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A Comparative Analysis of the Relative Efficacy of Vector-Control Strategies Against Dengue Fever

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Abstract Dengue is considered one of the most important vector-borne infection, affecting almost half of the world population with 50 to 100 million cases every year. In this paper, we present one of the simplest models that can encapsulate all the important variables related to vector control of dengue fever. The model considers the human population, the adult mosquito population and the population of immature stages, which includes eggs, larvae and pupae. The model also considers the vertical transmission of dengue in the mosquitoes and the seasonal variation in the mosquito population. From this basic model describing the dynamics of dengue infection, we deduce thresholds for avoiding the introduction of the disease and for the elimination of the disease. In particular, we deduce a Basic Reproduction Number for dengue that includes parameters related to the immature stages of the mosquito. By neglecting seasonal variation, we calculate the equilibrium values of the model's variables. We also present a sensitivity analysis of the impact of four vector-control strategies on the Basic Reproduction Number, on the Force of Infection and on the human

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prevalence of dengue. Each of the strategies was studied separately from the others. The analysis presented allows us to conclude that of the available vector control strategies, adulticide application is the most effective, followed by the reduction of the exposure to mosquito bites, locating and destroying breeding places and, finally, larvicides. Current vector-control methods are concentrated on mechanical destruction of mosquitoes' breeding places. Our results suggest that reducing the contact between vector and hosts (biting rates) is as efficient as the logistically difficult but very efficient adult mosquito's control.

Keywords Dengue · Basic reproduction number · Force of infection · Sensitivity analysis · Vector control

1 Introduction

The global expansion of dengue fever is a matter of great concern to public health authorities around the world (Guy et al. 2011). In terms of the population at risk, dengue is considered the most important vector-borne disease worldwide (Gubler 2002; WHO 2012). It is estimated that approximately 3.6 billion people, one-half of the world's population, live in parts of the world affected by dengue (Gubler 2002; Beatty et al. 2008; WHO 2009), and 120 million people are expected to travel to dengue-affected areas every year (UNWTO 2011). Between 50 and 100 million people are infected each year (Suaya et al. 2009), and the World Health Organization states that the number is rising due to human population growth and the increased spread of vector mosquitoes due to climate change (Khasnis and Nettlelman 2005). Recent studies suggest that the figures are much higher (Wilder-Smith et al. 2012), with as many as 230 million infections, tens of millions of cases of dengue fever (DF) and millions of cases of dengue hemorrhagic fever DHF (Beatty et al. 2008, 2011; Gubler 2011). The number of disability-adjusted life years (DALYs) worldwide is estimated to range between 528 and 621 per million population (Wilder-Smith et al. 2010, 2012), and the total cost of dengue cases in the affected areas of the world may be approximately 2 billion dollars annually (Suaya et al. 2009).

Dengue viruses are transmitted by mosquitoes of the genus *Aedes*, subgenus *Stegomyia* (Wilder-Smith et al. 2012). The principal vector, *Aedes Stegomyia aegypti*, is now well established in much of the tropical and subtropical world, particularly in urban areas. It is a domestic species, highly susceptible to dengue virus infection, feeding preferentially on human blood during the daytime and often taking multiple blood meals during a single gonotrophic cycle (Wilder-Smith et al. 2010). It typically breeds in clean stagnant water in artificial containers and is, therefore, well adapted to urban life. A second species, *Aedes Stegoymyia albopictus*, is generally considered less effective as an epidemic vector because, unlike *A. aegypti*, it feeds on many animals other than humans and is less strongly associated with the domestic environment (Lambrechts et al. 2010).

Several reasons have been proposed for the dramatic global emergence of dengue as a major public health problem. Major global demographic changes have occurred, the most important of which have been uncontrolled urbanization and con-

current population growth. The public health infrastructure of many affected countries has deteriorated. Increases in international travel provide an efficient mechanism for the human transport of dengue viruses between urban centers, resulting in the frequent exchange of dengue viruses. Climatic changes influence the mosquito's survival and proliferation (Massad et al. 2011). Finally, effective mosquito control is virtually nonexistent in many dengue-endemic countries (Luz et al. 2011; Massad and Coutinho 2011).

Essentially, the control of dengue has been based on three strategies (Reiter and Gubler 2001): source reduction (locating and destroying mosquitoes' breeding places), larvicides and ultra-low volume (ULV) application of aerosol adulticides. The first two strategies have been applied with varying degrees of success. However, there is still considerable controversy over the efficacy of the current methods for controlling adult mosquitoes (Reiter and Gubler 2001). At the time of the advent of DDT, *Aedes aegypti* was highly susceptible to this agent (Reiter and Gubler 2001). The successful application of DDT resulted in the eradication of *Aedes aegypti* from 22 countries in the Americas in 1962 and from all countries in the Mediterranean region in 1972. However, the fate of DDT is well known. DDT was abandoned due to the evolution of resistant insects and due to the environmental impacts of the insecticide. Therefore, the control of dengue shifted to other approaches: source reduction, larvicides and adulticides from other chemical families.

From a theoretical perspective, significant advances were made by Macdonald (1952) who proposed that the most effective control strategy against vector-borne infections is to kill adult mosquitoes. A recent analysis for another vector-borne disease, Chikungunya, was carried out by Dumont and Chiroleu (2010).

Recently, in a study for describing the dynamics of dengue, we showed that the models describing infections transmitted by blood-sucking insects are indeed very sensitive to the mosquitoes' mortality rate (Burattini et al. 2008).

Let us review what we did in previous papers (Coutinho et al. 2006; Burattini et al. 2008; Massad et al. 2011) on the same subject: In the paper by Coutinho et al. (2006), the model's basic structure was presented, and in particular it introduced a new seasonality factor. This seasonality factor in Coutinho et al. (2006) was designed to test one hypothesis to explain dengue's overwintering; in the paper by Burattini et al. (2008), the model presented by Coutinho et al. (2006) was numerically simulated in order to fit Singapore's data on dengue incidence for the period between 2000 and 2005. In addition, a partial sensitivity analysis was presented by Burattini et al. (2008), which intended to check if killing adult mosquitoes is the most effective strategy. This was demonstrated numerically in that paper. In addition, we studied the role of larvicide associated with adulticides to avoid the resurgence of outbreaks in Singapore. This study was based on numerical simulations only. The paper by Massad et al. (2011) is a review of the previous papers and an analysis of the impact of global warming on vector-borne infections.

