Applied Mathematical Modelling 43 (2017) 566–578

Contents lists available at ScienceDirect

Applied Mathematical Modelling

journal homepage: www.elsevier.com/locate/apm

Understanding epidemics from mathematical models: Details of the 2010 dengue epidemic in Bello (Antioquia, Colombia)

Diana Paola Lizarralde-Bejarano[a,*], Sair Arboleda-Sánchez[b], María Eugenia Puerta-Yepes[a]

[a] Grupo de Análisis Funcional y Aplicaciones, Universidad EAFIT, Carrera 49 No. 7 Sur-50, Medellín 050022, Colombia
[b] Grupo de Biología y Control de Enfermedades Infecciosas—BCEI, Universidad de Antioquia, Calle 70 No. 52-21, Medellín 050010, Colombia

ARTICLE INFO

Article history:
Received 25 September 2015
Revised 21 October 2016
Accepted 10 November 2016
Available online 7 December 2016

Keywords:
Dengue epidemic
Infection force
Mathematical model
Ordinary differential equations
Reproductive basic number

ABSTRACT

Dengue is the most threatening vector-borne viral disease in Colombia. At the moment, there is no treatment or vaccine available for its control or prevention; therefore, the main measure is to exert control over mosquito population. To reduce the economic impact of control measures, it is important to focus on specific characteristics related to local dengue epidemiology at the local level, and know the main factors involved in an epidemic. To this end, we used a mathematical model based on ordinary differential equations and experimental data regarding mosquito populations from Bello (Antioquia, Colombia) to simulate the epidemic occurred in 2010. The results showed that the parameters to which the incidence of dengue cases are most sensitive are the biting and mortality rates of adult mosquitoes as well as the virus transmission probabilities. Finally, we found that the Basic Reproductive Number (R_0) of this epidemic was between 1.5 and 2.7, with an infection force (Λ) of 0.061, meaning that R_0 values slightly above one are sufficient to result in a significant dengue outbreak in this region.

1. Introduction

Dengue is a viral disease transmitted by mosquitoes from Aedes genus, *Ae. aegypti* being its primary vector. Tropical and subtropical regions are the most strongly affected; in these regions, approximately 50–100 million people are infected annually [1]. Dengue can evolve into hemorrhagic fever or dengue shock syndrome, more complex forms of the disease, which can be fatal [2]. A person can become infected with Dengue virus (DENV) more than once because there are four serotypes [3]. Vector control is the predominant strategy for preventing the spread of DENV because there is neither an effective vaccine nor any treatment for the disease [1,4,5]; however, the attempted prevention strategies have shown a limited effect [6]. For this reason, multiple researches in areas such as biology, epidemiology, physics, and others have focused on the dynamics of DENV transmission with the purpose of identifying and understanding the key factors affecting its spread.

From a mathematical perspective, the dynamics of dengue have been studied using both statistical and deterministic methods. Using statistical methods, several authors have attempted to establish correlations between new dengue cases and climatic variables such as temperature, relative humidity, and precipitation; such methods have also been used to pre-

* Corresponding author.
E-mail addresses: paola.lizarralde@gmail.com (D.P. Lizarralde-Bejarano), sair.arboleda@udea.edu.co (S. Arboleda-Sánchez), mpuerta@eafit.edu.co (M.E. Puerta-Yepes).

http://dx.doi.org/10.1016/j.apm.2016.11.022
0307-904X/

dict potential outbreaks in specific areas [7–9]. As an alternative approach, deterministic techniques have been applied to better understand the transmission dynamics of DENV. In this approach, the model formulation process requires the clarification of assumptions, variables, and parameters related to DENV transmission; which have been required for establishing the threshold theorem involving the calculation of the Basic Reproductive Number, R_0 [10]. In most cases, deterministic models have used the ideas underlying the SIR (Susceptible–Infected–Recovered) model formulation developed by Kermack and McKendrick nearly a century ago [11]. The most relevant results for dengue analysis thus far were obtained using theoretical data and compartmental models considering both populations involved in the transmission process (humans and mosquitoes) [12], a variable human population [13], several serotypes [14], and different stages of vector development (egg, larva, and pupa) [15].

