *Aedes albopictus* (75% of trans-ovarial transmission described by Shroyer, 1990), but less so with *A. aegypti* (2.8% of trans-ovarial transmission described by Joshi et al., 2004). In addition, in a recent publication, Crochu et al. (2004) demonstrated the integration of flavivirus DNA sequences in the genome of Aedes spp. mosquitoes. This may, in the future, provide further evidence in favor of vertical transmission influencing the pattern of dengue epidemics.

2.2. Model's equations

The model describes the dynamic of dengue in its three components of transmission, namely human hosts, mosquitoes, and their eggs (the latter, as mentioned previously, includes the intermediate stages, like larvae and pupae). The

populations densities, in turn, are divided into susceptible humans, denoted by S_H, infected humans, I_H, recovered (and immune) humans, R_H, total humans, $N_H = S_H + I_H + R_H$, susceptible mosquitoes, S_M, infected and latent mosquitoes, L_M, infected and infectious mosquitoes, I_M, non-infected eggs, S_E, and infected eggs, I_E.

The model's dynamics is described by the set of equations.

$$
\begin{aligned}
\frac{dS_H}{dt} &= -ab_H I_M \frac{S_H}{N_H} - \mu_H S_H + r_H N_H \left(1 - \frac{N_H}{k_H}\right) \\
\frac{dI_H}{dt} &= ab_H I_M \frac{S_H}{N_H} - (\mu_H + \alpha_H + \gamma_H) I_H \\
\frac{dR_H}{dt} &= \gamma_H I_H - \mu_H R_H \\
\frac{dS_M}{dt} &= p_S (c - d \sin(2\pi f t + \phi)) \\
&\quad \times S_E \theta (c - d \sin(2\pi f t + \phi)) - \mu_M S_M - ab_M S_M \frac{I_H}{N_H} \\
\frac{dL_M}{dt} &= ab_M S_M \frac{I_H}{N_H} - e^{(-\mu_M \tau_1)} a S_M(t - \tau_1) \frac{I_H(t - \tau_1)}{N_H(t - \tau_1)} - \mu_M L_M \\
\frac{dI_M}{dt} &= e^{(-\mu_M \tau_1)} ab_M S_M(t - \tau_1) \frac{I_H(t - \tau_1)}{N_H(t - \tau_1)} - \mu_M I_M \\
&\quad + p_I (c - d \sin(2\pi f t + \phi)) I_E \theta (c - d \sin(2\pi f t + \phi)) \\
\frac{dS_E}{dt} &= [r_M S_M + (1 - g) r_M I_M] \left(1 - \frac{S_E + I_E}{k_E}\right) \\
&\quad - \mu_E S_E - p_S (c - d \sin(2\pi f t + \phi)) S_E \theta (c - d \sin(2\pi f t + \phi)) \\
\frac{dI_E}{dt} &= g r_M I_M \left(1 - \frac{S_E + I_E}{k_E}\right) - \mu_E I_E \\
&\quad - p_I (c - d \sin(2\pi f t + \phi)) I_E \theta (c - d \sin(2\pi f t + \phi)).
\end{aligned} \tag{1}
$$

Most of the terms in the system 1 can be understood by referring to Table 1, where the meaning and values of the parameters are described. Here we limit ourselves to explain some terms related to the equations for the mosquito and eggs subpopulations.

The fourth, fifth, and the sixth equations represent the susceptible, latent, and infected mosquitoes population densities, respectively. Susceptible mosquitoes varies in size with a time-dependent rate

$$p_S(c - d \sin(2\pi f t + \phi)) S_E \theta (c - d \sin(2\pi f t + \phi)).$$

The term $p_S S_E$ is the fraction of eggs hatching per unit time, and which survived the development through the intermediate stages (larvae and pupae).

Table 1 Parameter notation, biological meaning, values and sources.

Parameter	Meaning	Value	Source
a	Average daily biting rate	Variable	Gubler and Kuno (1997)
b_H, b_M	Fraction of actually infective bites	1	Hauck Center (2005)
μ_H	Humans natural mortality rate	4×10^{-5} per day	SEADE Foundation
r_H	Birth rate of humans	2.5 per day	SEADE Foundation
k_H	Humans carrying capacity	2×10^5	SEADE Foundation
α_H	Dengue-induced mortality in humans	10^{-3} per day	Gubler and Kuno (1997)
γ_H	Humans recovery rate	0.143 per day	Gubler and Kuno (1997)
p_S	Non-infected eggs hatching rate	0.15 per day	Beaty and Marquardt (1996)
c	Climatic factor modulating winters	0.07	Chosen
d	Climatic factor modulating winters	0.06	Chosen
f	Frequency of the seasonal cycles	2.8×10^{-3} per day	1 year
μ_M	Natural mortality rate of mosquitoes	0.263 per day	Beaty and Marquardt (1996)
τ	Extrinsic incubation period of dengue	7 days	Gubler and Kuno (1997)
α_M	Dengue-induced mortality in mosquitoes	Negligible	
r_M	Oviposition rate	50 per day	Beaty and Marquardt (1996)
p_I	Infected eggs hatching rate	0.15 per day	Chosen
g	Proportion of infected eggs	See text	
k_E	Eggs carrying capacity	10^6	Estimated
μ_E	Natural mortality rate of eggs	0.1 per day	Beaty and Marquardt (1996)

The time-dependent term $(c - d\sin(2\pi ft + \phi))\,\theta(c - d\sin(2\pi ft + \phi))$ simulates the seasonal variation in mosquitoes production from eggs. By varying c and d, we can simulate the duration and severity of the winters ($f = 1/365$ per day and so it fixes one cycle per year). Of course, the parameters determining the length and severity of the seasons should be equal for susceptible and infected eggs and we set them so. The Heaviside θ-function (a step function that is equal to zero when the argument is less than zero and one when the argument is greater or equal to zero) $\theta(c - d\sin(2\pi ft + \phi))$ prevents the term

$$(c - d\sin(2\pi ft + \phi))\theta(c - d\sin(2\pi ft + \phi)),$$

from becoming negative. If c is smaller than d, then the winter is long and severe. On the other hand, if c is greater than d, then the winter is short and mild. This will be discussed with more details in the next section.