The current paper is an analysis based on the basic model proposed by Coutinho et al. (2006). It presents an analysis of four control strategies used against the vectors of dengue. All the relevant stages are included and the ones not included (like larvae and pupae) can be trivially added to the model. A complete analysis of the sensitivity of transmission to the parameters can be easily carried out if necessary.

The analysis presented below is based on the steady-state equilibrium of the variables involved in the model. So, the seasonality factor was neglected. Our analysis, therefore, produces a rough average of the sensitivity of the infection to the parameters over one cycle (year). In addition, by performing the analysis at steady-state, we avoid all confusing transients. Moreover, seasonality neither influences the general behavior of the system nor modifies the qualitative results of the sensitivity analysis.

2 Methods

2.1 The Basic Model

The basic model that is used to calculate the efficiency of control strategies can be found in previous papers (Coutinho et al. 2006; Burattini et al. 2008; Massad et al. 2011).

The populations involved in the transmission are human hosts, mosquitoes and their eggs. For the purposes of this paper, the term "eggs" also includes the intermediate stages, such as larvae and pupae. Therefore, the population densities are divided into the following compartments: susceptible humans denoted S_H; infected humans, I_H; recovered (and immune) humans, R_H; total humans, N_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 variables appearing in the model are summarized in Table 1.

The model is defined by the following equations:

$$
\begin{aligned}
\frac{dS_H}{dt} &= -abI_M\frac{S_H}{N_H} - \mu_H S_H + r_H N_H\left(1-\frac{N_H}{\kappa_H}\right),\\
\frac{dI_H}{dt} &= abI_M\frac{S_H}{N_H} - (\mu_H+\alpha_H+\gamma_H)I_H,\\
\frac{dR_H}{dt} &= \gamma_H I_H - \mu_H R_H,\\
\frac{dS_M}{dt} &= pc_S(t)S_E - \mu_M S_M - acS_M\frac{I_H}{N_H},\\
\frac{dL_M}{dt} &= acS_M\frac{I_H}{N_H} - \gamma_M L_M - \mu_M L_M,\\
\frac{dI_M}{dt} &= \gamma_M L_M - \mu_M I_M + pc_S(t)I_E,\\
\frac{dS_E}{dt} &= \left[r_M S_M + (1-g)r_M(I_M+L_M)\right]\left(1-\frac{(S_E+I_E)}{\kappa_E}\right) - \mu_E S_E - pc_S(t)S_E,\\
\frac{dI_E}{dt} &= \left[gr_M(I_M+L_M)\right]\left(1-\frac{(S_E+I_E)}{\kappa_E}\right) - \mu_E I_E - pc_S(t)I_E,\\
N_H &= S_H + I_H + R_H,\\
N_M &= S_M + L_M + I_M,\\
N_E &= S_E + L_E,
\end{aligned}
\tag{1}
$$

Table 1 Model variables and their biological meaning

Variable	Biological Meaning
S_H	Density of susceptible humans
I_H	Density of infected humans
R_H	Density of recovered humans
S_M	Density of uninfected mosquitoes
L_M	Density of latent mosquitoes
I_M	Density of infected mosquitoes
S_E	Density of uninfected eggs (imm. stages)
I_E	Density of infected aquatic forms

where $c_S(t) = (d_1 - d_2 \sin(2\pi f t + \phi))$ is a factor mimicking seasonal influences in the mosquito population (Coutinho et al. 2005, 2006). The seasonal influence was considered in another paper (Coutinho et al. 2006). In this paper, as explained in the introduction, seasonality was neglected by making $c_S(t) = c_S = \text{constant}$.

Remark This model differs from the classical Ross–Macdonald model because the extrinsic incubation period in the classical Ross–Macdonald model is assumed to last τ days, whereas in model (1) we assumed an exponential distribution for the latency in the mosquitoes. The classical Ross–Macdonald model can be obtained from system (1) by replacing the fifth and sixth equations by

$$\frac{dL_M}{dt} = acS_M \frac{I_H}{N_H} - \mu_M L_M - acS_M(t-\tau)\frac{I_H(t-\tau)}{N_H(t-\tau)} e^{-\mu_M \tau},$$
$$\frac{dI_M}{dt} = acS_M(t-\tau)\frac{I_H(t-\tau)}{N_H(t-\tau)} e^{-\mu_M \tau} - \mu_M I_M + pc_S(t) I_E,$$

where τ is the extrinsic incubation period and μ_M is the mosquito mortality rate. The expressions developed below in this paper with Eqs. (1) can be replaced by the corresponding expressions of the classical Ross–Macdonald model described above by replacing $\frac{\gamma_M}{\gamma_M+\mu_M}$ by $e^{-\mu_M \tau}$. γ_M is related to τ by $\tau = \frac{1}{\mu_M} \ln[\frac{\gamma_M}{\gamma_M+\mu_M}]$.

Remark Seasonal influence in the mosquito population was not considered in this paper as mentioned above and in Amaku et al. (2013b). The reason for this is that including seasonal variation, that is, considering $c_S(t) \neq \text{constant}$ implies in additional analytical difficulties (see, for instance, Wahl and Nowak 2000; Bacaër and Guernaoui 2006; Wang and Zhao 2008). In most tropical regions, the mosquito population varies little throughout the year (Erickson et al. 2010) and, therefore, this additional complication is unnecessary. Furthermore, at least for part of the year, the equilibrium is reached even when seasonality is important. For regions where seasonal variation is important, we partly analyzed (Burattini et al. 2008) the sensitivity to the parameters of an approximated time-dependent reproductive number (Coutinho et al. 2006). The results are qualitatively similar to the ones we found in the present paper. Note, however, that this analysis can only be carried out numerically. The present paper is a first step towards getting the time-dependent solution of system (1) by perturbation

theory, so that the sensitivity to the parameters in the time-dependent case can be calculated analytically. We should stress that the purpose of the paper by Coutinho et al. (2006) was different from the present one. In the latter paper, we tried to understand overwintering of dengue in some regions of Brazil where seasonal transmission is important.

