Modelling the dynamics of dengue real epidemics

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In this work, we use a mathematical model for dengue transmission with the aim of analysing and comparing two dengue epidemics that occurred in Salvador, Brazil, in 1995–1996 and 2002. Using real data, we obtain the force of infection, $L$, and the basic reproductive number, $R_0$, for both epidemics. We also obtain the time evolution of the effective reproduction number, $R(t)$, which results in a very suitable measure to compare the patterns of both epidemics. Based on the analysis of the behaviour of $R_0$ and $R(t)$ in relation to the adult mosquito control parameter of the model, we show that the control applied only to the adult stage of the mosquito population is not sufficient to stop dengue transmission, emphasizing the importance of applying the control to the aquatic phase of the mosquito.

Keywords: dengue modelling; non-linear differential equations; epidemic time series; effective reproductive number

1. Introduction

Infectious diseases are still a relevant problem for humans. Nowadays, owing to the intense flow of people around the world and within cities, understanding the complex dynamics of infectious diseases is a multi-disciplinary issue. With regard to dengue, a vector-transmitted disease, there is no vaccine against any of the four serotypes of the virus, although many efforts have been made in that direction (Whitehead et al. 2007). As a result, controlling dengue transmission is based on the control of the aquatic and adult stages of the mosquito. So far, modelling the dynamics of dengue has been very helpful for testing both the adopted vector control strategies (Esteva & Yang 2005; Ferreira et al. 2008; Yang & Ferreira 2008) and the mode of action of future vaccines.

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In South and North America, there are records of the occurrence of all serotypes of the dengue virus, while in Brazil, until now, only three serotypes (DENV1, DENV2 and DENV3) have been reported (Teixeira et al. 2009). However, Brazil is responsible for 80 per cent of dengue cases in South America and 60 per cent of notified cases around the world. The circulation of the three serotypes represents an important risk factor for the occurrence of dengue haemorrhagic fever (DHF). Despite all the efforts applied by the Brazilian Dengue Control Program to stop dengue transmission, it is still a relevant problem in the first decade of this century (Coelho et al. 2008). Many factors have been associated with the failure of dengue control: the vector’s adaptive capacity, the insufficiency of the control technologies, the transmission force of the virus, the existence of four serotypes, etc.

In this study, two outbreaks of dengue disease that occurred in Salvador and Bahia, Brazil, in 1995–1996 and 2002 were analysed. In the first outbreak, only DENV2 was circulating, and no systematic vector population control was applied by the local health authorities. On the other hand, the second outbreak was caused by the DENV3 serotype, and a more systematic mosquito control was in course owing to the establishment of the Brazilian Dengue Control Program. In both epidemics, the population was naive for the circulating serotype. In a previous study some of us investigated the first epidemic (1995) using a cellular automata model (Santos et al. 2009) forced by seasonal factors owing to the strong correlation between the weekly number of cases and the rainfall in the city. In that study, the epidemic time series were reproduced quantitatively as well as their qualitative time–spatial patterns, and preliminary investigations were carried out on vector control throughout the model.

Now, a mathematical model (Yang et al. 2009a) can be used to analyse both dengue outbreaks in Salvador (1995–1996 and 2002) without and with vector control, respectively. Our focus is on the calculation of the basic reproductive number, $R_0$, of the actual epidemics as well as on the analysis of its time evolution, $R(t)$, since it changes during the epidemics. The basic reproductive number, $R_0$, is the most common measure of the strength of an epidemic. It is defined as the number of secondary infections generated by one primary case in a wholly susceptible population. An early estimate of $R_0$ for the outbreak of a particular disease can guide the control measures.

Our aim is to analyse comparatively the dynamics of both dengue outbreaks in order to investigate the effect of vector control and the susceptible population pool on the reduction in the intensity and duration of the epidemics.

This work is organized as follows. In §2, we formulate the model. In §3, we obtain the disease-free equilibrium, and we calculate the expression for $R_0$ and its values for the 1995–1996 and 2002 epidemics in Salvador. In §4, we calculate and discuss the time dependence of $R$ as well as its behaviour for the actual epidemics in Salvador in 1995–1996 and 2002. Finally, §5 closes this paper with concluding remarks and perspectives.