The term

$$p_{\mathrm{I}}(c - d\sin(2\pi ft + \phi))I_{\mathrm{E}}\theta(c - d\sin(2\pi ft + \phi)),$$

represents the rate by which infected eggs become infected adults. The term $p_{\mathrm{I}}\,I_{\mathrm{E}}$ is the fraction of infected eggs hatching per unit time, and which survived the development through the intermediate stages (larvae and pupae).

The phase ϕ, as described in Section 2.3, will be used to set the rate of eggs' hatching, the adult mosquitoes density, and the egg density at their minimum values at $t = 0$.

The seventh and the eight equations represent the dynamics of susceptible and infected eggs, respectively.

In the seventh equation, the term

$$[r_{\mathrm{M}}S_{\mathrm{M}} + (1 - g)r_{\mathrm{M}}I_{\mathrm{M}}]\left(1 - \frac{S_{\mathrm{E}} + I_{\mathrm{E}}}{k_{\mathrm{E}}}\right),$$

represent the oviposition rate of susceptible eggs born from both susceptible mosquitoes with rate

$$r_{\mathrm{M}}S_{\mathrm{M}}\left(1 - \frac{S_{\mathrm{E}} + I_{\mathrm{E}}}{k_{\mathrm{E}}}\right),$$

and from a fraction $(1 - g)$ of infected mosquitoes, with rate

$$(1 - g)r_{\mathrm{M}}I_{\mathrm{M}}\left(1 - \frac{S_{\mathrm{E}} + I_{\mathrm{E}}}{k_{\mathrm{E}}}\right).$$

The parameter g, therefore, represents the proportion of infected eggs laid by infected female mosquitoes.

The term $r_{\mathrm{M}}\,S_{\mathrm{M}}$ represents the maximum oviposition rate of female mosquitoes with the number of viable eggs being checked by the availability of breeding places

by the term

$$\left(1 - \frac{S_E + I_E}{k_E}\right).$$

The so-called egg's carrying capacity is

$$\frac{r_E - \mu_E}{r_E} k_E,$$

where k_E is a constant. We choose a density dependence on birth rather than on death. The control of the population could be done by a term including density-dependence in the mortality rate, but the net result would be qualitatively the same.
Finally, in the last equation, the term

$$g r_M I_M \left(1 - \frac{S_E + I_E}{k_E}\right),$$

represents the net rate by which infected eggs are produced by infected adult females, i.e., vertical transmission of dengue virus.

2.3. Entomology without disease

In this subsection, we analyze the behavior of the mosquito population density in the absence of disease. This implies that the only equations to be simulated are:

$$\begin{aligned}
\frac{dS_M}{dt} &= p_S(c - d\sin(2\pi f t + \phi))S_E\theta(c - d\sin(2\pi f t + \phi)) - \mu_M S_M \\
\frac{dS_E}{dt} &= r_M S_M \left(1 - \frac{S_E}{k_E}\right) - \mu_E S_E - p_S(c - d\sin(2\pi f t + \phi)) \\
&\quad \times S_E\theta(c - d\sin(2\pi f t + \phi)).
\end{aligned} \tag{2}$$

This pair of equations follows from Eq. (1) after making zero all the infected terms. It simulates the annual cycle of mosquitoes breeding. The system of Eq. (2) is a very simplified model for what is really known about the life cycle of mosquitoes. As mentioned previously, the immature stages between eggs and adults (larvae and pupae) are clumped in the eggs compartment. It is also an oversimplification of the annual seasons.

The initial conditions and the phase ϕ were chosen such that the density of susceptible mosquitoes ($S_M(0)$), the density of susceptible eggs ($S_E(0)$), and the rate of eggs' hatching are at their minimum. The minimum was determined by running the program for an arbitrary initial condition (compatible with k_E, and k_H) and setting $\phi = \pi/2$. By doing this, we guaranteed that variations in mosquitoes and eggs densities and in eggs' hatching rates are all synchronized (with peaks in 'summer' and troughs in 'winter').

Winters without eggs hatching were simulated by making d larger than c. This has the effect of making the term $(c - d\sin(2\pi ft + \phi))$ negative for some parts of the cycle. In these periods, the Heaviside function $\theta(c - d\sin(2\pi ft + \phi))$ makes the hatching of eggs equal to zero, thus reducing the adult forms. If d is set smaller than c, then very weak winters are simulated. Those variations in the length and strength of the winter have the obvious consequence of changing the quality of the summers, although the peak in eggs production in the summer is dependent on the parameter k_{E}, related to the eggs carrying capacity. Note that, in the particular case in which $d = 0$, we have a threshold in

$$c > \frac{\mu_{\mathrm{E}}\mu_{\mathrm{M}}}{p_{\mathrm{S}}(r_{\mathrm{M}} - \mu_{\mathrm{M}})}, \quad (r_{\mathrm{M}} > \mu_{\mathrm{M}}),$$

above which both the eggs and the mosquitoes settle at constant values.