2.2 Equilibrium Densities in the Absence of Seasonality

The equilibrium densities of model (1) can be calculated exactly in the case where seasonality can be neglected, i.e., with $c_S(t) = c_S = \text{constant}$.

We begin by examining the steady-state values with $\alpha_H = 0$, i.e., with no disease-induced mortality in the human population. This is a first approximation and it is a very good approximation in the case of dengue, which has a very low mortality rate (α_H is of the order of 10^{-4}/day). Because we set $\alpha_H = 0$, we denote the model variables with the zero superscript. By setting the derivatives in system (1) and α_H equal to zero, it is straightforward to solve the resulting system of nonlinear equations. The results are:

$$N_H^0 = \kappa_H \left(\frac{r_H - \mu_H}{r_H} \right), \tag{2}$$

$$N_M = N_M^0 = \frac{pc_S}{\mu_M} \kappa_E \left[1 - \frac{(\mu_M)(\mu_E + pc_S)}{r_M pc_S} \right], \tag{3}$$

$$N_E = N_E^0 = \kappa_E \left[1 - \frac{(\mu_M)(\mu_E + pc_S)}{r_M pc_S} \right]. \tag{4}$$

Note that N_M and N_E do not depend on the disease mortality in the human population, i.e., they do not depend on α_H. Also we get

$$I_H^0 = \frac{(\gamma_M + g\mu_M)a^2 bc N_M - N_H^0(\mu_H + \gamma_H)(\mu_M + \gamma_M)\mu_M(1-g)}{(\gamma_M + g\mu_M)a^2 bc \frac{N_M}{N_H^0}(1 + \frac{\gamma_H}{\mu_H}) + ac(\mu_H + \gamma_H)(\mu_M + \gamma_M)}, \tag{5}$$

$$R_H^0 = \frac{\gamma_H}{\mu_H} I_H^0, \tag{6}$$

$$S_H^0 = N_H^0 - I_H^0 - R_H^0, \tag{7}$$

$$S_M^0 = \frac{(1-\mathrm{g}) r_M N_M (\kappa_E - N_E) pc_S}{\kappa_E (\mu_M + ac \frac{I_H^0}{N_H^0})(\mu_E + pc_S) - g r_M pc_S (\kappa_E - N_E)}, \tag{8}$$

$$I_M^0 = \frac{(\mu_H + \gamma_H) I_H^0}{ab(1 - (1 + \frac{\gamma_H}{\mu_H}) \frac{I_H^0}{N_H^0})}, \tag{9}$$

$$L_M^0 = \frac{ac \frac{I_H^0}{N_H^0} S_M^0}{\gamma_M + \mu_M}, \tag{10}$$

$$S_E^0 = \frac{[r_M S_M^0 + (1-g) r_M (N_M - S_M^0)](\kappa_E - N_E)}{\kappa_E(\mu_E + pc_S)}, \tag{11}$$

$$I_E^0 = N_E^0 - S_E^0. \tag{12}$$

If $\alpha_H \neq 0$, the total numbers of mosquitoes and eggs do not change. The expression for N_H is complicated, but it is straightforward to calculate I_H as a function of N_H as follows:

$$\frac{I_H}{N_H} = \frac{(\gamma_M + g\mu_M)a^2 bc \frac{N_M}{N_H} - (\mu_H + \gamma_H + \alpha_H)(\mu_M + \gamma_M)\mu_M(1-g)}{(\gamma_M + g\mu_M)a^2 bc \frac{N_M}{N_H}(1 + \frac{\gamma_H}{\mu_H}) + ac(\mu_H + \gamma_H + \alpha_H)(\mu_M + \gamma_M)}. \tag{13}$$

Alternatively, we can write

$$\frac{I_H}{N_H} = -\frac{\mu_H}{\alpha_H} + \frac{r_H}{\alpha_H}\left(1 - \frac{N_H}{\kappa_H}\right). \tag{14}$$

If the disease induces mortality in the human population ($\alpha_H \neq 0$), N_H depends on α_H and is specified by a somewhat complicated expression. We will first obtain an expression for N_H as a function of α_H. This expression is based on perturbation theory. The exact expression for N_H is presented subsequently.

2.3 Estimating N_H by Perturbation Theory

An expression for N_H can be obtained with perturbation theory. First, we sum the first three equations of system (1) to obtain

$$\frac{dN_H}{dt} = r_H N_H\left(1 - \frac{N_H}{\kappa_H}\right) - \mu_H N_H - \alpha_H I_H. \tag{15}$$

At equilibrium, this expression yields

$$r_H N_H\left(1 - \frac{N_H}{\kappa_H}\right) - \mu_H N_H - \alpha_H I_H = 0. \tag{16}$$

Next, we expand N_H and I_H in powers of α_H:

$$N_H = N_H^{(0)} + \alpha_H N_H^{(1)} + \alpha_H^2 N_H^{(2)} + O\left(\alpha_H^3\right), \tag{17}$$

$$I_H = I_H^{(0)} + \alpha_H I_H^{(1)} + \alpha_H^2 I_H^{(2)} + O\left(\alpha_H^3\right), \tag{18}$$

where $N_H^{(0)} = N_H^0$ and $I_H^{(0)} = I_H^0$. Neglecting the higher-order terms (because α_H is assumed to be very small) in (17) and (18) and substituting in (16), we obtain, after some algebraic manipulations,

$$N_H = N_H^0 - \frac{\alpha_H I_H^0}{r_H - \mu_H}, \tag{19}$$

where N_H^0 and I_H^0 are given by Eqs. (2) and (5).

2.4 The Exact Calculation of N_H

The value of α_H for dengue is such that an individual who is sick for five days has a probability of dying of the order of 0.2 %, i.e., a negligible impact on human demography. However, although it is reasonable to neglect α_H for dengue, it is not reasonable to do so for other vector-borne infections, such as yellow fever or malaria. We therefore need the exact expression for N_H given below.