### 2. Formulation of the model

The model developed here is based upon the one given in Yang et al. (2009a), where the mosquito population, $M$, is divided into four components: aquatic ($A$), susceptible ($M_s$), exposed ($M_e$) and infectious ($M_i$), the last three being the
classes related to the winged female form of the mosquito. The entomological parameters are the intrinsic oviposition rate, $\delta$; the per capita mortality rate of adult female and aquatic forms, $\mu_a$ and $\mu_m$, respectively; and the per capita rate at which mosquitoes emerge from the aquatic phase and become female adults, $\gamma_m$. The remaining parameters are the carrying capacity, $C$, the fraction of female mosquitoes hatched from eggs, $k$, with $0 < k < 1$, and the control efforts, modelled by additional mortality rates applied to the aquatic and terrestrial phases of the mosquito, respectively $c_a$ and $c_m$.

The human population, $H$, is assumed to be constant with the per capita mortality rate given by $\mu_h$, and is divided into susceptible ($H_s$), exposed ($H_e$), infectious ($H_i$) and recovered ($H_r$) individuals.

Flows from the susceptible to infected classes of both populations depend on the biting rate of the mosquitoes, the transmission probabilities, as well as the number of infectives and susceptibles of each species. The per capita biting rate of mosquitoes, $b$, is the average number of bites per mosquito per day, while the transmission probability is the probability that an infectious bite produces a new case in a susceptible member of the other species. We denote by $\beta_h$ and $\beta_m$ the transmission probabilities from mosquito to human, and human to mosquito, respectively. Defining $b/H$ as the number of bites that a human receives from each mosquito, the infection rates per susceptible human and per susceptible vector are given by $(b\beta_h/H)M_i$ and $(b\beta_m/H)H_i$, respectively.

We assume that the populations of exposed (infected by not infectious) humans and mosquitoes become infectious at a rate $\theta_h$ and $\theta_m$, respectively; the reciprocal quantities $1/\theta_h$ and $1/\theta_m$ being the intrinsic and extrinsic periods of virus replication in humans and mosquitoes, respectively. In the case of the mosquitoes, the extrinsic period depends on the temperature (Focks et al. 1993). In fact, higher temperatures reduce $\theta_m$ by increasing the virus replication rate and intensify the efficiency of the vector in transmitting dengue by increasing the number of blood meals during a gonotrophic cycle (Dibo et al. 2008). The humans recover from the disease at a per capita constant rate $a_h$, where $1/a_h$ is the infectious period, meanwhile the mosquitoes remain infectious during their entire life. Finally, the aquatic and adult mosquito control rates are represented, respectively, by $c_a$ and $c_m$.

Since $H_t = H - H_s - H_i$, this is enough to consider the system in terms of the variables $A, M_s, M_e, M_i, H_s$ and $H_i$. Therefore, the dynamical system is given by

$$\begin{align*}
\frac{dA}{dt} &= k\delta(t) \left(1 - \left(\frac{A}{C}\right)\right) M - (\gamma_m(t) + \mu_a(t) + c_a(t)) A, \\
\frac{dM_s}{dt} &= \gamma_m(t) A - \frac{b\beta_m M_s H_i}{H} - (\mu_m(t) + c_m(t)) M_s, \\
\frac{dM_e}{dt} &= \frac{b\beta_m M_s H_i}{H} - (\theta_m(t) + \mu_m(t) + c_m(t)) M_e, \\
\frac{dM_i}{dt} &= \theta_m(t) M_e - (\mu_m(t) + c_m(t)) M_i, \\
\frac{dH_s}{dt} &= \mu_h (H - H_s) - \frac{b\beta_h H_s M_i}{H}, \\
\frac{dH_e}{dt} &= \frac{b\beta_h H_s M_i}{H} - (\theta_h + \mu_h) H_e \\
\frac{dH_i}{dt} &= \theta_h H_e - (\alpha_h + \mu_h) H_i.
\end{align*}$$

(2.1)

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Table 1. Parameters used in the model, biological description and range of values (Newton & Reiter 1992; Focks et al. 1993; McBridea & Bielefeldt-Ohmannb 2000; Yang et al. 2009a,b).