We also checked that the population of mosquitoes survives severe winters through the diapausing of eggs. The density of mosquitoes in the summer following a severe winter can be very large, depending on k_{E}.

3. An approximated threshold condition

In the first part of this section, we deduce a threshold condition for epidemics.

We want, with this threshold, to answer the following question: When can a vector-borne disease invade a population of susceptible humans in which two transmission components, namely eggs and mosquitoes, are time dependent?

A time-independent threshold for vector-borne diseases was first proposed by Macdonald (1952). It is called "the Basic Reproduction Number" and is normally denoted R_0 (see Lopez et al., 2002).

We describe, in this section, an intuitive approach to get this approximate time-dependent threshold. In the appendix, we discuss a simple model from which a time-dependent threshold follows analytically.

System (1) has 'no-mass,' i.e., it responds to perturbations instantaneously. We introduce some disease at time $t = 0$, and 'freeze' the system at time t. At this moment, we have infected compartments that we assume became instantaneously non-infective, and we investigate the effect of a small amount of infection introduced on the stability of the frozen equilibrium.

Thus, we consider a new system of equations consisting of the infective equations of the original system 1, substituting I_{H}, L_{M}, I_{M}, and I_{E} by i_{H}, l_{M}, i_{M}, and i_{E}, respectively:

$$\begin{aligned}
\frac{\mathrm{d}i_{\mathrm{H}}}{\mathrm{d}t} &= ab_{\mathrm{H}}\frac{S_{\mathrm{H}}}{N_{\mathrm{H}}}i_{\mathrm{M}} - (\mu_{\mathrm{H}} + \alpha_{\mathrm{H}} + \gamma_{\mathrm{H}})i_{\mathrm{H}} \\
\frac{\mathrm{d}l_{\mathrm{M}}}{\mathrm{d}t} &= ab_{\mathrm{M}}\frac{S_{\mathrm{M}}}{N_{\mathrm{H}}}i_{\mathrm{H}} - \mu_{\mathrm{M}}l_{\mathrm{M}} - \mathrm{e}^{(-\mu_{\mathrm{M}}\tau_{\mathrm{I}})}ab_{\mathrm{M}}\frac{S_{\mathrm{M}}(t-\tau_{\mathrm{I}})}{N_{\mathrm{H}}(t-\tau_{\mathrm{I}})}i_{\mathrm{H}}(t-\tau_{\mathrm{I}}) \\
\frac{\mathrm{d}i_{\mathrm{M}}}{\mathrm{d}t} &= \mathrm{e}^{(-\mu_{\mathrm{M}}\tau_{\mathrm{I}})}ab_{\mathrm{M}}\frac{S_{\mathrm{M}}(t-\tau_{\mathrm{I}})}{N_{\mathrm{H}}(t-\tau_{\mathrm{I}})}i_{\mathrm{H}}(t-\tau_{\mathrm{I}}) - \mu_{\mathrm{M}}i_{\mathrm{M}} \\
&\quad + p_{\mathrm{I}}(c - d\sin(\Phi))i_{\mathrm{E}}\theta(c - d\sin(\Phi))
\end{aligned} \tag{3}$$

$$\frac{\mathrm{d}i_\mathrm{E}}{\mathrm{d}t} = gr_\mathrm{M}\left(1-\frac{S_\mathrm{E}}{k_\mathrm{E}}\right)i_\mathrm{M} - \mu_\mathrm{E} i_\mathrm{E} - p_\mathrm{I}(c - d\sin(\Phi))i_\mathrm{E}\theta(c-d\sin(\Phi)),$$

where $\Phi = 2\pi f t + \phi$, and analyze the stability of the trivial solution $i_\mathrm{E} = 0, l_\mathrm{M} = 0$, $i_\mathrm{H} = 0$, and $i_\mathrm{M} = 0$, as if the system were autonomous (El'sgol'ts, 1966). For this, we assume the solutions:

$$\begin{aligned} i_\mathrm{H} &= c_1 \exp(\lambda t) \\ l_\mathrm{M} &= c_2 \exp(\lambda t) \\ i_\mathrm{M} &= c_3 \exp(\lambda t) \\ i_\mathrm{E} &= c_4 \exp(\lambda t). \end{aligned} \tag{4}$$

The characteristic equation associated to system (3) is then obtained:

$$\begin{vmatrix} -(\lambda+\gamma_\mathrm{H}+\alpha_\mathrm{H}+\mu_\mathrm{H}) & 0 & ab_\mathrm{H}\frac{S_\mathrm{H}(t)}{N_\mathrm{H}(t)} & 0 \\ ab_\mathrm{M}\frac{S_\mathrm{M}}{N_\mathrm{H}} - ab_\mathrm{M}\mathrm{e}^{(-\mu_\mathrm{M}\tau_\mathrm{I})}\frac{S_\mathrm{M}(t-\tau_\mathrm{I})}{N_\mathrm{H}(t-\tau_\mathrm{I})}\mathrm{e}^{-\lambda\tau_\mathrm{I}} & -(\lambda+\mu_\mathrm{M}) & 0 & 0 \\ ab_\mathrm{M}\mathrm{e}^{(-\mu_\mathrm{M}\tau_\mathrm{I})}\frac{S_\mathrm{M}(t-\tau_\mathrm{I})}{N_\mathrm{H}(t-\tau_\mathrm{I})}\mathrm{e}^{-\lambda\tau} & 0 & -(\lambda+\mu_\mathrm{M}) & p_\mathrm{I}(c-d\sin\Phi)\,\theta(c-d\sin(\Phi)) \\ 0 & 0 & gr_\mathrm{M}\left(1-\frac{S_\mathrm{E}}{k_\mathrm{E}}\right) & -\lambda-\mu_\mathrm{E}- p_\mathrm{I}(c-d\sin(\Phi))\,\theta(c-d\sin(\Phi)) \end{vmatrix} = 0. \tag{5}$$

