Assessing the effects of temperature on dengue transmission

H. M. YANG[1]*, M. L. G. MACORIS[2], K. C. GALVANI[2], M. T. M. ANDRIGHETTI[2]
AND D. M. V. WANDERLEY[2]

[1] *UNICAMP – IMECC, Departamento de Matemática Aplicada, Campinas, SP, Brazil*
[2] *SUCEN, Avenida Santo Antonio, Bairro Somenzari, Marília, SP, Brazil*

SUMMARY

The incidence of dengue infection, a vector-borne disease transmitted by the mosquito *Aedes aegypti*, shows clear dependence on seasonal variation. Based on the quantification method that furnishes the size of the *A. aegypti* population in terms of the estimated entomological parameters for different temperatures, we assessed the risk of dengue outbreaks. The persistence and severity of epidemics can be assessed by the basic reproduction number R_0, which varies with temperature. The expression for R_0 obtained from 'true' and 'pseudo' mass action laws for dengue infection is discussed.

Key words: Basic reproduction number, global warming, mass action law, mathematical modelling, risk of dengue with temperature.

INTRODUCTION

Dengue virus, a flavivirus transmitted by arthropods of the genus *Aedes*, is prevalent in different parts of the world. As a result of being pathogenic for humans and capable of transmission in heavily populated areas, dengue virus (arbovirus) can cause widespread and serious epidemics, which constitutes one of the major public health problems in many tropical and subtropical regions of the world where *Aedes aegypti* and other suitable mosquito vectors are present.

The epidemiological cycle occurs as follows. Female mosquitoes become infected during the bloodmeal from infectious individuals (the viraemic period) and they then transmit the infection during the next 7–14 days [1]. The infection in mosquitoes induces a low level of immunity [2] and it is believed, that they probably transmit the virus throughout their lifespan. An infectious mosquito can transmit the virus to a susceptible host during biting and feeding. When an infectious mosquito infects a susceptible host with dengue virus during the bloodmeal, dengue disease can evolve from asymptomatic or classical dengue fever to haemorrhagic dengue, in an average of 4–6 days, which can lead to the death of the host. Manifestation of symptoms varies between 3 and 7 days [3], and the virus circulates in the blood typically for 5 days [1]. Thereafter, the recovered individual develops lifelong specific immunity against the disease. The prevention against dengue disease is restricted to the controlling mechanisms applied to the vector, because immunization by vaccine remains unavailable.

The extrinsic incubation period of dengue virus in female mosquitoes is large compared to their survival time, which strongly depends on temperature [4]. For

* Author for correspondence: Prof. H. M. Yang, UNICAMP – IMECC, Departamento de Matemática Aplicada, Caixa Postal 6065, CEP 13083-859, Campinas, SP, Brazil.
(Email: hyunyang@ime.unicamp.br)

example, both extrinsic and survival time of female mosquitoes are quite similar during winter (low temperature); however, survival is quasi-fivefold higher than the extrinsic period during hot seasons. However, temperature also impacts on all other entomological parameters regarding the mosquito's life-cycle [5], and, as a consequence, the number of female mosquitoes varies according to seasonal variations. During favourable periods when the size of the mosquito population increases, the risk of dengue infection in humans also increases.

In order to prevent dengue outbreaks, periodic surveys designed to detect changes in key adult indices are important since they allow the detection of adult population fluctuations, which may prompt changes in vector control strategy. In this paper we develop a mathematical model aimed at assessing dengue transmission, taking into account the dependence on temperature of the *A. aegypti* population size. In order to achieve this task we consider the entomological parameters estimated in our companion paper [6] and use these in a simple mathematical model presented here. There are many mathematical models concerning the treatment of different aspects of dengue epidemics (e.g. [7–10]).

The paper is structured as follows. Next, simple deterministic models describing dengue transmission are presented. The following section presents dengue transmission dynamics taking into account the temperature-dependent entomological parameters. In the final section we discuss the results and present conclusions.

MODELLING DYNAMICS OF DENGUE TRANSMISSION

The incidence of dengue disease clearly shows seasonal variation. In wet and humid periods, the transmission of dengue virus is extremely high in comparison with periods of low temperature. To some extent, the intrinsic incubation and infectious periods of dengue virus vary insignificantly with temperature, because the activities of the virus occur inside the human body; nevertheless, the same is not true for mosquitoes (see, e.g. [11] for the duration of the sporogonic cycle at different ambient temperatures). However, in the present study we assume that the extrinsic incubation period is independent of temperature, in order to restrict the risk factor (or sentinel) of dengue outbreaks to the size of the female adult mosquito population. Because entomological parameters of *A. aegypti* vary broadly with temperature, the size of the mosquito population is strongly affected by temperature.

Dengue virus circulates due to the interaction between human and mosquito populations in urban areas. For this reason the dynamics of dengue transmission must take into account the role played by these populations. Abiotic influences like temperature are encompassed in the model's parameters.