<table>
<thead>
<tr>
<th>parameter</th>
<th>biological meaning</th>
<th>range of values</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>average oviposition rate</td>
<td>0–11.2 day(^{-1})(^a)</td>
</tr>
<tr>
<td>(\mu_m)</td>
<td>average mosquito mortality rate</td>
<td>0.02–0.09 day(^{-1})(^a)</td>
</tr>
<tr>
<td>(\mu_a)</td>
<td>average aquatic mortality rate</td>
<td>0.01–0.47 day(^{-1})(^b)</td>
</tr>
<tr>
<td>(\gamma_m)</td>
<td>average aquatic transition rate</td>
<td>0–0.19 day(^{-1})(^b)</td>
</tr>
<tr>
<td>(\theta_m)</td>
<td>extrinsic incubation</td>
<td>0.02–0.2 day(^{-1})(^c)</td>
</tr>
<tr>
<td>(\mu_h)</td>
<td>human mortality rate</td>
<td>0.0143–0.0167 year(^{-1})</td>
</tr>
<tr>
<td>(\theta_h)</td>
<td>intrinsic incubation rate</td>
<td>0.083–0.17 day(^{-1})</td>
</tr>
<tr>
<td>(\omega_h)</td>
<td>recovering rate</td>
<td>0.083–0.25 day(^{-1})</td>
</tr>
<tr>
<td>k</td>
<td>fraction of female mosquitoes hatched from all eggs</td>
<td>0–1</td>
</tr>
<tr>
<td>C</td>
<td>mosquito carrying capacity</td>
<td>—</td>
</tr>
<tr>
<td>b</td>
<td>average bite per mosquito per day</td>
<td>0–1</td>
</tr>
<tr>
<td>(\beta_m) and (\beta_h)</td>
<td>effective contact rates</td>
<td>0.75</td>
</tr>
<tr>
<td>(c_a) and (c_m)</td>
<td>control effort rates</td>
<td>0–1</td>
</tr>
</tbody>
</table>

\(^a\)For temperature \(T\) such that \(T \in [10.54, 33.41] ^\circ C.\)
\(^b\)For \(T \in [10, 40.6] ^\circ C.\)
\(^c\)For \(T \in [11, 36] ^\circ C.\)

We remark that the mosquito entomological parameters \(\delta(t), \gamma_m(t), \mu_a(t), \mu_m(t)\) and \(\theta_m(t)\) vary with the daily temperature and, therefore, are functions of the time \(t\). In particular, higher temperatures increase the mosquito’s survival and oviposition rates and accelerate its reaching the adult phase. Likewise, rainfall has a positive influence on mosquito breeding conditions, creating and maintaining natural and artificial oviposition containers (Dibo et al. 2008). Also, the parameters \(c_a(t)\) and \(c_m(t)\) are functions of time, since mosquito control is primarily carried out during the favourable period for a dengue epidemic outbreak. Moreover, the entomological parameter values considered in this study were estimated using the results described in Yang et al. (2009b, tables 4, 5, 8, 10). For temperature values not covered in these tables, we apply a linear interpolation to evaluate the mosquito parameters. In fact, once the parameter values are obtained using the dependent form described at Yang et al. (2009b), we consider them as constant values. Finally, the parameter ranges are summarized in Table 1.

3. Basic reproductive number

(a) Disease-free equilibrium

In order to obtain the disease-free equilibrium point of system (2.1), and an expression for \(R_0\) at the beginning of the epidemic, we assume that the entomological parameters \(\delta(t), \gamma_m(t), \mu_a(t), \mu_m(t)\) and \(\theta_m(t)\) and the control efforts given by \(c_a(t)\) and \(c_m(t)\) are constant. Therefore, the disease-free
equilibrium is $E_0 = (\tilde{A}, \tilde{M}_s, 0, 0, H, 0, 0)$, where $\tilde{A}$ and $\tilde{M}_s$ are the positive solution of the algebraic system

\begin{equation}
0 = k \delta (1 - A/C) M - (\gamma_m + \mu_a + c_a) A \quad \text{and} \quad 0 = \gamma_m A - (\mu_m + c_m) M_s
\end{equation}

(3.1)

given by

\begin{equation}
\tilde{A} = C \left(1 - \frac{1}{R_M}\right) \quad \text{and} \quad \tilde{M}_s = \frac{\gamma_m \tilde{A}}{(\mu_m + c_m)},
\end{equation}

(3.2)

where $R_M$ in the expression above denotes the ‘basic offspring’ of the mosquito population given by

\begin{equation}
R_M = \frac{k \delta \gamma_m}{(\mu_m + c_m)(\gamma_m + \mu_a + c_a)}.
\end{equation}

(3.3)

We note that $R_M > 1$ is a necessary condition to have a positive population of mosquitoes. Moreover, according to expression (3.3), the action of vector control on both the aquatic and terrestrial phases reduces the basic offspring, and as a consequence the mosquito susceptible population.