If all the roots of Eq. (5) have negative real parts, then the equilibrium without disease is stable, i.e., the origin is an attractor. As shown in Lopez et al. (2002), the first root that crosses the imaginary axis does so through the real axis and this happens when

$$R(t) = \frac{ab_\mathrm{M}}{(\gamma_\mathrm{H}+\alpha_\mathrm{H}+\mu_\mathrm{H})}\frac{S_\mathrm{M}(t-\tau_\mathrm{I})}{N_\mathrm{H}(t-\tau_\mathrm{I})}\frac{a\exp(-\mu_\mathrm{M}\tau_\mathrm{I})\,b_\mathrm{H}c}{\mu_\mathrm{M}}\frac{S_\mathrm{H}(t)}{N_\mathrm{H}(t)} + \frac{p_\mathrm{I}(c-d\sin\Phi)\,gr_\mathrm{M}\left(1-\frac{S_\mathrm{E}(t)}{k_\mathrm{E}}\right)\theta(c-d\sin(\Phi))}{\mu_\mathrm{M}(\mu_\mathrm{E}+p_\mathrm{I}(c-d\sin\Phi)\,\theta(c-d\sin(\Phi)))} > 1. \tag{6}$$

As mentioned earlier, the phase is set at $\phi = \pi/2$ and the initial condition is such that the susceptible mosquito and eggs densities are at their lowest values.

Note that the maximum value of $R(t)$ is dependent on the maximum values of $S_\mathrm{M}(t)$ and $S_\mathrm{H}(t)$. Therefore, provided that $S_\mathrm{M}(t) \le S_\mathrm{M}(0)$ and $S_\mathrm{H}(t) \le S_\mathrm{H}(0)$, the maximum value of $R(t)$ can only diminish with time.

We claim that 6 is an approximate version of the reproductive number of system 1. In the time intervals for which $R(t)$ is greater than one, the infection is amplified and in the time intervals for which $R(t)$ is less than one, the infection dies out. Note that, for small t, the first term in Eq. (6) is

exactly the expression proposed in Macdonald (1952) for the basic reproduction number.

4. Understanding the possible behaviors of the system

In the first part of this section, we explain the delay observed in dengue outbreaks between the peak in mosquitoes density and the initial rising in dengue cases. We do so by introducing a small amount of disease into a previously uninfected population when the rate of eggs hatching is at its minimum ($\phi = \pi/2$), and the susceptible mosquito and eggs densities are at their lowest values. In the second part, we show how dengue overwintering occurs and discuss and explain the only two different patterns of cyclic dengue outbreaks.

4.1. Delay in dengue epidemics

It has been observed that aedes population density peaks about 1 month after the beginning of the rainy season (in southeastern Brazil in the month of October), but dengue epidemics typically appear some 3 or 4 months after that (Fig. 1). Although our model of seasonality is too crude to fit any data (as those from Fig. 1) with any degree of accuracy, the delay can be seen in the simulations of the model shown in Fig. 2. In this figure, we show the case in which 50% of the hatched eggs from infected females are infected. The daily biting rate is of the same order as described in the literature (Rodahin and Rosen, 1997; Forattini et al., 1995; Massad et al., 2001; Forattini, 2002). The resulting average daily men-biting rate, i.e., the average per capita biting rate at $t = 0$,

$$\mathrm{MBR} = \frac{S_{\mathrm{M}}(0)}{N_{\mathrm{H}}} a,$$

was set as 0.065 bites per day and the initial conditions were such that the densities of susceptible mosquitoes ($S_{\mathrm{M}}(0)$) and eggs ($S_{\mathrm{E}}(0)$) and the hatching rate were at their minimum. Then a small amount of disease was introduced. The result of this simulation can be seen in Fig. 2.

One can note that the mosquito population density drops sharply in the winter (troughs in the fine lines).

The delay between the peak in the mosquitoes population density and the peak in dengue epidemics is of the order of 100 days, which corresponds to actual situations in endemic areas as shown in Fig. 1.

Let us try to understand qualitatively the origin of the delay observed in dengue. This is due to the cyclic pattern of the mosquito population density. During the dry season, as mentioned earlier, the mosquito population density drops to very low levels, below the threshold, $R = 1$, for transmission. In early spring, the population density of mosquitoes begins to increase until it reaches a critical level at which the threshold crosses one and transmission begins, thus the delay.

As can be seen from the first term of Eq. (6), this critical level also depends on the fraction of the infected mosquito that survives the extrinsic incubation period

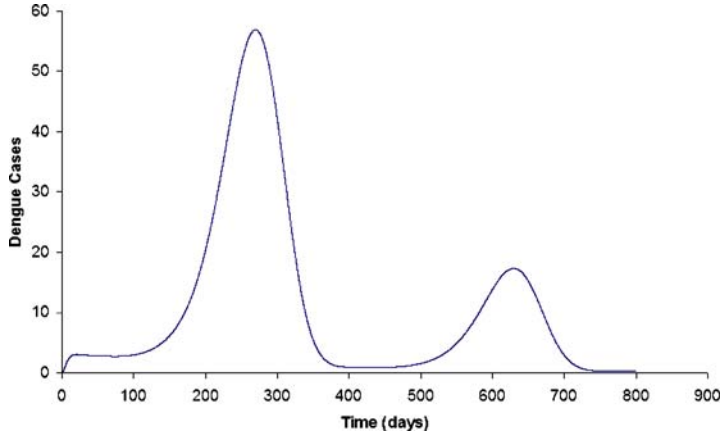

Fig. 3 The first pattern of outbreak, obtained with a value of men-biting rate, MBR = 0.052 per day. One can see a succession of two outbreaks forming a damped oscillation pattern until the disease disappears.

with probability $e^{(-\mu_M \tau_1)}$ and become infective. The longer the extrinsic incubation period, the larger the delay.