First, we define

$$\Gamma = (\gamma_M + g\mu_M)a^2bcN_M, \tag{20}$$

where N_M is given by Eq. (3), and

$$\theta = (\mu_H + \gamma_H + \alpha_H)(\mu_M + \gamma_M). \tag{21}$$

Next, we define

$$\Pi = acr_H\theta, \tag{22}$$

$$\Theta = -\left[ac\theta\kappa_H(r_H - \mu_H) - \Gamma r_H\left(1 + \frac{\gamma_H}{\mu_H}\right) + \theta\mu_M\alpha_H\kappa_H(1-g)\right], \tag{23}$$

and

$$\Omega = -\Gamma\kappa_H(r_H - \mu_H)\left(1 + \frac{\gamma_H}{\mu_H}\right) + \Gamma\alpha_H\kappa_H. \tag{24}$$

Finally,

$$N_H = \frac{-\Theta + \sqrt{\Theta^2 - 4\Pi\Omega}}{2\Pi}. \tag{25}$$

This expression reduces to Eq. (2) if $\alpha_H = 0$.

Note that, from Eq. (13) and (25), we can deduce that model (1) presents no backward bifurcation. This is in contrast to the findings of Garba et al. (2008), and it will be discussed in a future publication.

2.5 Sensitivity of the Variables to the Parameters

If seasonality is neglected (i.e., $c_S(t) = \text{constant}$), the variables attain steady states, as we have shown above. To estimate the sensitivity of a model variable in steady state, V_i, to a parameter θ_j, we consider the relative variation in the parameter, $\frac{\Delta\theta_j}{\theta_j}$. This variation will correspond to a variation $\frac{\Delta V_i}{V_i}$ in the model variable V_i given by

$$\frac{\Delta V_i}{V_i} = \frac{\theta_j}{V_i}\frac{[V_i(\theta_j + \Delta\theta_j) - V_i(\theta_j)]}{\Delta\theta_j}\frac{\Delta\theta_j}{\theta_j}. \tag{26}$$

This expression can be approximated by (Chitnis et al. 2008; Massad et al. 2009)

$$\frac{\Delta V_i}{V_i} = \frac{\theta_j}{V_i}\frac{\partial V_i}{\partial\theta_j}\frac{\Delta\theta_j}{\theta_j} + \frac{1}{2!}\frac{\theta_j^2}{V_i^2}\frac{\partial^2 V_i}{\partial\theta_j^2}\left(\frac{\Delta\theta_j}{\theta_j}\right)^2 + \cdots. \tag{27}$$

Usually, the second- and higher-order terms can be neglected, provided that the relative variation in the parameter, $\frac{\Delta\theta_j}{\theta_j}$, is sufficiently small.

2.6 The Sensitivity of the Basic Reproduction Number to the Model's Parameters

Linearizing the second, the fifth, the sixth and the eight equations of model (1) around the trivial solution (no-infection), we obtain the threshold normally denoted R_0 in the literature (details can be found in Coutinho et al. (2006)):

$$R_0 = \frac{a^2 bc(\overline{N}_M/\overline{N}_H)(g\mu_M + \gamma_M)}{(\mu_H + \alpha_H + \gamma_H)(\mu_M + \gamma_M)\mu_M(1-g)}, \tag{28}$$

where $\overline{N}_M$ and $\overline{N}_H$ respectively denote the density of mosquitoes and of humans in the absence of disease. Note that if $g = 0$, i.e., there is no vertical transmission, the expression (28) for R_0 reduces to the classical Macdonald equation (Lopez et al. 2002). As mentioned above, to obtain the classical Macdonald equation, we replace $\frac{\gamma_M}{\gamma_M+\mu_M}$ by $e^{-\mu_M \tau}$. The case of $g \to 1$ will be examined in the Discussion section.

Alternatively, we can deduce a threshold, T_h, for the existence of endemic equilibrium values for the human prevalence of the disease. This threshold is given by Eq. (13):

$$\frac{I_H}{N_H} = \frac{(\gamma_M + g\mu_M)a^2 bc\frac{N_M}{N_H} - (\mu_H + \gamma_H + \alpha_H)(\mu_M + \gamma_M)\mu_M(1-g)}{(\gamma_M + g\mu_M)a^2 bc\frac{N_M}{N_H}(1 + \frac{\gamma_H}{\mu_H}) + ac(\mu_H + \gamma_H + \alpha_H)(\mu_M + \gamma_M)}.$$

If

$$\frac{I_H}{N_H} \geq 0,$$

then an endemic state exists. For this outcome, it suffices that

$$(\gamma_M + g\mu_M)a^2 bc\frac{N_M}{N_H} - (\mu_H + \gamma_H + \alpha_H)(\mu_M + \gamma_M)\mu_M(1-g) \geq 0, \tag{29}$$

or

$$T_h = \frac{a^2 bc(N_M/N_H)(g\mu_M + \gamma_M)}{(\mu_H + \alpha_H + \gamma_H)(\mu_M + \gamma_M)\mu_M(1-g)} \geq 1,$$

which coincides with expression (28) if $T_h \leq 1$ because then $N_M = \overline{N}_M$ and $N_H = \overline{N}_H$. This result also holds if $\alpha_H = 0$, i.e., if the disease has no influence on the population size. Note that in our model, because the disease has no influence on the size of the mosquito population, $N_M = \overline{N}_M$ always holds.

We begin the sensitivity analysis by considering the impact of a form of control of dengue vectors that is still unusual, namely, reducing the contact of the population with mosquito bites. This form of control is represented by mosquito shields (repellent-impregnated cloths), repellents and the use of bed-nets. The use of bed-nets is very effective against malaria (Fegan et al. 2007) because it reduces the amount of contact between the anopheline vectors and susceptible humans, the biting rate parameter a of model (1). We are aware that this strategy is effective against Anopheles

mosquitoes because these vectors bite at twilight and early at night. In contrast, Aedes mosquitoes bite primarily during the day. We include this analysis here for the sake of generality and also because the use of repellents and mosquito shields can produce the same reduction in the biting rate a and can be applied against Aedes mosquitoes. The partial derivative of R_0 with respect to a is given by

$$\frac{\partial R_0}{\partial a} = \frac{R_0}{a}\left[2 - \frac{a}{N_H}\frac{\partial N_H}{\partial a}\right]. \tag{30}$$