The dynamics of *A. aegypti* encompassing egg phase, two successive aquatic phases (larval and pupal) and one adult form is reported in a companion paper [6], and is modified to describe dengue virus infecting mosquitoes. The *A. aegypti* female population is divided into three compartments: M_1, M_2 and M_3, which are the numbers at time t of, respectively, susceptible, exposed and infectious mosquitoes. Disregarding the transovarian transmission, all emerging mosquitoes are classified as susceptible. Similarly, the human population is divided into four compartments according to the natural history of the disease: s, e, i and r, which are the fractions at time t of, respectively, susceptible, exposed, infectious and recovered persons. The mosquito population is allowed to vary along time t, while the human population is assumed to be constant, with N being the total number of the human population.

Dengue transmission is sustained by the flows among human and mosquito compartments according to the dengue epidemic cycle presented in the previous section. Susceptible humans are infected during the bloodmeal by infectious mosquitoes, with the *per capita* transmission coefficient (or rate) being designated β'_h, which depends on the frequency of bites given to humans by mosquitoes. The exposed persons are then transferred to the infectious class by rate α, where $1/\alpha$ is the average intrinsic incubation period. These infectious individuals are removed to the recovered (immune) class after an average recovery period $1/\eta$, where η is the recovery rate. Neither loss of immunity (we are restricted to only one serotype infection) nor induced mortality due to the disease are considered, and a constant mortality rate μ in humans is assumed. With regard to the vector, the susceptible mosquitoes are infected at a total rate β_m, which is the product between the human population size N and the *per capita* rate β'_m. It should be noted that the constant population of humans allows both coefficients β_m and β'_m to change according to $\beta_m = N\beta'_m$ in every time t, making them equivalent. These exposed mosquitoes are transferred to the

infectious class at a rate γ, where $1/\gamma$ is the average extrinsic incubation period, and remain infective until death. The total size of the mosquito population, which varies, is designated by $M = M_1 + M_2 + M_3$.

Based on the above considerations, the dynamics of dengue transmission can be described by

$$
\left.
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t} A &= kf\phi\,(M_1 + M_2 + M_3)\left(1 - \frac{A}{C}\right) - (\pi_q + \mu_q)A \\
\frac{\mathrm{d}}{\mathrm{d}t} M_1 &= \pi_q A - (\beta_m i + \mu_f)M_1 \\
\frac{\mathrm{d}}{\mathrm{d}t} M_2 &= \beta_m i M_1 - (\gamma + \mu_f)M_2 \\
\frac{\mathrm{d}}{\mathrm{d}t} M_3 &= \gamma M_2 - \mu_f M_3,
\end{aligned}
\right\}
\tag{1}
$$

in the female mosquito population, and by

$$
\left.
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t} s &= \mu - (\beta'_h M_3 + \mu)s \\
\frac{\mathrm{d}}{\mathrm{d}t} e &= \beta'_h M_3 s - (\alpha + \mu)e \\
\frac{\mathrm{d}}{\mathrm{d}t} i &= \alpha e - (\eta + \mu)i,
\end{aligned}
\right\}
\tag{2}
$$

in the human population; where $r = 1 - s - e - i$ are the (decoupled from the system) recovered individuals. The entomological parameters (see [6] for details) are the intrinsic oviposition rate ϕ, the *per capita* mortality rate of adult females and aquatic forms μ_f and μ_q, while π_q is the *per capita* rate at which mosquitoes emerge from the aquatic phase. The remaining parameters are the carrying capacity C, the fraction of eggs hatching to larvae k, with $0 < k < 1$, and the fraction of female mosquitoes hatched from all eggs f, with $0 < f < 1$.

The system of equations (1) and (2) describes the transmission of dengue virus involving two coupled populations. This system determines the behaviour (or trajectory along time) of each compartment until reaching the steady state, which depends on the capacity of dengue transmission. The goal of the analysis of the steady state is the assessment of the control strategies to eradicate dengue transmission.

There are three equilibrium points. First, steady state is assigned by S_0 with coordinates (values of the compartments at equilibrium) $\bar{A} = \bar{M}_1 = \bar{M}_2 = \bar{M}_3 = 0$, $\bar{s} = 1$ and $\bar{e} = \bar{I} = 0$. This equilibrium point is characterized by the absence of mosquitoes, and all humans are in the susceptible compartment. The second is the trivial (with regard to absence of disease) equilibrium point, which characterizes mosquito and human populations occupying the same region without propagation of dengue disease, described by S_m with

coordinates $\bar{A}$, $\bar{M}_1 = \bar{M}$, $\bar{M}_2 = \bar{M}_3 = 0$, $\bar{s} = 1$ and $\bar{e} = \bar{i} = 0$, where the coordinates of the susceptible mosquito population at equilibrium $\bar{A}$ and $\bar{M}$ are

$$
\left.
\begin{aligned}
\bar{A} &= C\left(1 - \frac{1}{Q_0}\right) \\
\bar{M} &= \frac{\pi_q}{\mu_f} C\left(1 - \frac{1}{Q_0}\right),
\end{aligned}
\right\}
\tag{3}
$$

where the basic offspring number Q_0 is given by

$$
Q_0 = \frac{\pi_q k f \phi}{(\pi_q + \mu_q)\mu_f}.
\tag{4}
$$

These two equilibrium points were analysed in [6].