4.2. Dengue overwintering and extinction

As it occurs with other vector-borne infections, environmental and climatic conditions, as well as the stock of susceptible humans, determine the existence, intensity, and duration of dengue outbreaks. This can be viewed in Figs. 3–6 in which we show and explain the two patterns of dengue recurrent outbreaks, as predicted by the model.

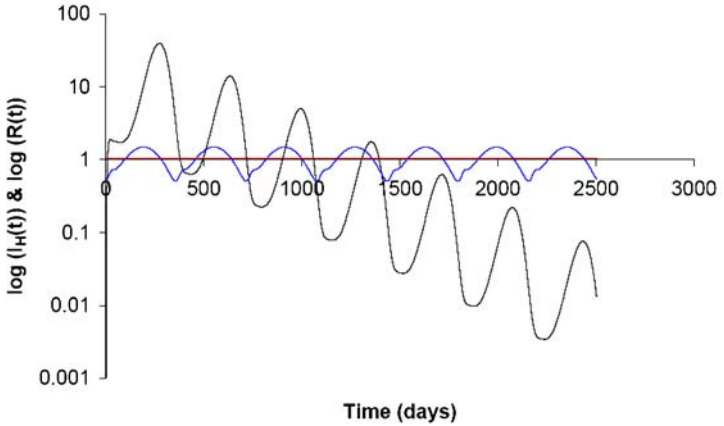

Fig. 4 Both the time variation in $R(t)$ (log scale) and in the total amount of infection, $I_H(t)$ (log scale) with the same conditions as in Fig. 3. It can be noted that the peaks and troughs of $I_H(t)$ shown occur approximately when $R(t)$ crosses 1, from above downwards and from below upwards, respectively.

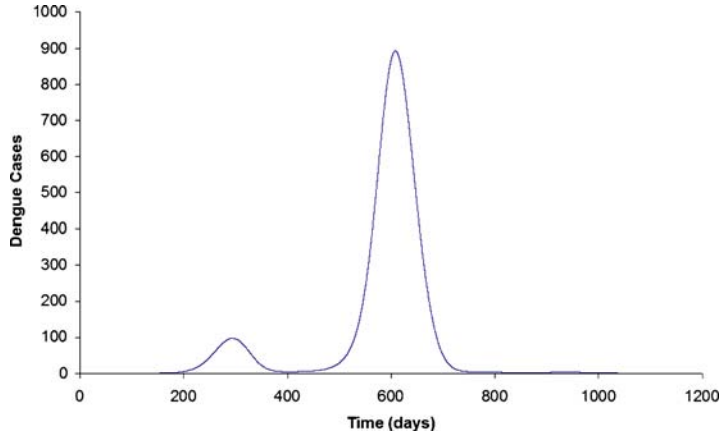

Fig. 5 The second pattern of outbreaks, in which $R(t) > 1$ for a greater part of the year in the first outbreak, was obtained with a value of the men-biting rate, MBR $= 0.065$ per day.

In the first pattern shown in Fig. 3, obtained with a value of men-biting rate, MBR $= 0.052$ per day, we see a succession of outbreaks forming a damped oscillation pattern until the disease disappears.

This dumped oscillation can be understood as follows. As mentioned earlier, in the time intervals for which $R(t)$ is greater than one, the infection is amplified and in the time intervals for which $R(t)$ is less than one, the infection dies out. The previous discussion suggests that the average value of $R(t)$ in 1 year, $\overline{R}$, determines whether the disease will increase ($\overline{R} > 1$) or decrease ($\overline{R} < 1$) in the following year.

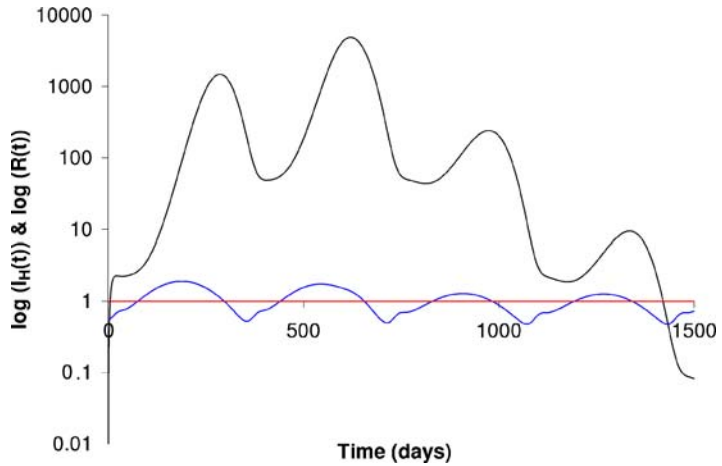

Fig. 6 Both the time variation in $R(t)$ and in the total amount of infection, $I_H(t)$, for the same case as in Fig. 5. Again, it can be noted that the peaks and troughs of $I_H(t)$ occur approximately when $R(t)$ crosses 1, from above downwards and from below upwards, respectively, and that the effect of herd immunity can be seen by a decrease in the time interval in which $R(t) > 1$.