\((b)\) $R_0$ expression for the model

Using the next generation operator approach (Diekmann & Heesterbeek 2000; Van den Driessche & Watmough 2002), we compute the basic reproductive number, $R_0$, associated with the disease-free equilibrium. The non-negative matrix, $K$, of the infection terms ($M_e, M_i, H_e, H_i$) and the non-singular M-matrix, $T$, of the transition terms are given, respectively, by

\[
K = \begin{pmatrix}
0 & 0 & 0 & \frac{b \beta_m \tilde{M}_s}{H} \\
0 & 0 & 0 & 0 \\
0 & b \beta_h & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
\]

and

\[
T = \begin{pmatrix}
\theta_m + \mu_m + c_m & 0 & 0 & 0 \\
-\theta_m & \mu_m + c_m & 0 & 0 \\
0 & 0 & \theta_h + \mu_h & 0 \\
0 & 0 & -\theta_h & \mu_h + \alpha_h
\end{pmatrix}.
\]

In Diekmann & Heesterbeek (2000) and Van den Driessche & Watmough (2002), it is shown that the basic reproductive number, $R_0$, is equal to the spectral ratio
of the matrix $KT^{-1}$. Recall that the spectral ratio of a matrix is equal to its larger eigenvalue. In this case, it can be seen that

$$\begin{pmatrix}
\frac{1}{(\theta_m + \mu_m + c_m)} & 0 & 0 & 0 \\
\frac{-1}{(\theta_m + \mu_m + c_m)(\mu_m + c_m)} & \frac{1}{(\mu_m + c_m)} & 0 & 0 \\
0 & 0 & \frac{1}{(\theta_h + \mu_h)} & 0 \\
0 & 0 & -\frac{1}{(\theta_h + \mu_h) (\alpha_h + \mu_h)} & \frac{1}{(\alpha_h + \mu_h)}
\end{pmatrix},$$

and therefore

$$\begin{pmatrix}
0 & 0 & -\frac{\theta_h b \beta_m \bar{M}_s}{(\theta_h + \mu_h) (\alpha_h + \mu_h) H} & \frac{b \beta_m \bar{M}_s}{(\alpha_h + \mu_h) H} \\
0 & 0 & 0 & 0 \\
-\frac{\theta_m b \beta_h}{(\theta_m + \mu_m + c_m)(\mu_m + c_m)} & \frac{b \beta_h}{(\mu_m + c_m)} & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}.$$

The eigenvalues of $KT^{-1}$ are zero of multiplicity 2, and

$$\pm \sqrt{\frac{\theta_h \theta_m b^2 \beta_h \beta_m}{(\theta_h + \mu_h)(\theta_m + \mu_m + c_m)(\alpha_h + \mu_h)(\mu_m + c_m) H}} \bar{M}_s.$$  

Therefore,

$$R_0 = \sqrt{\frac{\theta_h \theta_m b^2 \beta_h \beta_m}{(\theta_h + \mu_h)(\theta_m + \mu_m + c_m)(\alpha_h + \mu_h)(\mu_m + c_m) H} \bar{M}_s}. \quad (3.4)$$

Observe that $R_0$, the reproduction number of dengue, depends on the vital parameters of mosquito and human, on the fraction between the susceptible mosquito and the total human population sizes and also on the product of the transmission coefficients and the square of the mosquitoes’ biting rate, $b^2 \beta_h \beta_m$, emphasizing that a new case of dengue can occur only after two bites from the same mosquito.