Finally, the steady state corresponding to dengue settled at an endemic level S_d has positive coordinates $\bar{A}$, $\bar{M}_1$, $\bar{M}_2$, $\bar{M}_3$, $\bar{s}$, $\bar{e}$ and $\bar{i}$ given by

$$
\left.
\begin{aligned}
\bar{A} &= C\left(1 - \frac{1}{Q_0}\right) \\
\bar{M}_1 &= \frac{(\gamma + \mu_f)\mu_f(\alpha + \mu)(\eta + \mu)}{\beta'_h \beta_m \alpha \gamma \left[1 - \dfrac{(\alpha + \mu)(\eta + \mu)}{\alpha\mu}\bar{i}\right]} \\
\bar{M}_2 &= \frac{\mu_f(\alpha + \mu)(\eta + \mu)\bar{i}}{\beta'_h \alpha \gamma \left[1 - \dfrac{(\alpha + \mu)(\eta + \mu)}{\alpha\mu}\bar{i}\right]} \\
\bar{M}_3 &= \frac{(\alpha + \mu)(\eta + \mu)\bar{i}}{\beta'_h \alpha \left[1 - \dfrac{(\alpha + \mu)(\eta + \mu)}{\alpha\mu}\bar{i}\right]}
\end{aligned}
\right\}
$$

(with $\bar{M}_1$ being valid when $\bar{i} \neq 0$; otherwise, $\bar{M}_1 = \bar{M}$) for the mosquito and human populations:

$$
\left.
\begin{aligned}
\bar{s} &= 1 - \frac{(\alpha + \mu)(\eta + \mu)}{\alpha\mu}\bar{i} \\
\bar{e} &= \frac{\eta + \mu}{\alpha}\bar{i},
\end{aligned}
\right\}
$$

where $\bar{i}$ is given by

$$
\bar{i} = \frac{R_0 - 1}{\dfrac{\beta_m}{\mu_f} + \dfrac{(\alpha + \mu)(\eta + \mu)}{\alpha\mu}R_0},
$$

with Q_0 being given by equation (4), and the basic reproduction number R_0 is given by

$$
R_0 = \frac{\gamma\left[\dfrac{\pi_q}{\mu_f}C\left(1 - \dfrac{1}{Q_0}\right)\right]\beta'_h \alpha \beta_m}{(\gamma + \mu_f)\mu_f(\alpha + \mu)(\eta + \mu)},
\tag{5}
$$

where the term within square brackets in the numerator is the total number of mosquitoes in the steady state, $\bar{M} = \bar{M}_1 + \bar{M}_2 + \bar{M}_3$. The decoupled fraction of the recovered individuals is $\bar{r} = 0$ for S_0 and S_m, and $\bar{r} = 1 - \bar{s} - \bar{e} - \bar{i}$, for S_d.
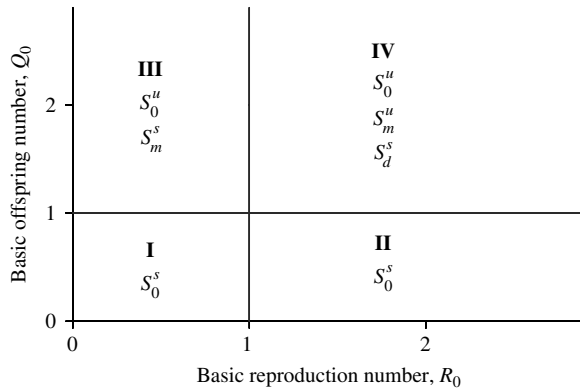
Fig. 1. The basins of attraction considering the positive parameters Q_0 and R_0. The superscripts s and u stand for, respectively, stable and unstable.

The Appendix gives the steady-state analysis corresponding to the above three equilibrium points: the steady state regarding the mosquito-free community S_0 is stable if $Q_0 \leqslant 1$; the equilibrium where the community is disease-free S_m, is stable if $Q_0 > 1$ and $R_0 \leqslant 1$; and dengue settled at an endemic level S_d is stable if $Q_0 > 1$ and $R_0 > 1$. Hence, depending on the values assigned to Q_0 and R_0, one of three equilibrium points acts as an attractor. Figure 1 summarizes the basins of attraction. The changes of the attraction equilibrium point (bifurcations) in the positive parameter space (Q_0, R_0) occur for lines $Q_0 = 1$ and $R_0 = 1$. In region I ($Q_0 < 1$ and $R_0 < 1$) and in region II ($Q_0 < 1$ and $R_0 > 1$) the unique equilibrium point is S_0, which is stable. This is the reason no bifurcation occurs when line $R_0 = 1$ is crossed when passing from region I to region II. In region III ($Q_0 > 1$ and $R_0 < 1$) there exist two equilibrium points S_0 and S_m, which are, respectively, unstable and stable. When passing from region I to region III, crossing line $Q_0 = 1$, one bifurcation occurs: i.e. as S_m becomes stable S_0 becomes unstable. In region IV ($Q_0 > 1$ and $R_0 > 1$) there exist three equilibrium points S_0, S_m and S_d, which are unstable, unstable and stable, respectively. In going from region II to region IV, crossing line $Q_0 = 1$, S_d becomes stable and S_0 becomes unstable; however, the passage from region III to region IV, crossing line $R_0 = 1$, results in another bifurcation: S_d becomes stable and S_m becomes unstable. In the accumulation point ($Q_0 = 1$ and $R_0 = 1$) any type of bifurcation can occur. Note that region II is the most dangerous, due to the fact that we can have the bifurcation from being mosquito-free to the prevalence of dengue disease in this region, if the basic offspring number can be increased, i.e. > 1. This is perfectly possible if the temperature increases in this region and alters the entomological parameters in order to achieve $Q_0 > 1$.