The average $\overline{R}$ for a period T starting at t is defined as:

$$\overline{R}_T = \frac{\int_t^{t+T} R(s)\mathrm{d}s}{T}. \tag{7}$$

It is easy to conclude that the value of $\overline{R}_T$ in the first year is the highest possible (in the presence of diseases) because, as mentioned earlier, $S_{\mathrm{M}}(t) \leq S_{\mathrm{M}}(0)$ and $S_{\mathrm{H}}(t) \leq S_{\mathrm{H}}(0)$.

In the appendix, we demonstrate that for a simple model, the number of infected individuals at time $(t + T)$ is related to the number of infected individuals at time t by the average threshold condition (see Eq. (A.7)).

Thus, examining Fig. 4 it is possible to understand why the disease disappears. In it, we show that the system oscillates and the average value of $R(t)$ in the first year is below one ($\overline{R} = 0.997$) and so the disease introduced at time zero dies out in a dumped oscillation pattern because $\overline{R}$ diminishes for subsequent years. In Fig. 4, we also show both the time variation in $R(t)$ and in the amount of infected humans, $I_{\mathrm{H}}(t)$.

It can be noted that the peaks and troughs of $I_{\mathrm{H}}(t)$ shown in Fig. 4 occur approximately when $R(t)$ crosses 1, from above downwards and from below upwards, respectively.

The second pattern was obtained with a value of the men-biting rate, MBR = 0.065 per day. The simulation of the epidemics in this case is shown in Fig. 5.

The amplitude of the initial outbreaks increases until the fraction of immune individuals reaches a herd immunity threshold and the disease dies out in a damped oscillation pattern. This can be better understood by examining Fig. 6, which shows the time variation of $R(t)$. In this case, the average value of $R(t)$ in the first year is above one ($\overline{R} = 1.23$) and drops to $\overline{R} = 0.91$ in the third year, forcing the disease to die out from thereafter. This is a consequence of herd immunity as it reduces the value of $S_{\mathrm{H}}(t)$ and, therefore, the value of $R(t)$ as in Eq. (6).

In Fig. 6, we also show both the time variation in $R(t)$ and in the amount of infection, $I_{\mathrm{H}}(t)$, for this case.

As $\overline{R}$ is greater than 1 for the first and second years, the maximum value of $I_{\mathrm{H}}(t)$ increases in those years, decreasing thereafter. In addition, it can be noted that the peaks and troughs of $I_{\mathrm{H}}(t)$ occur approximately when $R(t)$ crosses 1, from above downwards and from below upwards, respectively, and that the effect of herd immunity can be seen by a decrease in $R(t)$.

One important aspect is that the two patterns analyzed earlier represent the two only epidemiological outcomes of our model, i.e., a relatively low intensity of transmission (case 1, Figs. 3 and 4) and a high intensity of transmission (case 2, Figs. 5 and 6). In the latter, whenever the intensity of transmission is too high we can have only a single outbreak but this is a particular case of situation 2. We shall show in the next section, a few real outbreaks which conform with our results.

For both patterns, the simulation clearly shows the overwintering of dengue epidemics and its disappearance after some time. The proportion of infected eggs laid, of course, by infected females was set at $g = 0.5$, a fraction of which

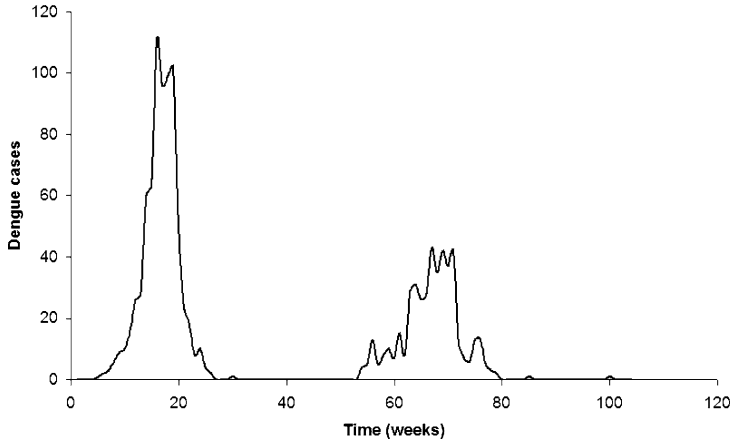

Fig. 7 In this figure, we show the outbreaks that occurred in the city of Araçatuba in the years of 2000 and 2001. It looks like a case of the first pattern as shown in Fig. 3.

$p_I = 0.15$ hatches, evolving into adult females. The maximum of the product $g \times p_I \times (I_M/(I_M + S_M))$ obtained in our simulations is compatible with the transovarial transmission described in the literature (Rodahin and Rosen, 1997).

It should be mentioned that complete extinction of the disease in deterministic models like the present one is achieved when the computer turns unrealistically low densities into zero. For the parameters chosen in the simulations of Figs. 3–6, the disease decays to unrealistically low densities, which the software we applied (Berkley Madonna, 8.0.1) set as equal to zero for values below 10^{-45}. For another set of parameters, the disease might fail to reach 10^{-45} and would come back after some time; but, in this case, we would introduce an appropriate Heaviside function to force the disease to become extinct after those unrealistically low levels were reached.

Figures 7 and 8 shows two real cases of dengue outbreaks in the State of São Paulo, southeastern Brazil. In Fig. 7, we show the outbreaks that occurred in the city of Araçatuba in the years of 2000 and 2001. It looks like a case of the first pattern as shown in Fig. 3.

In Fig. 8 we show the outbreak that occurred in the city of São José do Rio Preto in the same years. It looks like a case of the second pattern as shown in Fig. 5.