Next, we analyze the impact of reducing the carrying capacity of the immature forms, κ_E, on the magnitude of R_0. This reduction represents a component of the strategy of mechanical control, i.e., the identification and destruction of the places where Aedes mosquitoes breed. The partial derivative of R_0 with respect to κ_E is given by

$$\frac{\partial R_0}{\partial \kappa_E} = R_0\left\{\frac{pc_S}{N_M\mu_M}\left[1 - \frac{\mu_M(\mu_E + pc_S)}{r_M pc_S}\right] - \frac{1}{N_H}\frac{\partial N_H}{\partial \kappa_E}\right\}. \tag{31}$$

The use of larvicides is assumed to increase the mortality rate of the larvae, μ_E. Therefore, the impact of such a strategy is a function of the partial derivative of R_0 with respect to μ_E, which is

$$\frac{\partial R_0}{\partial \mu_E} = -R_0\left(\frac{\kappa_E}{r_M N_M} + \frac{1}{N_H}\frac{\partial N_H}{\partial \mu_E}\right). \tag{32}$$

Finally, we take the partial derivative of R_0 with respect to the mosquito mortality rate μ_M to estimate the impact of the application of adulticides as a control strategy against the dengue vectors. The result is given by

$$\frac{\partial R_0}{\partial \mu_M} = R_0\left[\frac{1}{\mu_M + \gamma_M} + \frac{1}{\mu_M(1-g)} - \frac{pc_S\kappa_E}{\mu_M^2 N_M} - \frac{1}{N_H}\frac{\partial N_H}{\partial \mu_M}\right]. \tag{33}$$

Given these partial derivatives, we can calculate the sensitivity of R_0 to the four parameters above and thereby estimate the relative efficiencies of the control strategies for avoiding the introduction of dengue into a non-infected area. To perform these calculations, we consider Eq. (27) for each of the parameters. For dengue, the last term in Eqs. (30)–(33), involving the derivative of N_H, is always very small relative to the previous terms. The results of the sensitivity analysis, with parameter values as in Table 2, are shown in Table 3.

2.7 The Sensitivity of the Force of Infection and the Human Prevalence to the Model's Parameters

The concept of 'force of infection' for vector-borne infection first appeared in the seminal works of Ronald Ross (1911), who termed it the effective inoculation rate and denoted it as h, for 'dependent happening'. The concept was further elaborated by George Macdonald (1952) who, in a now-famous Appendix to his paper '*The Analysis of Equilibrium in Malaria*', defined the inoculation rate as

$$h = mabs, \tag{34}$$

Table 2 Model parameters, biological meaning, values and sources. The mean, variance, and 95 % CI were obtained with Monte Carlo simulations

Parameter	Meaning	Value (Baseline)	Mean	Variance	95 % CI	Source
a	Average daily rate of biting	0.164	0.1682	0.026	9.8×10^{-3}	Yasuno and Tonn (1970)
b	Fraction of bites actually infective	0.6	0.6062	0.296	0.0337	Ocampo and Wesson (2004)
μ_H	Human natural mortality rate	3.5×10^{-5} days^{-1}	3.55×10^{-5}	1.019×10^{-9}	2.00×10^{-6}	Index Mundi (2011)
r_H	Birth rate of humans	9.5×10^{-5} days^{-1}	9.531×10^{-5}	8.959×10^{-9}	5.3×10^{-6}	Index Mundi (2011)
κ_H	Carrying capacity of humans	5×10^{6}	5.0123×10^{6}	2.052×10^{13}	2.81×10^{5}	Index Mundi (2011)
α_H	Dengue mortality in humans	3.5×10^{-4} days^{-1}	3.473×10^{-4}	1.00×10^{-7}	1.97×10^{-5}	Halstead (1990)
γ_H	Human recovery rate	0.143 days^{-1}	0.1434	0.017	8.097×10^{-3}	Halstead (1990)
P	Hatching rate of susceptible eggs	0.15 days^{-1}	0.151	0.019	8.55×10^{-3}	Forattini (1996)
γ_M	Latency rate in mosquitoes	0.143 days^{-1}	0.1434	0.017	8.097×10^{-3}	Burattini et al. (2008)
μ_M	Natural mortality rate of mosquitoes	0.09 days^{-1}	0.08329	1.5×10^{-4}	5.52×10^{-3}	Brownstein et al. (2003)
r_M	Oviposition rate	50 days^{-1}	51.8295	2073.9	2.8226	Brownstein et al. (2003)
G	Proportion of infected eggs	0.1	0.0964	0.008	5.684×10^{-3}	Assumed
κ_E	Carrying capacity of eggs	9.8×10^{7}	9.787×10^{7}	8.003×10^{15}	5.545×10^{6}	Assumed
μ_E	Natural mortality rate of eggs	0.1 days^{-1}	0.101	0.008	5.6644×10^{-3}	Brownstein et al. (2003)
C	Dengue susceptibility of A. aegypti	0.54	0.5265	0.249	0.03191	Ocampo and Wesson (2004)
c_S	Climatic factor	0.07	0.07	0.004	0.00398	Assumed

Table 3 Results of the sensitivity analysis according to the general Eq. (27). The results represent the relative amount of variation (expressed in percentual variation) in the variable if we vary the parameters by 1 %

Variable	Mean	95 % Confidence Interval
R_0	1.74	1.45–2.07
λ	2.59×10^{-5}	1.48×10^{-5}–3.96×10^{-5}
I_H/N_H	1.04×10^{-4}	3.84×10^{-5}–1.34×10^{-4}
Parameter		**Mean**
Sensitivity of R_0 to the control parameters		
a		1.94
κ_E		0.69
μ_E		$(-)\ 8.28 \times 10^{-4}$
μ_M		$(-)\ 2.42$
Sensitivity of λ to the control parameters		
a		5.02
κ_E		2.32
μ_E		$(-)\ 1.93 \times 10^{-3}$
μ_M		$(-)\ 5.40$
Sensitivity of I_H/N_H to the control parameters		
a		2.67
κ_E		1.34
μ_E		$(-)\ 2.31 \times 10^{-2}$
μ_M		$(-)\ 3.20$

where m is the mosquito density relative to the human population ($\frac{N_M}{N_H}$ in our notation), a is the mosquito's daily rate of biting, b is the probability of infection from mosquitoes to humans, and s is a quantity that Macdonald termed the 'Sporozoite Rate', i.e., the prevalence of infection in the mosquitoes ($\frac{I_M}{N_M}$ in our notation). Note that Eq. (34) is now expressed as

$$\lambda = ab\frac{I_M}{N_H}, \tag{35}$$

where

$$I_M = \frac{N_H(\mu_H + \alpha_H + \gamma_H)\frac{I_H}{N_H}}{ab(1 - (1 + \frac{\gamma_H}{\mu_H})\frac{I_H}{N_H})}. \tag{36}$$

Before we analyze the sensitivity of the force of infection to the model's parameters related to control, we first deduce a relationship between λ and R_0.