No dengue model can be regarded as "universal" because dengue epidemiology exhibits specific features in each region such as climatic factors (temperature, precipitations, relative humidity), human population density, and mosquito bionomic features, among others, [7,16–18]; for this reason, models must be fitted using data from the study region to make them more realistic and, furthermore, must be validated using real data. To this end, we applied a compartmental model including information on both humans and mosquitoes to model the epidemic that occurred in 2010 in Bello (Antioquia), an endemic municipality in Colombia. Most of the data used were obtained from Bello human population and from experimental assays on mosquito population collected in this municipality, allowing the identification of the most important parameters that contributed to the development of the 2010 epidemic and the calculation of important parameters such as R_0 and the infection force, Λ.

2. Materials and methods

2.1. Mathematical model

It is known that Dengue virus has four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4); however, we considered only one of them to build the model because no record of the number of cases produced by each serotype was available for Bello.

We developed a model following the concepts presented in [15]. The difference between the model developed in this study and the model developed in [15] is that we identified and experimentally quantified parameter f, which represents the fraction of female mosquitoes produced by hatching eggs ($0 < f < 1$). This parameter is observable once the mosquitoes have completed their development, and we include it in the equation as representing the number of susceptible mosquitoes, unlike in [19]. This model includes two populations: mosquito population and human population. We used M to denote the size of mosquito population, which can vary over time, and H to denote the size of human population, which is considered to remain constant (birth and death rate equal to μ_h) over the studied time period (one year). The assumption that H is constant was because the average population growth rate in Bello, in a year, is about 1%. For mosquito population, we considered the aquatic immature stages – egg E, larva L, and pupa P – and the adult phase M (females only); the last was divided into three subpopulations, representing susceptible M_s, exposed M_e, and infectious M_i mosquitoes. Analogously, for human population, we considered four subpopulations: susceptible H_s, exposed H_e, infectious H_i, and recovered H_r humans.

In the model, the development of mosquito begins with the number of eggs E at time t, which increases with the per capita oviposition rate $\delta(1-\frac{E}{C})$, where δ is the intrinsic oviposition rate per capita, and C is the carrying capacity of the environment. The number of eggs decreases according to the transition rate from eggs to larvae γ_e and the eggs mortality rate μ_e. The number of larvae L at time t increases with the transition rate from eggs to larvae γ_e and decreases with the transition rate from larvae to pupae γ_l and larvae mortality rate μ_l. Likewise, the number of pupae P at time t increases with the transition rate from larvae to pupae γ_l and decreases with the transition rate from pupae to adults γ_p and the pupae mortality rate μ_p. In this manner, the population of adult mosquitoes, including females and males, increases at rate γ_p. Because DENV transmission involves only female mosquito, we included the parameter f, which represents the fraction of female mosquitoes produced during hatching of all eggs. Thus, the population of susceptible females M_s increases at rate $f\gamma_p$, because we removed the number of males $\gamma_p(1-f)P$ that completed the development cycle.

Dengue transmission begins when a susceptible *Ae. aegypti* female feeds on the blood of an infectious human, thereby becoming an exposed mosquito with a transmission rate $b\beta_m\frac{H_i}{H}$, that depends on (a) the mosquitoes' biting rate, b, which is the average number of bites per mosquito per time unit, (b) the probability of a mosquito becomes infected after biting a human with DENV, β_m, and (c) the proportion of infected humans, H_i/H. The exposed mosquito becomes infectious when the extrinsic incubation period is completed, which occurs at a rate θ_m, where $1/\theta_m$ is the duration of the extrinsic incubation period. Analogously, susceptible humans become exposed humans at a rate $b\beta_h\frac{M_i}{M}$, where β_h is the probability that a person becomes infected after have been bitten by infected mosquito with DENV. When the intrinsic incubation period is complete the exposed human becomes infectious, which occurs at a rate θ_h, where $1/\theta_h$ is the duration of the intrinsic incubation period. Finally, infected humans recover at a rate γ_h, where $1/\gamma_h$ is the duration of the recovery period [13]. Fig. 1 shows all transitions described above.