In order to state the $R_0$ dependence on control parameters $c_m$ and $c_a$ substituting equation (3.2) into equation (3.4) leads to

$$R_0 = \sqrt{\frac{C \gamma m \theta_h \theta_m b^2 \beta_h \beta_m}{H(\theta_h + \mu_h)(\theta_m + \mu_m + c_m)(\alpha_h + \mu_h)(\mu_m + c_m)^2 \left(1 - \frac{1}{R_M}\right) \bar{M}_s}. \quad (3.5)$$

Based on expressions (3.3) and (3.5), as $R_M$ depends on both dengue control parameters $c_m$ and $c_a$, related to the adult and aquatic phases of the mosquito respectively, it is easy to see that $R_0$ also depends on both actions. Moreover, according to expression (3.5), it is more relevant in the calculation of $R_0$ to vary $c_m$ than $c_a$, as was expected after the outbreak triggers.

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Estimation of $R_0$ for actual epidemics

There are many ways to estimate $R_0$ for vector-transmitted diseases using actual data of epidemics (Massad et al. 2010). In this study, we estimated $R_0$ from the initial growth phase of the epidemics (Massad et al. 2001). Following Favier et al. (2006), we assume that, at the beginning of the epidemic, the cumulative number of cases, $K(t)$, varies as $K \propto \exp(At)$, where $A$ is the force of infection. In this case, the number of infectious and exposed vectors and the number of infectious and exposed hosts vary similarly,

$$
M_e(t) \sim M_{e0} \exp(At), \\
H_e(t) \sim H_{e0} \exp(At), \\
M_i(t) \sim M_{i0} \exp(At), \\
H_i(t) \sim H_{i0} \exp(At),
$$

(3.6)

where $M_{e0}$, $H_{e0}$, $M_{i0}$ and $H_{i0}$ are constants. Further, the number of non-susceptible hosts and vectors can be assumed negligible,

$$
M_s(t) = \bar{M}_s \\
H_s(t) = H.
$$

(3.7)

Substituting equations (3.6) and (3.7) in the expression for the derivative of $M_e, H_e, M_i$ and $H_i$ (system 2.1), we obtain

$$
\begin{align*}
\frac{A}{(\theta_m + \mu_m + c_m)} + 1 \left[ \frac{A}{(\theta_h + \mu_h)} + 1 \right] M_{e0} &= \frac{b\beta_m \bar{M}_s}{(\theta_m + \mu_m + c_m)H} \bar{H}_i0, \\
\frac{A}{(\theta_h + \mu_h)} + 1 \left[ \frac{A}{(\theta_h + \mu_h)} + 1 \right] H_{e0} &= \frac{b\beta_h}{(\theta_m + \mu_m + c_m)M_i0}, \\
\frac{A}{(\mu_m + c_m)} + 1 \left[ \frac{A}{(\alpha_h + \mu_h)} + 1 \right] M_{i0} &= \frac{\theta_m}{(\mu_m + c_m)M_e0}, \\
\frac{A}{(\alpha_h + \mu_h)} + 1 \left[ \frac{A}{(\alpha_h + \mu_h)} + 1 \right] H_{i0} &= \frac{\theta_h}{(\alpha_h + \mu_h)H_{e0}}.
\end{align*}
$$

(3.8)

Multiplying the left- and right-hand sides of the above equations and using the definition of $R_0$ given by equation (3.4) leads to the following relation between the basic reproductive number, $R_0$, and the force of infection, $A$:

$$
R_0^2 = \left( \frac{A}{\theta_m + \mu_m + c_m} + 1 \right) \left( \frac{A}{\theta_h + \mu_h} + 1 \right) \left( \frac{A}{\mu_m + c_m} + 1 \right) \left( \frac{A}{\alpha_h + \mu_h} + 1 \right).
$$

(3.8)