The same phenomenon of dengue overwintering can be studied in the absence of vertical transmission of dengue virus in the mosquitoes population density ($g = 0$). In this case, the overwintering only occurs with particularly favorable conditions for dengue transmission, such as a longer survival of infected mosquitoes females, milder winters, and higher men-biting rates, because in such conditions only the first term of Eq. (6) survives. In order to get the same intensity of transmission over the dry season in the absence of vertical transmission, we had to almost double the contact rate between infected mosquitoes and susceptible humans, or to significantly increase female mosquitoes survival. Some indirect experimental evidence support the previous results. For instance, dengue virus strains infecting a less aggressive vector as *A. albopictus* must have a high rate of vertical transmission, as

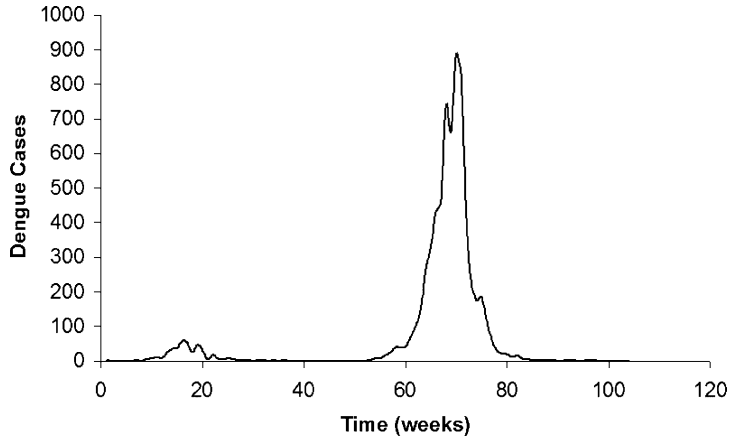

Fig. 8 In this figure, we show the outbreaks that occurred in the city of São José do Rio Preto in the same years. It looks like a case of the second pattern as shown in Fig. 5.

shown by Shroyer (1990). On the other hand, a dengue virus strain infecting a more aggressive vector, as *A. aegypti*, apparently can afford to have a less important vertical transmission (Joshi et al., 2002).

As mentioned earlier, the computer, or properly introduced Heaviside function, makes the disease-free solution as the only possible stable (oscillating) solution. This is because of herd immunity and because we do not consider the case when both the human and mosquitoes populations have a positive growth. Without immunity the disease oscillates. To illustrate this we carried out a simulation in which the infected individuals can recover and return to the susceptible state (no immunity, i.e., a S–I–S type of infection). The system oscillates and this can be seen in Fig. 9

4.3. Sensitivity of the patterns to the amount of disease introduced

It can be numerically checked that when the transmission is relatively low, i.e., when $\overline{R} < 1$ an increase in the amount of the disease introduced at $t = 0$ changes the pattern shown in Fig. 3 by increasing the peaks almost linearly. In Fig. 3, we introduced at $t = 0$, 550 infected eggs. When we introduced 55 infected eggs, the peaks amplitudes were divided by 10. Naturally, if a large amount of disease is introduced, then herd immunity can distort the pattern.

In the case when transmission is relatively high, i.e., when $\overline{R}$ is above one, an increase in the amount of disease introduced at $t = 0$ can distort the pattern due to herd immunity. If the amount of disease introduced is sufficiently large, we can observe just a single peak, i.e., the disease disappear by a substantial decrease in the number of susceptibles.

5. Summary and conclusions

In this paper, we constructed a theoretical framework to investigate the two hypotheses for dengue overwintering, namely, particularly long-lived mosquito

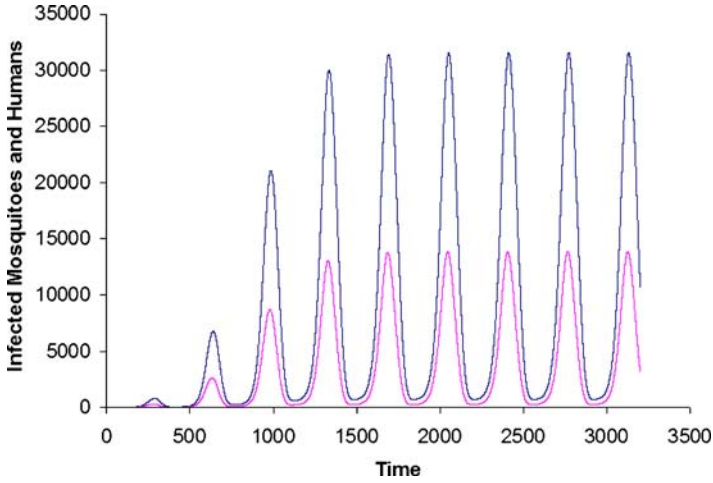

Fig. 9 Simulation of a simple model without immunity (S–I–S), in which the infected individuals can recover and return to the susceptible state. *Dark line* represents the infected humans and *light line* represents the infected mosquitoes.

females and trans-ovarial infection. We also investigated if the model could reproduce the delay between mosquitoes population density and the peak in dengue cases.

The model allowed us to demonstrate that both hypotheses of dengue overwintering are possible, although under usual field conditions the hypothesis of vertical transmission appears to be more plausible. Long-lived females can also explain overwintering, but to get the same intensity of transmission over the dry season in the absence of vertical transmission, we had to almost double the contact rate between infected mosquitoes and susceptible humans.

It was found that both trans-ovarian transmission and long-lived females reproduce the delay between mosquitoes population density and the peak in dengue cases, which can be as high as 100 days in southeastern Brazil.