The model proposed based on these assumptions is given by the following system of differential equations, where the variable t (time) is measured in weeks:

$$\frac{dE}{dt} = \delta\left(1-\frac{E}{C}\right)M - (\gamma_e+\mu_e)E$$

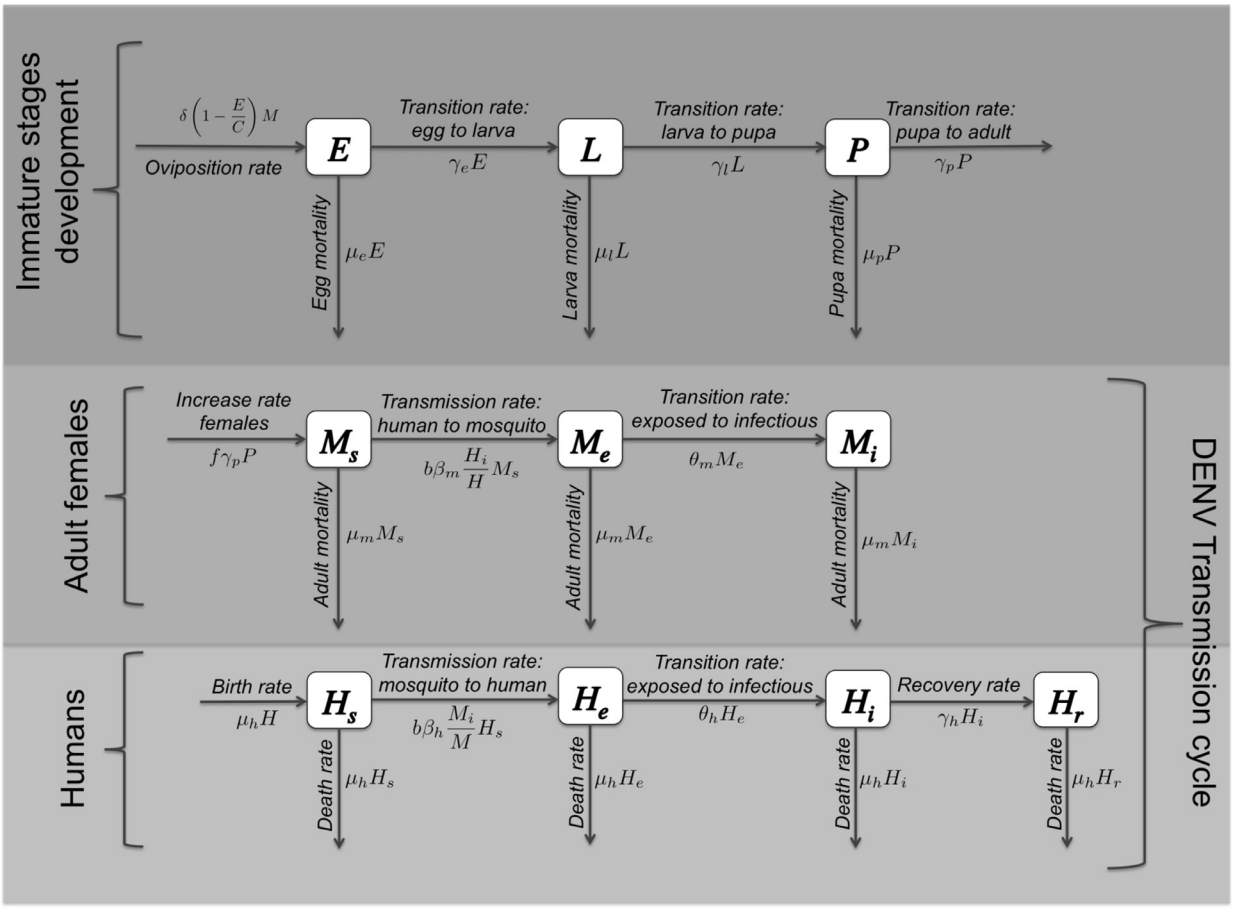

Fig. 1. Dengue transmission model: all stages of vector were included. Flow diagram summarizing the transitions from one compartment to another in the model (1) is shown. It is assumed that the population is divided into immature stages (mosquito), adult females (mosquito) and humans.

$$
\begin{aligned}
\frac{dL}{dt} &= \gamma_e E - (\gamma_l + \mu_l)L \\
\frac{dP}{dt} &= \gamma_l L - (\gamma_p + \mu_p)P \\
\frac{dM_s}{dt} &= f\gamma_p P - b\beta_m \frac{H_i}{H} M_s - \mu_m M_s \\
\frac{dM_e}{dt} &= b\beta_m \frac{H_i}{H} M_s - (\theta_m + \mu_m)M_e \\
\frac{dM_i}{dt} &= \theta_m M_e - \mu_m M_i \\
\frac{dH_s}{dt} &= \mu_h H - b\beta_h \frac{M_i}{M} H_s - \mu_h H_s \\
\frac{dH_e}{dt} &= b\beta_h \frac{M_i}{M} H_s - (\theta_h + \mu_h)H_e \\
\frac{dH_i}{dt} &= \theta_h H_e - (\gamma_h + \mu_h)H_i \\
\frac{dH_r}{dt} &= \gamma_h H_i - \mu_h H_r.
\end{aligned} \tag{1}
$$