We interpret the basic reproduction number R_0, and change β_m by $N\beta'_m$ in equation (5). In terms of the *per capita* dengue transmission coefficients β'_h and β'_m, R_0 can be rewritten as

$$R_0 = \frac{\gamma}{\gamma + \mu_f} \times \frac{\bar{M}\beta'_h}{\mu_f} \times \frac{\alpha}{\alpha + \mu} \times \frac{N\beta'_m}{\eta + \mu}. \quad (6)$$

Assume that one infectious mosquito is introduced into a completely susceptible population of mosquitoes and humans, which have potentially infective sizes $\bar{M}$ and N, respectively. This uniquely infectious mosquito bites an average $\bar{M}\beta'_h/\mu_f$ number of susceptible humans (β'_h/μ_f is the *per capita* number of bites) during the infectious period. Afterwards, these exposed humans must survive the intrinsic incubation period, with probability $\alpha/(\alpha + \mu)$, and, then, are bitten on average by $N\beta'_w/(\eta + \mu)$, the number of susceptible mosquitoes during the infectious period. Finally, the probability that these exposed mosquitoes survive the extrinsic incubation period and become infectious mosquitoes is given by $\gamma/(\gamma + \mu_f)$. Therefore, R_0 is the average number of secondary infectious mosquitoes produced by one infectious mosquito introduced into a completely homogeneous and susceptible population of mosquitoes and humans. For this reason, dengue epidemics fade out if the average number of secondary infections is lower than unity. This number also measures both the severity of the infection in a community and the efforts necessary to eradicate the epidemic. The introduction of one infectious human follows a similar pattern.

There are two ways to define the *per capita* incidence [12]. One is to assume that the rate of new infections occurs according to the contact between the numbers of susceptible and infectious individuals. In this case we use the *per capita* transmission coefficients β'_h and β'_m, and this kind of modelling is known as the 'pseudo' mass action law. On the other hand, the 'true' mass action law considers the fractions of susceptible and infectious individuals, using the total transmission coefficients β_h and β_m. When the populations are not allowed to vary (constant) in time, both kind of mass action laws are interchangeable. However, the figure is completely different when one or more populations are allowed to vary. In our case, the mosquito population is allowed to vary, while the human population is maintained constant. Hence, the infection in mosquitoes does not matter in the formulae for the basic reproduction number.

In equation (6) the expression for R_0 arises due to the assumption of the 'pseudo' mass action law for infection in humans (the *per capita* incidence is proportional to the number of infectious mosquitoes, $\beta'_h M_3$), and it can be written as

$$R_0 = \frac{\beta'_h \beta'_m}{\beta^{th}},$$

where β^{th} is the threshold transmission coefficient involving the product of the *per capita* dengue transmission coefficients β'_h and β'_m, given by

$$\beta^{th} = \frac{(\gamma + \mu_f)\mu_f^2(\alpha + \mu)(\eta + \mu)}{\gamma \alpha \pi_l \left(1 - \dfrac{1}{Q_0}\right) CN}. \tag{7}$$

When $Q_0 < 1$, we have a human population living free of mosquitoes, and this situation is strongly robust. Note that the absence of mosquito population resulted in $\beta^{th} < 0$, which mathematically means $R_0 < 0$, but biologically is meaningless. Hence, the dengue risk is real and can be measured if Q_0 increases and becomes > 1, in which case R_0 becomes positive. As Q_0 increases, β^{th} decreases, and eventually surpasses the threshold value $\beta'_h \beta'_m$, yielding $R_0 > 1$ at which point dengue epidemics can be triggered.

However, the 'true' mass action law yields the basic reproduction number expressed in terms of the total transmission coefficients, because we must use the total transmission coefficient β_h in equation (2), i.e. we must substitute $\beta'_h M_3$ by $\beta_h M_3/M$, since

$$\beta'_h M_3 = M\beta'_h \frac{M_3}{M} = \beta_h \frac{M_3}{M_1 + M_2 + M_3}.$$

Due to the appearance of the fraction of infectious mosquitoes, we implicitly assume that $M > 0$, or, equivalently, $Q_0 > 1$. Hence, by changing $\bar{M}\beta'_h$ to β_h and $N\beta'_m$ to β_m in equation (6), the basic reproduction number R_0 can be written as

$$R_0 = \frac{\beta_h \beta_m}{\bar{\beta}^{th}},$$

where $\bar{\beta}^{th}$ is the threshold transmission coefficient involving the product of the total dengue transmission coefficients β_h and β_m, given by

$$\bar{\beta}^{th} = \frac{(\gamma + \mu_f)\mu_f(\alpha + \mu)(\eta + \mu)}{\gamma \alpha}. \tag{8}$$

Note that $\bar{\beta}^{th}$ does not depend on the mosquito and human populations $\bar{M}$ and N as does $\bar{\beta}^{th}$. Therefore $\bar{\beta}^{th}$ never assumes a negative value.