We begin by substituting I_M of Eq. (36) in Eq. (35) to obtain

$$\lambda = \frac{(\mu_H + \alpha_H + \gamma_H)\frac{I_H}{N_H}}{(1 - (1 + \frac{\gamma_H}{\mu_H})\frac{I_H}{N_H})}. \tag{37}$$

If $\alpha_H \approx 0$, the human prevalence, $\frac{I_H}{N_H}$, can be expressed in terms of R_0 as follows:

$$\frac{I_H}{N_H} = \frac{\mu_M(1-g)(R_0-1)}{\mu_M(1-g)R_0(1+\frac{\gamma_H}{\mu_H})+\mu_H ac}. \tag{38}$$

Therefore,

$$\lambda = \frac{\mu_M(1-g)(\mu_H+\alpha_H+\gamma_H)\mu_H(R_0-1)}{\mu_M(1-g)(\mu_H+\gamma_H)+\mu_H ac}. \tag{39}$$

The partial derivatives of λ and $\frac{I_H}{N_H}$ with respect to the parameters θ_j are readily calculated, and the sensitivity of λ and $\frac{I_H}{N_H}$ to the parameters is estimated.

3 Results

3.1 Numerical Simulations

We simulated model (1) with the parameter values available from the literature. However, it is known that these parameters vary with the place, local temperature, climatic factors, mosquito strains, and human demography. Therefore, we applied a Monte Carlo simulation algorithm (Amaku et al. 2009) to generate parameter distributions that could mimic real conditions. We used a Beta-distributed random number generator with equal parameters to guarantee the symmetry of the distribution around the mean. Because the Beta distribution with equal parameters has a mean of 0.5, we multiplied the final result by 2. We ran the Monte Carlo algorithm 1000 times to generate the distributions of the parameters. The parameters' baseline values, the mean values of the simulation, the variance, and the 95 % confidence intervals for each parameter are shown in Table 2.

3.2 Results of the Sensitivity Analysis

Table 3 shows the results of the sensitivity analysis according to the general Eq. (27). The results represent the relative amount of variation (expressed in percentual variation) in the variable if we vary the parameters by 1 %.

Note from Table 3 that R_0, λ and $\frac{I_H}{N_H}$ show the greatest sensitivities to the mosquito's mortality rate μ_M, followed by the biting rate a and the carrying capacity of the immature stages κ_E. In addition, R_0, λ and $\frac{I_H}{N_H}$ are very insensitive to the larval mortality rate μ_E. Accordingly, a reduction of 1 % in the biting rate a or the carrying capacity of the immature stages κ_E decreases R_0 by 1.94 % and 0.69 %, respectively, it decreases λ by 5.02 % and 2.32 %, and decreases $\frac{I_H}{N_H}$ by 2.67 % and 1.34 %, respectively. Also, an increase of 1 % in the mosquito mortality rate μ_M causes a decrease of 2.42 % in R_0, of 5.40 % in λ and of 3.20 % in $\frac{I_H}{N_H}$. In contrast, increasing the larval mortality rate μ_E by 1 % decreases R_0, λ and $\frac{I_H}{N_H}$ by only 0.000828 %, 0.00193 %, 0.0231 %, respectively. These differences in the sensitivity of R_0, λ and $\frac{I_H}{N_H}$ to parameter variation can be understood from Eq. (27). Although the partial derivatives of λ with respect to the parameters are smaller than the partial

derivatives of R_0 with respect to the parameters, the ratio $\frac{\theta_j}{\lambda} \gg \frac{\theta_j}{R_0}$. The same applies for $\frac{I_H}{N_H}$.

4 Discussion

The knowledge of dengue epidemiology accumulated over the past decades enables us to conclude that the transmission thresholds and the intensity of dengue transmission are determined by several factors: the level of immune protection of the population involved; the serotype of dengue virus circulating at each time; the density, longevity and biting behavior of the mosquitoes; the climate; and the demography of the human hosts (Rodrigues et al. 2012). Despite the current development of a safe and effective tetravalent vaccine (Guy et al. 2011), vector control is still the only available strategy to minimize the number of cases within the affected populations. To date, however, the effectiveness of the strategies for controlling Aedes mosquitoes has been limited. The analysis presented in this paper is intended to contribute to the efforts to check the advance of dengue to areas still free from the disease and to reduce transmission in endemic areas.

This paper presents the most complete analysis of what is a basic model for dengue transmission. All the relevant stages are included and the ones not included (like larvae and pupae) can be trivially added to the model.

The current paper is an analysis of the basic model proposed by Coutinho et al. (2006) and numerically studied by Burattini et al. (2008). The fact that the extrinsic incubation period is changed from being modeled as a fixed time delay to being modeled as an exponentially distributed time period is not relevant for the proposed analysis. As mentioned above, the expressions developed below in this paper with Eqs. (1) can be replaced by the corresponding expressions of the classical Ross–Macdonald model described above by replacing $\frac{\gamma_M}{\gamma_M+\mu_M}$ by $e^{-\mu_M \tau}$. In other words, the results of the analysis are the same, irrespective of the way we choose to model the incubation period. Actually, the main difference between this paper and the previous ones (Coutinho et al. 2006; Burattini et al. 2008; Massad et al. 2011) is that in the current study we analyze the sensitivity of the endemic equilibrium to variation in the parameters related to transmission in a much more complete way than before. The sensitivity analysis presented in the previous papers consisted only in the derivation of the partial derivatives of R_0 with respect to the parameters. This is only part of the sensitivity analysis. In the present paper, the calculation of sensitivity of R_0 to the parameters is completed (Eq. (27)). In addition, we calculated the equilibrium prevalence for the model, obtaining expressions that are completely new, like Eq. (37) which relates the force of infection to the prevalence of the disease in humans and to the parameters of transmission relative to the human hosts only. With this expression we propose the estimation of the force of infection for dengue as a function of the equilibrium prevalence in humans.