The model (1) enables the evaluation of control strategies at any stage of development of mosquito. For the purposes of the present paper, we formulated a less complex model than the model (1) based on the following consideration: for the mosquito population, we consider the larval and pupal stages collectively as the aquatic phase A, which increases with the per capita oviposition rate $\delta(1-\frac{A}{C})$, and decreases according to the transition rate from the aquatic phase to the adult phase

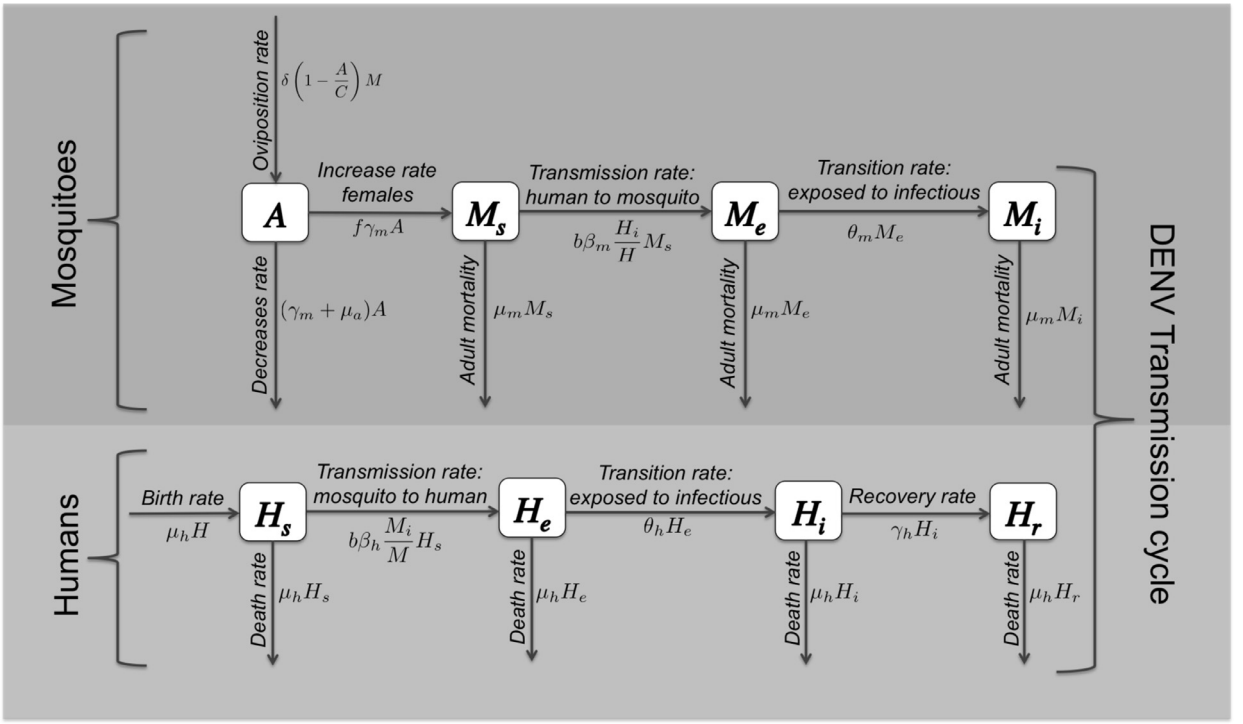

Fig. 2. Dengue transmission model: aquatic phase was grouped in the variable *A*. Flow diagram summarizing the transitions from one compartment to another in the model (2) is shown. It is assumed that the population is divided into aquatic phase *A*, adult females *M* and humans *H*.