When there is an absence of good estimates for the dengue transmission coefficients β'_h and β'_m (or β_h and
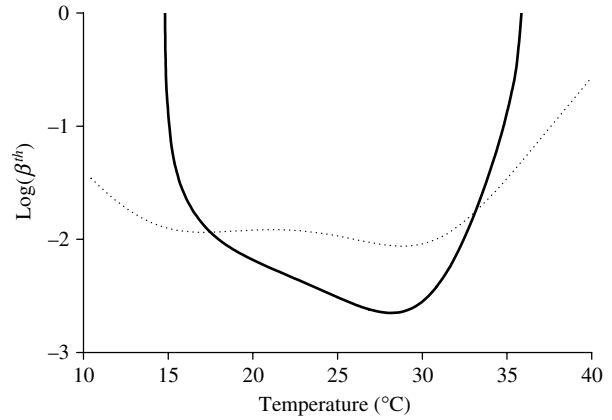

Fig. 2. The threshold transmission coefficients β^{th} and $\bar{\beta}^{th}$ as a function of temperature are shown. The thick curve corresponds to β^{th}, while the dotted curve corresponds to $\bar{\beta}^{th}$. The risk of dengue epidemics is high (and the epidemics settle at a high level) for lower values of the threshold transmission coefficients. We set $\alpha = 0.2$, $\gamma = 0.125$, $\eta = 0.25$ and $\mu = 0.000043$ (all in days^{-1}).

β_m), then β^{th} or $\bar{\beta}^{th}$ can be used instead to assess the potential risk of dengue epidemics. Note that the chance of a dengue outbreak increases inversely proportional to the threshold transmission coefficients. The threshold transmission coefficient β^{th} and the basic offspring number Q_0, which appear in its definition, depend on all entomological parameters, while the threshold transmission coefficient $\bar{\beta}^{th}$ depends only on the mortality rate of female mosquitoes μ_f.

In next section we assess the effects of temperature on dengue transmission.

ASSESSING THE EFFECTS OF TEMPERATURE ON DENGUE RISK

The ecological and epidemiological results obtained from the mathematical modelling reported in [6] are used to assess the risk of dengue depending on temperature.

As stated in the previous section, the intrinsic and extrinsic incubation periods, $1/\alpha$ and $1/\gamma$, are assumed to be constant with temperature. Therefore, the risk of a dengue outbreak is assessed by taking into account only the variations in the entomological parameters with temperature. Figure 2 gives the threshold transmission coefficients β^{th} and $\bar{\beta}^{th}$ as a function of temperature. The curve corresponding to the threshold transmission coefficient β^{th} was obtained using $NC = 1$; however, by increasing this value tenfold, the curve moves down one unity (using log-scale), decreasing the threshold transmission coefficient $\bar{\beta}^{th}$, and,

consequently, increasing the possibility of a dengue outbreak. In the case of $\bar{\beta}^{th}$, which depends on the temperature only through the mortality rate of female mosquitoes and does not depend on N and C explicitly, we observe a very low sensitivity for temperature. Because in this model ('true' mass action law) it is implicitly assumed that the mosquito population exists, we must take into account the regions where mosquitoes are prevalent, $Q_0 > 1$, as well as $\beta'_h \beta'_m > \bar{\beta}^{th}$.

When there are no precise estimates of the transmission coefficients, the corresponding threshold values can be seen as an alternative for assessing dengue outbreaks or the severity of dengue epidemics. With regard to the curve corresponding to β^{th} in Figure 2, if we assume that the transmission coefficients in a certain geographic region are β_h^S and β_m^S, a horizontal line can be drawn with value $\log(\beta_h^S \beta_m^S)$ in the $\log(\beta^{th}) \times T$ coordinates, which intercepts the curve β^{th} at two temperatures, i.e. T_1 and T_2. If this selected region is situated between T_1 and T_2, dengue epidemics can be triggered, and the temperature at which the level of the epidemic is most severe is $\sim 28\,^{\circ}\text{C}$, where β^{th} assumes the lowest value. This finding shows that the increase in temperature, e.g. due to global warming, does not necessarily increase the incidence of dengue disease.

The basic reproduction ratio R_0 is a quotient between the product of transmission coefficients and the corresponding threshold value. For this reason, the difference between them, defined by $\beta^{th} - \beta_h \beta_m$, to some extent measures the welfare of a community (or region) regarding dengue disease. If this difference is positive and very high, the community is practically free of dengue outbreaks (i.e. $\beta_h \beta_m < \beta^{th}$); otherwise, if this difference is negative and very high, dengue outbreaks will be very severe. However, the levels of recurrent dengue epidemics are not only dependent on the transmission coefficients, but also on the fractions of the susceptible populations of mosquitoes and humans: if both fractions are almost 1 (exactly 1 when dengue disease is introduced into completely susceptible populations), the next dengue outbreak will be more severe [13].