Furthermore, the current and complete sensitivity analysis includes the force of infection and the prevalence of dengue in humans. Finally, the sensitivity of the basic reproduction number and the force of infection to the biting rate is also a quite new finding.

Ellis et al. (2011) have approached the problem of the sensitivity of dengue by numerically simulating two coupled models, one describing the vector population and the other the host population. These models are extremely complex, including a total of 99 parameters for the vector and host populations. Although the calculations based on these models are very important, they mask the dynamics involved. In contrast, the dynamics of dengue constitute the main interest of our paper. Our model contains only 16 parameters and admits an analytical solution that can be compared with the classical models designed for the study of vector-borne infections. These differences notwithstanding, the results of Ellis et al. (2011) are qualitatively similar to the results that we obtained.

Some of the findings of the current paper are qualitatively similar to previous results. However, this is the first paper that proposes a quantification of the relative efficacy of different control strategies. In other words, we are now able to say by how much killing adult mosquitoes is more efficient than killing immature stages, for instance.

Our results identify the control of adult mosquitoes as the most effective strategy to reduce both R_0, λ and $\frac{I_H}{N_H}$. However, we are aware that the effectiveness of this strategy is severely constrained, e.g., by the difficulty of achieving sufficiently high coverage of the surfaces used by the mosquitoes for resting (Integrated Vector Management 2012; Rodrigues et al. 2012) and by the limitations of ultra-low volume insecticide spraying, which involves a low probability of contact between adult mosquitoes and the insecticide droplets (Reiter and Gubler 2001).

The second most effective strategy is the reduction of the contact between the vectors and hosts, quantified by the daily biting rate a. This strategy has been successfully applied in malaria control, e.g., through the use of insecticide-impregnated bed-nets. This approach to malaria control is effective (Brownstein et al. 2003) because the malaria mosquito bites at night. Aedes mosquitoes, in contrast, are day-biting mosquitoes, and bed nets are not a feasible method to avoid their bites. In certain countries, however, people habitually take a *siesta*, a rest during the afternoon (Reiter and Gubler 2001). In addition, insecticide-treated clothes (ITCs) used as personal protection against malaria infection (Reiter and Gubler 2001) are beginning to be tested against dengue (Wilder-Smith et al. 2012).

The next strategy suggested by the analysis of the model's sensitivity involves the carrying capacity of the immature stages, κ_E. This strategy is associated with the mechanical control of the sources of the mosquitoes. Our assumption is that by destroying mosquitoes' breeding places, we are reducing κ_E.

It is probable that this approach is the most widespread strategy for the control of dengue in endemic regions. However, the results obtained from this strategy have been disappointing. It is probable that these disappointing results are due to the lack of cooperation by the affected communities, which often hampers the application of the method. Unfortunately, R_0 was not found to be very sensitive to this strategy. A 1 % reduction in κ_E yielded only a 0.69 % reduction in R_0. The force of infection, in contrast, was shown to be relatively sensitive to variation in κ_E. A 1 % reduction in this parameter yielded a 2.32 % reduction in λ. Finally, a 1 % reduction in κ_E caused a reduction of 1.34 % in the human prevalence.

The least effective strategy analyzed was the use of larvicide. This strategy is expected to increase the mortality rate of immature stages, μ_E. Both R_0 and λ vary

by a fraction on the order of 10^{-3} percent, and $\frac{I_H}{N_H}$ varies by a fraction on the order of 10^{-2} percent if we vary μ_E by 1 %.

Some health authorities are convinced that to kill eggs/larvae is better than to kill adult mosquitoes. This is intuitively incorrect because killing one egg/larvae kills one adult mosquito; but killing one adult mosquito kills hundreds of eggs/larvae and our model quantifies this and other effects. This proposal, however, does not take into account the many logistic difficulties in implementing the adulticide strategy. Our main conclusion provides a rational explanation for the failure of dengue control and a strong argument to consider adulticides, in spite of their inconveniences. Even worse, the paradigm among dengue authorities that the application of adulticides is close to impossible is hindering entomological research in the area of insecticides and their application in field conditions.

Obviously, the possible control strategies analyzed in this paper are expected to be applied in combination, although we studied each of them in isolation. In addition, it is necessary to carry out a study of financial costs and logistic feasibility to determine the most effective vector control strategy against dengue. In a future paper, we intend to analyze the effect of a combination of strategies numerically using a Monte Carlo simulation and also to consider the effects of the uncertainties on the parameters on the calculated values of R_0, λ and $\frac{I_H}{N_H}$. This is not straightforward as discussed in Silverman et al. (2004), Coutinho et al. (2004) and Cousins and James (2006).

The theoretical case of 100 % vertical transmission ($g = 1$), i.e., the case in which all of the eggs from the latent and infected mosquitoes are infected, is interesting. In fact, a structural change occurs in our model if $g \to 1$. The populations of susceptible and infected eggs become completely decoupled. It can be verified that the disease can sustain itself even without human hosts. Actually, as shown by previous authors (Adams and Boots 2010), this is the only way in which the infection circulates exclusively among the vectors in the absence of hosts.

In addition, if $g = 1$ and human hosts are introduced into the system, the evolution of the system over time results in a situation in which all mosquitoes are infected because all of the eggs of the infected mosquitoes are infected. Therefore, if $g = 1$ and human hosts are introduced, the population of susceptible mosquitoes and eggs decreases to zero. This result can be verified from Eqs. (8) and (11).

Our approach has some important simplifications with respect to reality. The first one is the homogeneous mixing assumption. According to this assumption, the density of every subpopulation is the same everywhere and from the model it seems as if every single infected mosquito has the same probability of contacting every host. Actually, this is not true and it is a notational artifact. In the Appendix, we explain how this notational artifact can be eliminated. Furthermore, we show how to relax the homogeneous mixing assumption and analyze some consequences of this.

The second limitation is that the model predicts a stable endemic equilibrium, which is seldom observed. One reason for this is that in this model, for simplification, we exclude seasonality, which precludes the existence of such equilibrium for long periods of time. The relative sensitivity of the variables to the parameters, however, is also valid (actually to a very good approximation) for non-equilibrium situations. This has already been demonstrated by numerical simulations of a model very similar to the one we are dealing with in this paper (Coutinho et al. 2006; Burattini et al. 2008;

Massad et al. 2011). Finally, the actual values of some of the parameters used in the simulations are not known, and we had to take advantage of Monte Carlo simulations. The relative sensitivity to the parameters, however, is not affected by the uncertainties in the parameter's values.