Since the number of new cases in a week, $I(t)$, is the derivative of $H_i(t)$ in relation to $t$, then, at the beginning of the epidemics, $I(t) \sim A\bar{H}_i0 K(t)$. As $H_{i0} = 1$, plotting the number of new cases per week against the cumulative number of cases $K(t)$, the phase of exponential growth of the cumulative number of cases is evidenced by a linear growth of the curve, the slope of which is the force of infection and which can be computed by a least-square linear fit of this linear phase (Favier et al. 2006). For the data of the 1995–1996 dengue outbreak in the city of Salvador and Bahia, Brazil, shown in figure 1a, we obtain
Figure 1. (a) The time series of new cases of dengue in the city of Salvador in 1995–1996 and (b) the weekly number of cases against the cumulative number of cases for the dengue outbreak in Salvador in 1995–1996. The dashed box indicates the growing linear parts of the plots corresponding to the initial exponential growth of the epidemics. The least-squares linear fit of the linear phase gives $L = 0.43 \pm 0.02$ week$^{-1}$ based on the slope shown in figure 1b. Using the average temperature record in the same year at Salvador, $T = 25.8 \pm 0.4^\circ$C, provided by the Brazilian National Institute of Meteorology (INMET), the mosquito entomological parameters are $\mu_m = 0.0302$ day$^{-1}$ (with minimum and maximum values relative to the mean temperature range of 0.0296 and 0.0308 day$^{-1}$) and $\theta_m = 0.0957$ day$^{-1}$ (with minimum and maximum values relative to the mean temperature range of 0.0938 and 0.0977 day$^{-1}$) (Yang et al. 2009b). The human mean parameters are $\alpha_h = 0.125$ day$^{-1}$, $\mu_h = 4 \times 10^{-5}$ day$^{-1}$ and $\theta_h = 0.17$ day$^{-1}$. Substituting these parameter values and $c_m \approx 0$ (no systematic vector control was in place during this epidemic) in expression (3.8), we obtain an estimation of $R_0 = 2.85$ (with minimum and maximum values relative to the human parameter’s range (table 1) of $R_0 = 2.77$ and 3.70).

Using expression (3.8), we measured the adult control efforts, represented by the parameter $c_m$, necessary to reduce the dengue incidence (figure 2), i.e. to diminish $R_0 < 1$. Observe that adult control mechanisms, applied to the mosquito adult form during the dengue outbreak, cannot reduce $R_0$ to values smaller than 1, and, therefore, these mechanisms are not sufficient to contain the dengue epidemic. Moreover, figure 2 shows that the control efficacy is greater for $c_m < 0.2$ for a significant reduction in $R_0$. Since control strategies have a cost for governmental authorities, there is no doubt that developing
theoretical and experimental techniques to identify the optimal control strategy is a central challenge in dengue mosquito control. The result above, $R_0 \geq 1$ for any value of $c_m$ ($0 < c_m < 1$), indicates that other mechanisms related to the effective control actions of the aquatic phase are necessary to avoid dengue outbreaks, reducing the force of infection before its triggering. It is shown, by means of the mathematical modelling analysis, that the combination of control actions of the aquatic and adult phases is essential to control the disease, as was indicated by other models used to analyse actual epidemic data (Burattini et al. 2008).

In the case of Salvador’s dengue outbreak that occurred in 2002, control mechanisms against the adult mosquito population were applied, mostly in places where a high number of cases of classic and mainly DHF were notified. Therefore, for the data from the 2002 dengue outbreak in Salvador, shown in figure 3a, we obtain $A = 0.38 \pm 0.02$ week$^{-1}$ based on the slope shown in figure 3b. For the temperature data recorded in 2002 we calculated an average temperature of $T = 25.6 \pm 0.4\, ^\circ\text{C}$, which is similar to that obtained in 1995; therefore, the estimated value for the mosquito entomological parameters are the same. According to the local authorities, the systematic vector control starts in March, which corresponds to the ninth week of the outbreak. So we may assume that, at the very beginning of the 2002 outbreak, there was no effective adult mosquito control ($c_m \simeq 0$). Analogously to the first epidemic, we obtained an estimation of $R_0 = 2.65$ (with minimum and maximum values relative to the human parameter range (table 1) of $R_0 = 2.50$ and 3.30), which is in the range of $R_0$ for the first epidemic. However, comparing figures 1 and 3, it is easy to see that the weekly number of cases assumes higher values (maximum $\simeq$3000) in 2002 than in 1995 (maximum $\simeq$850), indicating that the transmission force in 2002 was higher than in 1995. As a consequence, the reduction in the susceptible population is greater in 2002 than in 1995–1996. According to the recorded
Figure 3. (a) The time series of new cases of dengue in the city of Salvador in 2002 and (b) the weekly number of cases against the cumulative number of cases for the dengue outbreak in the city of Salvador in 2002. The dashed box indicates the growing linear parts of the plot corresponding to the initial exponential growth of the epidemic. The least-squares linear fit of the linear phase gives $A = 0.38 \pm 0.02$ with correlation coefficient $R \approx 1.0$.

data, the incidences (the total number of cases divided by the total population) are 546.73 (1995), 1423.20 (1996), 802.19 (2002) and 39.70 (2003), revealing that in 2003 there was no epidemic scenario. Since the incidence’s reduction from 2002 to 2003 is 95 per cent, we have not included the data from 2003 in figure 3a.