The basic reproduction ratio R_0 depends on the transmission coefficients, which are assumed to be temperature independent. However, both parameters are dependent on the number of bites that a female mosquito gives to humans in order to mature the fertilized eggs. Our companion paper [6], shows that the oviposition is absent at low temperature, and this number increases with temperature, practically in line with temperature from 15 °C, and decreases for high temperature. If the number of bites is approximated with the number of eggs laid by female mosquitoes, the capacity of the vector to transmit the disease is limited to the extreme temperatures. Note that at around 15–16 °C, the first day at which female mosquitoes laid eggs, is higher than for 15 days, and discounting the time necessary to mature fertilized eggs, we have day 12 as the age of the mosquitoes first biting. This indicates that the biting behaviour of female mosquitoes is delayed, and when compared with the extrinsic incubation period of around 10 days, the possibility of dengue virus inoculation in humans is not negligible, because female mosquitoes survive for around 30 days [6]. Even allowing the transmission coefficients to vary with temperature, Figure 2 is a good indicator of the risk of dengue according to temperature.

The basins of attraction in Figure 1 shed some lights on the invasion and colonization by *A. aegypti* and the outbreak of dengue epidemics. Let us apply these findings to São Paulo State, Brazil. São Paulo State can be approximated roughly by a parallelogram of dimension 690 km in the northwest-southwest direction and 440 km in the northeast-southwest direction. The Atlantic Ocean is at the southern frontier, and Mato Grosso State at the northern border. At the eastern side, there are two states: Rio de Janeiro occupying a small part in the extreme of the southern frontier, and Minas Gerais State occupying almost the entire eastern frontier. At the western frontier is Paraná State.

São Paulo State is situated in a subtropical region, with a hot and rainy summer season, where the mosquito *A. aegypti* was re-introduced in 1985 from the northern border, and advanced continuously in a southerly direction [14]. The *A. aegypti* invasion initiated from Mato Grosso State and followed a southerly direction, to the Atlantic Ocean, where the mosquitoes arrived in 1994 [15]. The northern region of São Paulo State is characterized by an annual mean temperature of >18 °C and an annual mean rainfall of <1400 mm, while the middle region of São Paulo State has an annual mean temperature and rainfall of, respectively, 17 °C and 1500 mm [14].

After colonization by *A. aegypti*, dengue epidemics were first observed in 1987, but systematical and annual occurrences of epidemics started in 1990. According to the Epidemiological Vigilance Centre [16, 17], the number of cases of dengue from 1995 until 2007 were, respectively, 6048, 7104, 2040, 10 630,

15 082, 3532, 51 668, 39 179, 20 390, 3049, 5433, 50 022 and 90 252.

However, there is a belt of tropical forest (Mata Atlântica), 80 km from the Atlantic Ocean, where the annual mean temperature is low. In this region São Paulo City and its neighbouring cities are situated, comprising ∼20 million inhabitants. Due to low temperature in winter seasons, this region is relatively safe from dengue colonization, in spite of the recent sporadic dengue epidemics that occurred in the outskirts of São Paulo City during the summer seasons.

Excluding a small tropical forest belt, São Paulo State can be matched with region IV in the basins of attraction shown in Figure 1. This region is characterized by $Q_0 > 1$ and $R_0 > 1$, for this reason *A. aegypti* was successfully introduced in 1985 (bifurcation from S_0 to S_m, both equilibria unstable), and in 1990, dengue disease settled at an endemic level (bifurcation from S_m to S_d, the latter equilibrium stable). However, the region comprising São Paulo City and its surrounding cities can be matched with region II (Fig. 1), because the invasion and colonization by mosquitoes had already occurred in all frontiers of this region. Additionally, this region is heavily populated and there is an abundance of a variety of breeding sites capable of receiving eggs and developing immature forms. As this region is characterized by $Q_0 < 1$ and $R_0 > 1$, an increase in temperature may increase the basic offspring number to >1 and drive to region IV. A bifurcation from absence of mosquitoes to the onset of dengue epidemics can then be observed (bifurcation from S_0 to S_m and then, S_m to S_d; or a dangerous bifurcation from S_0 to S_d).

DISCUSSION AND CONCLUSION

We developed a mathematical model to in order to assess the effects of temperature on the risk of dengue outbreak.

To assess the effects of temperature on dengue epidemics, we yielded the basic reproduction number R_0. In the absence of real estimates for dengue transmission coefficients, we took, as the risk factor of dengue epidemics, the threshold transmission coefficient β^{th} or $\bar{\beta}^{th}$, in the sense that the lower this threshold number, the higher was the possibility of dengue outbreak. In particular, the curve for β^{th} (Fig. 2) is roughly inverse with respect to the curve obtained for Q_0 (see [6]), and one reason for this behaviour is that we did not allow the disease-related

parameters (intrinsic and extrinsic incubation periods and recovery rate) to vary with temperature. Hence, the basic offspring number Q_0 can be taken as the measure of the potential risk of dengue outbreak and also with regard to the severity of dengue epidemics. It should be noted that the temperature at which the lowest value for β^{th} occurs is 28·0 °C, which is 1·2 °C lower than the temperature at which the maximum value for Q_0 occurs (see [6]).

In our companion paper [6] we conjectured that female mosquitoes survive for the same periods of time during the interval $15 < T < 30$ °C, because they bite more and require greater physiological efforts to maturate fertilized eggs. Moreover, dengue virus could potentially increase the lifespan of infected mosquitoes without decreasing their biting activities. The basic reproduction number R_0 depends linearly on the lifespan of female mosquitoes, $1/\mu_f$, according to equation (5). Then, the spread of dengue disease increases due to the virus activities inside the infected mosquitoes and also due to the fact that the biting activities increase with temperature.