The remarkable growing of the dengue cases worldwide demonstrates that all the strategies employed so far against dengue failed. The hundreds of millions of cases every year testify for that point of view. Our paper was intended to help the health authorities choose the strategies that are probably (theoretically) the best to control dengue.

As mentioned above, our paper is intended to contribute to a central debate concerning dengue control, namely, the search-and-destroy breeding places versus the application of adulticides. Our contribution is to calculate the relative efficacy of each of those strategies (along with others) and this is done in the sensitivity analysis section. However, to do so the equilibrium analysis is an unavoidable step. Other very important issues were considered by other authors: fluctuations in dengue hemorrhagic fever (Aguiar et al. 2013); multi-strain epidemiological models (Kooi et al. 2013); the effect of introducing sterile insects to control their population (Anguelov et al. 2012); a recent analysis of the effect of vector control for another vector-borne disease, Chikungunya, was carried out by Dumont and Chiroleu (2010).

The model presented in this paper contains parameters that are measurable. What people normally fail to realize is that there are legal, practical and economical requirements involved in the measurement of these parameters. These requirements are often contradictory. For example, in some case we must use a small crew of public health workers but have to obtain the data in short time.

Sometimes the errors involved in some parameters are very difficult to estimate. For example, to measure the mortality due to some diseases we need to know the number of infected people and the number of deaths among them. For economical reasons, the number of infected people is estimated clinically and, therefore, not very accurately (Is this person suffering from dengue? This is answered clinically). On the other hand, the number of deaths from the disease are very precisely measured in autopsies (If a person dies from dengue this can be precisely determined).

Finally, it is important to emphasize that the model presented in this paper has no backward bifurcation. Backward bifurcation would imply that dengue control would be much more difficult than it already is. This is because, according to the model presented in this paper, the reduction of R_0 below unit should suffice to stop the transmission.

This contrasts with the conclusion of Pinho et al. (2010) who applied an inadequate way to estimate the impact of reducing R_0 below unit on dengue transmission (Amaku et al. 2013a).

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Appendix: Some Comments on the Meaning of the Model's Equations

In this appendix, we show how to include spatial heterogeneities in the model and, by doing so, we clarify the meaning of the model's equations.

First, we assume that mosquitoes have a limited range of flight, which implies that the probability of transmission of infection from one infected mosquito to one susceptible host varies according to the distance between them.

Consider the first equation of system (1),

$$\frac{dS_H}{dt} = -abI_M\frac{S_H}{N_H} - \mu_H S_H + r_H N_H\left(1 - \frac{N_H}{\kappa_H}\right). \tag{40}$$

All the variables are *densities*. This implies that we are considering a very large region where the populations of mosquitoes and hosts are constant, that is, do not vary from point to point. Then, one might think that in Eq. (40) a mosquito in a certain place can bite a host which can be very far from it. This is not reasonable and it is not true for Eq. (40). To see this, consider the parameter a, the mosquitoes' biting rate. We can write this as $a = a'A$, where a' is the biting rate per unit area and A is the area where the mosquitoes' flight ranges. Therefore, only humans inside this area are bitten by this mosquito. But, since the humans and mosquitoes populations are assumed as homogeneously distributed, this does not appear in the equations because in parameter a this effect is hidden.

Let us now introduce spatial heterogeneity. For this we should specify the position $\vec{r}$, representing the spatial location of individuals. Thus, let $S_H(\vec{r})\,ds$ be the number of human susceptibles in the small area ds around the position $\vec{r}$.

Let us now consider how $S_H(\vec{r})\,ds$ varies with time. Let $I_M(\vec{r}')\,ds'$ be the number of infected mosquitoes in the small area ds' around the position $\vec{r}'$. The total number of bites the infected mosquitoes population inflicts in a time interval dt is $a'I_M(\vec{r}')\,ds'\,dt$. A fraction of those bites $F(|\vec{r}-\vec{r}'|)$ is inflicted on the hosts at position $\vec{r}$, that is, $S_H(\vec{r})\,ds$. Of course, $F(|\vec{r}-\vec{r}'|)$ is a decreasing function of the distance $|\vec{r}-\vec{r}'|$ between infected mosquitoes and susceptible humans. Thus, Eq. (40) becomes

$$\begin{aligned}\frac{dS_H(\vec{r})}{dt} = -b\frac{S_H(\vec{r})}{N_H(\vec{r})}\int d\vec{s}'\,a'(\vec{r}')F\left(|\vec{r}-\vec{r}'|\right)I_M(\vec{r}') - \mu_H S_H(\vec{r}) \\ + r_H N_H(\vec{r})\left(1 - \frac{N_H(\vec{r})}{\kappa_H(\vec{r})}\right).\end{aligned} \tag{41}$$

All the other equations in system (1) should be similarly modified and, of course, the result is very difficult to integrate. When $a'(\vec{r}')F(|\vec{r}-\vec{r}'|)$ is equal to $a'A\theta(|\vec{r}-\vec{r}'|)$, and the densities are homogeneously distributed in space, we have

$$b\frac{S_H(\vec{r})}{N_H(\vec{r})}\int d\vec{s}'\,a'(\vec{r}')F\left(|\vec{r}-\vec{r}'|\right) = b\frac{S_H}{N_H}I_M\int d\vec{s}'\,a'(\vec{r}')F\left(|\vec{r}-\vec{r}'|\right) = b\frac{S_H}{N_H}I_M a, \tag{42}$$

and Eq. (41) reduces to (40).

The above formalism is necessary when we are dealing with large regions of space, where heterogeneities are significant. However, for small regions, where heterogeneities can be neglected, the system of Eqs. (1) of the main text is a good

approximation. The relative sensitivity of the transmission variables to the studied parameters, however, is not expected to be significantly influenced by spatial heterogeneities. Of course, the value of the transmission variables may vary from place to place but the *relative* sensitivity, the main objective of the present analysis, of these variables to the parameters should be the same.

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