γ_m and the mortality rate in the aquatic phase μ_a. For the model (2) we use a similar interpretation as well as the model (1) in relation to equations that corresponds to susceptible, exposed, and infectious mosquitoes; and susceptible, exposed, infectious and recovery humans. The model formulated based on these assumptions is given by the following system of differential equations, where the variable t (time) is measured in weeks:

$$\begin{aligned}
\frac{dA}{dt} &= \delta\left(1-\frac{A}{C}\right)M-(\gamma_m+\mu_a)A\\
\frac{dM_s}{dt} &= f\gamma_m A-b\beta_m\frac{H_i}{H}M_s-\mu_m M_s\\
\frac{dM_e}{dt} &= b\beta_m\frac{H_i}{H}M_s-(\theta_m+\mu_m)M_e\\
\frac{dM_i}{dt} &= \theta_m M_e-\mu_m M_i\\
\frac{dH_s}{dt} &= \mu_h H-b\beta_h\frac{M_i}{M}H_s-\mu_h H_s\\
\frac{dH_e}{dt} &= b\beta_h\frac{M_i}{M}H_s-(\theta_h+\mu_h)H_e\\
\frac{dH_i}{dt} &= \theta_h H_e-(\gamma_h+\mu_h)H_i\\
\frac{dH_r}{dt} &= \gamma_h H_i-\mu_h H_r
\end{aligned} \tag{2}$$

with $H=H_s+H_e+H_i+H_r$. The first four equations correspond to the mosquito dynamics, and the last four correspond to the human dynamics. The Fig. 2 summarizes the model formulated (2).

Since the objective of this work is to simulate and explain the epidemic occurred in Bello in 2010, initially we implemented the endemic channel following methodology presented in [20] in order to determine the beginning and ending of the epidemic (see Fig. 3).

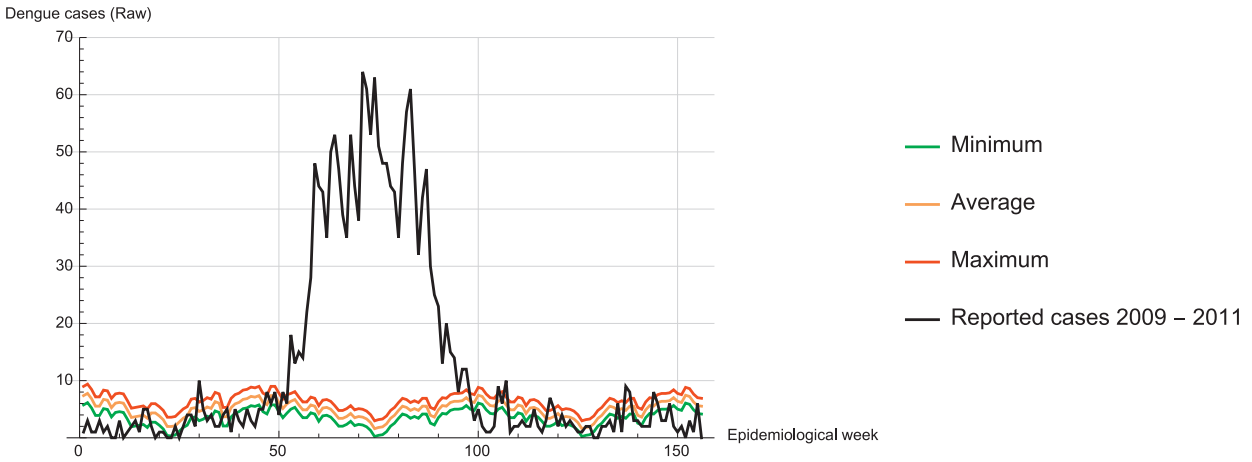

Fig. 3. Endemic channel showing dengue epidemic occurred in Bello in 2010. The region below the green line represents the *endemic area* or *success zone*. The region between the green and orange lines represents the *safety zone*. The region between the orange and red lines represents the *alarm zone*. Finally, the region above the red line represents the *epidemic zone*. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2. Parameter estimation: experimental and non-experimental approaches

2.2.1. Experimental assays

By performing experimental assays under laboratory conditions, we estimated the following entomological parameters: the transition rate from the aquatic phase to the adult phase γ_m, the mortality rates of the aquatic and adult phases (μ_a and μ_m, respectively), and the per capita oviposition rate δ. Immature stages from the mosquito were collected in natural breeding sites located in Bello municipality, and then we reared in the laboratory at 27 ± 1°C, 70 – 80% of relative humidity, and a day length of 12 h. Eggs from fifth generation (F5) were submerged in dechlorinated water; then, larvae emerged were counted. Afterwards, ecdysis was recorded and counted daily at a set time (8:00 a.m.) to determine the mean developmental period of each larval and pupal stage. The survival rate was expressed as the percentage of individuals that reached the next instar. The mean time for larval and pupal development, and the sex ratio of the emerged adults were also estimated [21].