4. Effective reproductive number

When an epidemic starts in a partially susceptible population or control measures of the disease have been implemented, it is more convenient to work with the effective reproductive number, $R(t)$, defined as the number of secondary infections arising from a primary case with symptom onset at week $t$. Under such conditions, the assumption of a constant environment and exponential increase of new cases is untenable. The value of $R(t)$ is an indication of the severity of the epidemic, and gives information about the measures needed to control the disease.

Estimates for $R(t)$ can be obtained from the incidence curve of the infectious humans using the following equation derived from the renewal equation for a birth process:

$$F(t) = \frac{b(t)}{\int_{-\infty}^{t} b(t - a) g(a) \, da}, \quad (4.1)$$

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where, in the epidemiological context, \( b(t) \) accounts for the number of new cases at week \( t \) and \( g(a) \) is the generation interval distribution for the disease, which is defined as the probability distribution function for the time from infection of an individual to the infection of a secondary case by that individual.

In this section, we apply the method given in Wallinga & Lipsitch (2007) to the model (2.1) using data from the 1995 and 2002 dengue outbreaks in the city of Salvador. The developed model (2.1) has exposed and infective stages in both human and mosquito populations. The rates of leaving the exposed and infectious classes are constant and denoted by \( s_1 = \theta_m + \mu_m + c_m \), \( s_2 = \mu_m + c_m \), \( s_3 = \theta_h + \mu_h \) and \( s_4 = \alpha_h + \mu_h \). Therefore, the generation interval distribution is the combination of the four exponential distributions \( s_1 e^{-s_1 t} \), \( s_2 e^{-s_2 t} \), \( s_3 e^{-s_3 t} \), \( s_4 e^{-s_4 t} \) with a mean \( T_c = 1/s_1 + 1/s_2 + 1/s_3 + 1/s_4 \) given by

\[
g(t) = \sum_{i=1}^{4} \frac{s_1 s_2 s_3 s_4 e^{-s_i t}}{\prod_{j=1, j\neq i}^{4} (s_j - s_i)} \tag{4.2}
\]

with \( t \geq 0 \) (Akkouchi 2008). The relations above are valid when the infection force, \( A \), satisfies the following relation: \( A > \min(-s_1, -s_2, -s_3, -s_4) \) (Wallinga & Lipsitch 2007). Also, as we are dealing with distribution, \( \int_0^\infty g(t) \, dt = 1 \).

Substituting \( g(t) \) into equation (4.1) and using the epidemiological data of figures 4a and 5a, we compute \( F(t) \), and since the number of human secondary cases derived from a human primary case is equal to \( R^2(t) \), then

\[
R(t) = \sqrt{F(t)}. \tag{4.3}
\]

Figures 4 and 5 show the time evolution of the effective reproductive number \( R(t) \), respectively, to the dengue outbreaks in 1995–1996 and 2002. The results are shown for \( t \geq 9 \) because the technique that generates equation (4.2) is not valid for lower values of \( t \) and, therefore, cannot be used to estimate \( R(t) \) using (4.3). Analysing figure 4, we observe that \( R(t) \) assumes values greater than 1 at the end of 1995, prompting a second dengue outbreak in 1996 when the temperature
and rainfall favoured the proliferation of the mosquito *Aedes aegypti*, and, in consequence, dengue transmission. On the contrary, figure 5 shows that in 2002 the value of $R(t)$ does not assume values greater than 1 after the first decrease, corroborating the endemic dengue situation observed in 2003. Also, we observe a reduction in the duration of the epidemic in 2002 by a half in relation to the epidemic in 1995. There are many factors that may contribute to these different epidemiological scenarios, including:

— the rapid depletion of the human susceptible pool owing to the intense transmission force of DENV3 in 2002, which was greater than the DENV2 transmission force related to the outbreak of 1995;
— the more systematic control actions applied in Brazil since 2002, which is when the National Program of Dengue Control was established, because a sudden increase in and rapid spreading of dengue outbreaks increases the occurrence of dengue haemorrhagic cases.