Finally, in the present study we dealt with annual mean entomological values. In a further paper, we will allow the entomological parameters to vary with time, and, consequently, to vary with temperature, and will perform the sensitivity analysis of the basic offspring number and basic reproduction number for the entomological parameters. The varying size of the mosquito population will be matched to the seasonally varying number of dengue cases in order to estimate the transmission coefficients.

APPENDIX A

Steady states

We present the stability analysis of the equilibrium points S_0, S_m and S_d. The local stability analysis (some basic ideas about stability analysis is given in [6]) is assessed to determine the roots of the characteristic equation $\Lambda(\lambda) \equiv \det(J^* - \lambda I)$, where J^* is the Jacobian matrix corresponding to the system of equations (1) and (2) evaluated at one of the equilibrium points S_0, S_m and S_d, and I is a 7×7 identity matrix.

The roots of the characteristic equation corresponding to the mosquito-free community S_0 are

$$\lambda_1 = -(\eta + \mu), \lambda_2 = -(\alpha + \mu), \lambda_3 = -\mu, \lambda_4 = -\mu_f,$$
$$\lambda_5 = -(\gamma + \mu_f),$$

and the remaining two solutions are those given in [6]. Hence, equilibrium point S_0 is locally asymptotically stable if $Q_0 < 1$.

To show the global stability of the equilibrium point S_0, note that the region of biological interest Ω, defined as

$$\Omega = \{(A, M_1, M_2, M_3, s, e, i)$$
$$\in R_+^7 \,|\, 0 \leqslant A \leqslant C, s + e + i \leqslant 1\}$$

is positively invariant for the system of equations (1) and (2). The global stability of the equilibrium point S_0 can be proved for $Q_0 \leqslant 1$ using the function $V: R_+^7 \to R$ given by

$$V = \frac{\pi_q}{\pi_q + \mu_q} A + M_1 + M_2 + M_3,$$

whose orbital derivative is

$$\dot{V} = -\mu_f \left[\frac{Q_0 A}{C} + (1 - Q_0) \right] (M_1 + M_2 + M_3).$$

Note that $\dot{V} < 0$ for $Q_0 < 1$, and for $Q_0 = 1$ we have $\dot{V} = 0$ if $M_1 + M_2 + M_3 = M = 0$ or $A = 0$. From inspection of equation (1) it can be seen that the maximal invariant set contained in $\dot{V} = 0$ is the trivial equilibrium point S_0. Then, from La Salle–Lyapunov Theorem [18], the equilibrium point S_0 is globally asymptotically stable for $Q_0 \leqslant 1$. Hence, the human population living without mosquitoes is a robust situation, and humans are protected against dengue epidemics.

One of the roots of the characteristic equation corresponding to the disease-free community S_m is $\lambda_1 = -\mu$. Two other roots are solutions given in [6], which have negative real part if $Q_0 > 1$. The remaining four roots are solutions of the equation

$$\Lambda_c(\lambda) = \lambda^4 + c_3 \lambda^3 + c_2 \lambda^2 + c_1 \lambda + c_0,$$

where the coefficients are

$$\left.\begin{aligned}
c_3 &= \alpha + \eta + \gamma + 2\mu + 2\mu_f \\
c_2 &= (\alpha + \mu)(\eta + \mu) + (\alpha + \eta + 2\mu)(\gamma + 2\mu_f) + (\gamma + \mu_f)\mu_f \\
c_1 &= (\alpha + \mu)(\eta + \mu)(\gamma + 2\mu_f) + (\alpha + \eta + 2\mu)(\gamma + \mu_f)\mu_f \\
c_0 &= (\alpha + \mu)(\eta + \mu)(\gamma + \mu_f)\mu_f(1 - R_0),
\end{aligned}\right\}$$

with the basic reproduction number R_0 being given by equation (5). When $R_0 < 1$, the polynomial $\Lambda_c(\lambda)$ as all solutions with negative part real, because the Routh–Hurwitz criteria [19] $c_3 > 0$, $c_1 > 0$, $c_0 > 0$ and $c_3 c_2 c_1 > c_1^2 + c_3^2 c_0$ are satisfied. The last inequality can be rewritten as

$$\frac{c_1(c_3 c_2 - c_1) - c_3^2(\alpha + \mu)(\eta + \mu)(\gamma + \mu_f)\mu_f}{c_3^2} > -\alpha\gamma\bar{M}\beta_h'\beta_m,$$

and we have shown that $c_1 (c_3 c_2 - c_1) - c_3^2 (\alpha + \mu)(\eta + \mu) (\gamma + \mu_f)\mu_f > 0$. Hence, equilibrium point S_m is locally asymptotically stable if $Q_0 > 1$ and $R_0 < 1$.