Emerged adults were introduced into plastic cages (with a capacity of 500 cm^3 each) and provided with a 10% sucrose solution and a damp substrate for laying eggs. Six days post-emergence, females were fed on chicken blood, and they were fed twice per week. Eggs were collected once per week, allowing two days for embryonic development prior to dry storage under laboratory conditions mentioned above. Daily observations of adult survivorship and fecundity were recorded to determine the longevity and reproductive parameters of the mosquito population. Daily fecundity was expressed as the number of eggs laid per female per day.

2.2.2. Carrying capacity

To determine the carrying capacity of the system, we used entomological information collected by officials from Dirección Local de Salud de Bello (DLSB), who performed a vector surveillance survey every three months. DLSB officials randomly visited houses to examine water containers and to evaluate and eliminate possible mosquito breeding sites, in accordance with WHO guidelines [22]. They also visited the houses of patients with dengue fever to eliminate breeding sites, and perform spraying campaigns during epidemics. These activities spanned the entire municipality.

We estimated the parameter C using *Ae. aegypti* breeding sites reported during 2010 in all Bello neighborhoods. We designated a house as the basic sampling unit. The house was determined *"positive"* if, during systematic searches, officials found water containers with larvae, pupae, or exuviae. House addresses sampled in 2010 were tabulated, and geographic coordinates were assigned using the Google Earth software (2013). A total of 4344 houses were visited and sampled for *Ae. aegypti* immature stages. From such houses, approximately 170 were found to be positive for mosquitoes breeding, and 80% could be georeferenced satisfactorily ($\pm$20 m of precision). The parameter ranges are summarized in Table 1.

2.2.3. Non-experimental approaches

Values for the intrinsic incubation period, extrinsic incubation period, and recovery rate were taken from the literature [23] because such data have been broadly analyzed in several studies and these are similar among several populations (Table 1). Other parameters, such as the probability of DENV transmission from mosquito to human and from human to mosquito, were not possible to estimate experimentally because of evident ethical implications. However, in the section *Results*, we present a relationship between this probabilities since mathematical model, which let us define some possible ranges with biological sense. Ranges for these parameters are summarized in the Table 1.

Table 1
The parameters used in the model, their biological descriptions, and their ranges of values.

Parameter	Meaning	Possible values per day	Possible values per week
b	Biting rate	[0, 1]	[0, 4]
δ	Per capita oviposition rate	[8, 24]	[55, 165]
γ_m	Transition rate from the aquatic phase to the adult phase	[0.125, 0.2]	[0.875, 1.4]
μ_a	Mortality rate in the aquatic phase	[0.001, 0.5]	[0.007, 0.3]
μ_m	Mortality rate in the adult phase	[0.008, 0.03]	[0.06, 0.20]
f	Fraction of female mosquitoes hatched from all eggs	[0.42, 0.55]	[0.42, 0.55]
C	Carrying capacity of the environment	[6400, 95, 000]	[6400, 95, 000]
μ_h	Birth and death rate of the human population	0.00006	0.0004
β_h	Transmission probability from mosquito to human	[0, 1]	[0, 1]
β_m	Transmission probability from mosquito to human	[0, 1]	[0, 1]
θ_m	Transition rate from exposed to infectious mosquitoes	[0.08, 0.13]	[0.58, 0.88]
θ_h	Transition rate from exposed to infectious humans	[0.1, 0.25]	[0.7, 1.75]
γ_h	Recovery rate	[0.07, 0.25]	[0.5, 1.75]

Table 2
The initial conditions used in the model, their descriptions, and their ranges of values.

Initial condition	Meaning	Range
$A(0)$	Initial condition for the aquatic phase	[5755, 17, 265]
$M_s(0)$	Initial condition for susceptible mosquitoes	[0, 1, 200, 000]
$M_e(0)$	Initial condition for exposed mosquitoes	[0, 100]
$M_i(0)$	Initial condition for infectious mosquitoes	[0, 100]
$H_s(0)$	Initial condition for susceptible humans	[244, 402, 321, 734]
$H_e(0)$	Initial condition for exposed humans	[18, 72]
$H_i(0)$	Initial condition for infectious humans	[6, 24]
$H_r(0)$	Initial condition for recovered humans	[81, 405, 158, 809]