In Bahia state, in 2002, the adult vector control strategies were in place. However, they were not applied with high frequency and complete coverage of the city area. The strategies consisted of the application of ultra-low volume insecticide at intervals of eight days by the public health agents in regions of the city where dengue transmission was confirmed. According to the local authorities, at the end of 2002, 75 per cent of the city area was covered at least by one application of larvicide, mainly in the regions of notified severe cases. Moreover, other actions such as a media programme were set up in order to remove the breeding grounds and to avoid the occurrence of new breeding grounds. As usual, the Premise Index (PI), the proportion of buildings with an *Aedes* focus, was used to measure the risk of dengue: from 1 to 3 per cent, medium risk; above 3 per cent high risk. The data recorded during the dengue outbreak of 2002 in

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Salvador show a decrease in the PI of 5.77, 3.19, 2.88, 2.58 and 1.66 estimated at intervals of 10 weeks. Although there was a significant reduction in the PI at the end of the year, the values still showed a medium risk of dengue. Therefore, the outbreak pattern observed in figure 5 may be associated with other factors besides vector control, such as the reduction in the susceptible human pool owing to the high transmission force required for DENV3.

Finally, figure 6 shows the effect of the adult control application on the effective reproductive number. Comparing the time series of $R(t)$ with (solid line) and without (dashed line) control, we can see that the increase in the control mechanisms caused the reduction in the number of dengue cases, as was expected. Nevertheless, the reduction in the number of new dengue cases at the beginning of the epidemic may have led to a resurgence of the dengue outbreak ($R(t) > 1$) after a time interval as a consequence of the remaining and new born susceptible human pool, as was observed by Yang & Ferreira (2008). Note that, owing to the fact that the epidemic data are input data for the calculation of $R(t)$ by equation (4.3), the seasonal features and the incidental effect of vector controls are taken into account in that calculation. Moreover, in a real situation when control mechanisms are applied, the increase of $c_m$ affects the data, reducing the value of $\Lambda$, which is not considered here; therefore, we are super-estimating $\hat{R}(t)$. Overall, the duration of the epidemic has not changed, only its intensity.

5. Conclusion

In this study, we comparatively analysed dengue epidemics that occurred in Salvador, Brazil, in 1995–1996 and 2002 based on a non-linear differential equations model, showing the effect of vector control. The analysis was performed in terms of the basic reproductive number, $R_0$, as well as its time evolution, $R(t)$, which are calculated using real epidemic time series. Both expressions depend on...
the model assumptions and are functions of the model’s parameters. The value of $R_0$ is greater than 1 for the epidemic in 1995–1996 for any chosen value of the vector control parameter, indicating that other strategies would be necessary besides the adult vector control, such as the control of the mosquito’s aquatic phase, to reduce its force of infection and therefore to control the epidemic. Analogously, the epidemic that occurred in 2002 leads to a similar value of $R_0$. However, the time evolution of the effective reproduction number $R(t)$ shows, for the two dengue outbreaks (1995–1996 and 2002), two distinct scenarios related to the intensity and duration of the epidemic and also related to the resurgence in the next year of a new epidemic peak, corresponding to values of $t$ such that $R(t) > 1$ for the first epidemic in contrast with no values of $t$ with $R(t) > 1$ in the second epidemic. During 2002, although the National Program of Dengue Control was established, the values of PI greater than 1 indicate a medium risk of dengue. So there is no consensus on whether the decrease in the number of dengue cases during the 2002 outbreak is more related to the transmission force required for DENV3 that quickly increased the herd immunity of the human population pool, or to vector control actions applied in Salvador in 2002, or to both factors. Finally, we show that reducing the number of new dengue cases by some control mechanisms obviously leads to the reduction in the total number of cases, but this allows a resurgence of the epidemic process ($R(t) > 1$) as a consequence of the remaining and new born susceptible human pool. Indeed, we intend to achieve an optimum dengue control programme which reduces the total number of cases without promoting a new dengue outbreak.

In a future study, we intend to apply the analysis developed here to compare the distinct dengue patterns observed in Brazilian cities. Preliminary results using the non-autonomous model show that the high sensitivity of the mosquito entomological parameters to temperature can explain the different periodicity and intensity of dengue outbreaks.

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