The characteristic equation corresponding to dengue disease settled at an endemic level S_d is given by $\Lambda(\lambda) = -\Lambda_b(\lambda)\Lambda_5(\lambda)$, where $\Lambda_b(\lambda)$ is that given in [6] ($Q_0 > 1$ to satisfy Routh–Hurwitz criteria), and

$$\Lambda_5(\lambda) = (\beta_m \bar{i} + \mu_f + \lambda)(\bar{M}_3 \beta_h' + \mu + \lambda)(\alpha + \mu + \lambda)$$
$$\times (\eta + \mu + \lambda)(\gamma + \mu_f + \lambda) - \alpha\gamma\bar{M}_1\beta_h'\beta_m\bar{s}\,(\mu + \lambda),$$

where the independent term is given by

$$\Lambda_5(0) = (\beta_m\bar{i} + \mu_f)(\bar{M}_3\beta_h' + \mu)(\alpha + \mu)(\eta + \mu)(\gamma + \mu_f)$$
$$- \alpha\gamma\bar{M}_1\beta_h'\beta_m\bar{s}\mu$$
$$= \left(\mu\beta_m + \beta_m\beta_h'\bar{M}_3 + \mu_f\beta_h'\frac{\bar{M}_3}{\bar{i}} \right)$$
$$\times \frac{R_0 - 1}{\dfrac{\beta_m}{\mu_f} + \dfrac{(\alpha + \mu)(\eta + \mu)}{\alpha\mu} R_0},$$

with $\bar{i} > 0$ and $\bar{M}_3 > 0$. This term is positive if $R_0 > 1$, and according to conjecture in [20], $\Lambda_5(\lambda)$ has all solutions with negative part real. Remembering that $\Lambda_b(\lambda)$ has solutions with negative real part if $Q_0 > 1$, then the non-trivial equilibrium point S_d is locally asymptotically stable when $R_0 > 1$ and $Q_0 > 1$.

ACKNOWLEDGEMENTS

DECLARATION OF INTEREST

None.

REFERENCES

1. **Mandell GL, Bennett JE, Dolin R.** *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* Philadelphia: Elsevier Inc., 2005, pp. 3662.

2. **Tripet F, Aboagye-Antwi F, Hurd H.** Ecological immunology of mosquito-malaria interactions. *Trends in Parasitology* 2008; **24**: 219–227.

3. **Veronesi R.** *Doenças Infecciosas e Parasitárias.* Rio de Janeiro: Ed. Guanabara Koogan, 1991, pp. 1082.

4. **Nelson MJ.** *Aedes aegypti: Biologia y Ecologia*, Washington, DC: Organización Panamericana de la Salud, 1986, pp. 50.

5. **Rueda LM, et al.** Temperature development and survival rates of *Culex quinquefasciatus* and *Aedes aegypti* (Diptera: Culicidae). *Journal of Medical Entomology* 1990; **27**: 892–898.

6. **Yang HM, et al.** Assessing the effects of temperature on the population of *Aedes aegypti*, the vector of dengue. *Epidemiology and Infection* 2009. doi:10.1017/S0950268809002040.

7. **Esteva L, Vargas C.** Coexistence of different serotypes of dengue virus. *Journal of Mathematical Biology* 2003; **46**: 31–47.

8. **Esteva L, Yang HM.** Mathematical model to assess the control of *Aedes aegypti* mosquitoes by the sterile insect technique. *Mathematical Biosciences* 2005; **198**: 132–147.

9. **Feng Z, Velasco-Hernandez V.** Competitive exclusion in a vector-host model for the dengue fever. *Journal of Mathematical Biology* 1996; **35**: 523–544.

10. **Newton EA, Reiter A.** A model of the transmission of dengue fever with an evaluation of the impact of ultra-low-volume (ULV) insecticide applications on dengue epidemics. *American Journal of Tropical Medicine and Hygiene* 1992; **47**: 709–720.

11. **Lindsay SW, Birley MH.** Review: climate change and malaria transmission. *Annals of Tropical Medicine and Parasitology* 1996; **90**: 573–588.

12. **Li MY et al.** Global dynamics of a SEIR model with varying total population size. *Mathematical Biosciences* 1999; **160**: 191–213.

13. **Yang HM.** Modelling vaccination strategy against directly transmitted diseases using a series of pulses. *Journal of Biological Systems* 1998; **6**: 187–212.

14. **Glasser CM.** Study of the infestation of the State of São Paulo by *Aedes aegypti* and *Aedes albopictus* [in Portuguese]. Dissertation, FSP, Universidade de São Paulo, São Paulo, 1997.

15. **Maidana NA, Yang HM.** Describing the geographic propagation of dengue disease by travelling waves. *Mathematical Biosciences* 2008; **215**: 64–77.

16. **Epidemiological Vigilance Centre** (http://www.cve.saude.sp.gov.br/htm/zoo/den_dir06.htm). Accessed 27 September 2007.

17. **Epidemiological Vigilance Centre** (http://www.cve.saude.sp.gov.br/htm/zoo/den_2se07.htm). Accessed 10 April 2008.

18. **Hale JK.** *Ordinary Differential Equations.* New York: John Wiley and Sons, 1969, pp. 332.

19. **Edelstein-Keshet L.** *Mathematical Models in Biology* (Birkhäuser Mathematics Series). New York: McGraw-Hill Inc., 1988, pp. 586.

20. **Leite MBF, Bassanezi RC, Yang HM.** The basic reproduction ratio for a model of directly transmitted infections considering the virus charge and the immunological response. *IMA Journal of Mathematics Applied in Medicine and Biology* 2000; **17**: 15–31.