We also investigated the causes of dengue extinction. In the first case analyzed, dengue disappear due to the fact that the system is below the threshold most of the time. In the second case, the fraction of immune individuals reaches a herd immunity threshold and the disease dies out in a damped oscillation pattern.

In conclusion, the purposes of this work, namely to test the two hypotheses of dengue 'overwintering' (the vertical transmission and the survival of infected females throughout winter) and to explain the delay in the epidemics peak as compared to the peak in the mosquitoes population density were successfully achieved.

Acknowledgements

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Appendix

In this appendix, we examine an exact model in which this can be show exactly that there is a time-dependent threshold, $R(t)$, such that when $R(t)$ is less than 1 the disease dies out and when $R(t)$ is greater than 1 the disease invade the population.

This model is an Susceptible–Infected–Removed (S–I–R) type of model with a contact parameter that is time dependent to simulate seasonality. The equations for susceptible individuals, $S(t)$, infected individuals, $I(t)$, and removed individuals, $R(t)$, are:

$$\begin{aligned}
\frac{\mathrm{d}S(t)}{\mathrm{d}t} &= -\beta(t)S(t)I(t)/N(t) + \mu(I(t) + R(t)) \\
\frac{\mathrm{d}I(t)}{\mathrm{d}t} &= \beta(t)S(t)I(t)/N(t) - (\mu + \gamma)I(t) \\
\frac{\mathrm{d}R(t)}{\mathrm{d}t} &= \gamma I(t) - \mu R(t),
\end{aligned} \tag{A.1}$$

where $N(t)$ is the total population, μ the natural mortality rate, γ the removal rate, and $\beta(t)$ is given by:

$$\beta(t) = \beta_0(c - d\sin(2\pi ft + \phi))\theta(c - d\sin(2\pi ft + \phi)), \tag{A.2}$$

where c, d, f, and ϕ are as described in the main text, and θ is the Heaviside θ-function that guarantees that $\beta(t)$ does not become negative.

It is obvious that the number of infected individuals increases if

$$\beta(t)S(t)/N(t) - (\mu + \gamma) > 0, \tag{A.3}$$

or

$$R(t) = \frac{\beta(t)}{\mu + \gamma}\frac{S(t)}{N(t)} > 1, \tag{A.4}$$

or it decreases if

$$\beta(t)S(t)/N(t) - (\mu + \gamma) < 0, \tag{A.5}$$

or if $R(t) < 1$.

From the second equation of system (A.1) one can deduce that

$$\log(I(t + T)) - \log(I(t)) = (\mu + \gamma)\int_t^{t+T} [R(s) - 1]\,\mathrm{d}s, \tag{A.6}$$

from which we deduced that the number of infected individuals at time $(t + T)$ will increase (decrease) when the average value of $R(t)$ is greater (less) than 1, i.e.,

$$I(t + T) = I(t)\exp[(\mu + \gamma)T(\overline{R}_T - 1)], \tag{A.7}$$

where $\overline{R_T}$ is given by Eq. (7) from the main text.

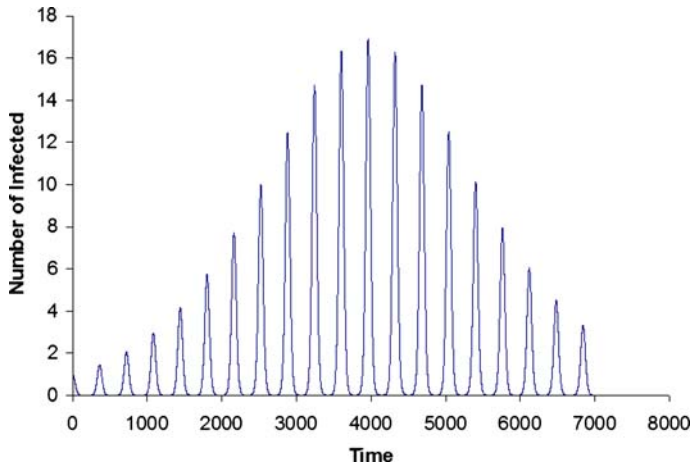

Fig. 10 The resulting pattern of the simulation of system (A.2). We numerically checked that if the average value of $R(t)$ in one year is greater (less) than 1, then the number of infected individuals increase (decrease) in the following year. So, up to year 11, the average value of $R(t)$ for every single year is greater than one dropping to below one after that. Note that the maximum value of $I_{\mathrm{H}}(t)$ increases while $\overline{R}$ is above 1.

We simulate system (A.1) with $\beta_0 = 12.51 \times 10^{-2}$ per days; $\mu = 3.9$ per day; $\gamma = 12.5 \times 10^{-1}$ per day; $\phi = \pi/2$; and c and d are same described in Table 1. The results can be seen in Fig. 10.

In Fig. 10, we show the resulting pattern of the simulation. We numerically checked that if the average value of $R(t)$ in 1 year is greater (less) than the number of infected individuals increase (decrease) in the following year. So, up to year 11, the average value of $R(t)$ for every single year is greater than one dropping to below one after that. Note that the maximum value of $I_{\mathrm{H}}(t)$ increases while $\overline{R}$ is above 1.

Of course, when $R(t)$ crosses the threshold 1 upwards, the disease increase, and when $R(t)$ crosses the threshold downwards, the disease decreases.

Similar thresholds were deduced for other models, like a S–E–I–R type of model and the Ross–Macdonald vector-borne model (see Lopez et al., 2002) with seasonality in the birth rate of mosquitoes. We found that average value of $R(t)$ in 1 year, $\overline{R}$, determines whether the disease will increase ($\overline{R} > 1$) or decrease ($\overline{R} < 1$) at time $t + T$.

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