2.3. Initial conditions

We established the following initial conditions for the model defined in (2). For the total human population, we used a size of 403,235, as recorded for the urban area of Bello (Antioquia) in 2010 (DANE 2010). Size of the susceptible human population at the beginning of the epidemic was estimated between 244, 402 and 321, 734, based on the risk map developed for Bello by Arboleda and Peterson [17], in which the probability of infection was 0.3 in 2008 and 2009, with a standard deviation of 0.096. For the infectious human population, we considered, as the initial condition, the number of cases reported at the beginning of the epidemic. In this survey, the epidemic began in the epidemiological weeks 51 of 2009 where there were six reported cases in Bello municipality. Because of under-reporting concerns, which can affect up to 75% of the total number of cases occurring anywhere DENV transmission is present [24], we assumed that the initial number of infectious human individuals should lie in the range of 6–24.

According to WHO, the symptoms of dengue appear between four and ten days after the mosquito infectious bite; therefore, we considered that at the beginning of epidemic, the number of exposed humans should be equal to the number of reported cases in the second epidemic week. In Bello' case, this criterion yielded a value of 18 exposed humans. Furthermore, to take into account again the under-reporting issue, we concluded that the initial condition for the number of exposed humans should be between 18 and 72 people. Given that Bello is endemic for dengue, we cannot consider the total human population as susceptible, due to part of them has been developed permanent or partial immunity to DENV at the time of the survey. For that reason, we considered that at the beginning of the epidemic, the number of immune people was between 81,405 and 158,809.

Regarding to initial condition of the mosquito population in the aquatic phase, we assumed a range of 5755 to 17,265 individuals according with the sample collected by DLSB and DANE information about population, we deduced that 5755 to be positive breeding sites with one or three individuals per hatchery. For adult population, we assumed three susceptible mosquitoes per person based on entomological findings for Bello [16] . Exposed and infectious mosquitoes were both considered to be equal to the maximum total number of exposed and infectious humans at beginning of the epidemic, in this case, 96. This assumption was adopted because of the unavailability of more specific information. We considered a range of values from zero to 100 to be a conservative estimate. Ranges for initial conditions of Bello are summarized in Table 2.

Finally, for some initial conditions and non experimental parameters, we used the real data to estimate its values, considering our own ranges, in accordance with characteristics of Bello municipality (see Tables 1 and 2).

2.4. Basic reproductive number R_0: approaching its calculation from two perspectives

The value of R_0 can be interpreted as the average number of secondary cases that a single case can produce if it is introduced into a susceptible population. This number provides information regarding whether an epidemic will occur [25].

For DENV transmission, there are two different populations involved in the transmission process; thus, for individuals to become infected, interaction between these two populations is required.

Henceforth, we considered both the mosquito population and human population constant. With respect to the mosquito population, we can observe from the model (2) an asymptotic behavior over time toward the carrying capacity of the environment, i.e. the mosquito population tends to a constant value when t tends to infinity. The human population can be assumed constant in this work because the growth rate is about 1% per year, which is not significantly large in the period of time analyzed (one year).

Human population satisfied that $H = H_s + H_e + H_i + H_r$, which implies that $H_r = H - H_s - H_e - H_i$, thus the equation for recovery humans H_r can be eliminated. Then, we have the following system:

$$\begin{aligned}
\frac{dA}{dt} &= \delta\left(1 - \frac{A}{C}\right)M - (\gamma_m + \mu_a)A \\
\frac{dM_s}{dt} &= f\gamma_m A - b\beta_m \frac{H_i}{H} M_s - \mu_m M_s \\
\frac{dM_e}{dt} &= b\beta_m \frac{H_i}{H} M_s - (\theta_m + \mu_m)M_e \\
\frac{dM_i}{dt} &= \theta_m M_e - \mu_m M_i \\
\frac{dH_s}{dt} &= \mu_h H - b\beta_h \frac{M_i}{M} H_s - \mu_h H_s \\
\frac{dH_e}{dt} &= b\beta_h \frac{M_i}{M} H_s - (\theta_h + \mu_h)H_e \\
\frac{dH_i}{dt} &= \theta_h H_e - (\gamma_h + \mu_h)H_i.
\end{aligned} \tag{3}$$

The equilibrium points of system (3) are given by the constant solutions of the algebraic system obtained by equating the derivatives to zero:

$$\begin{aligned}
\delta\left(1 - \frac{A}{C}\right)M - (\gamma_m + \mu_a)A &= 0 \\
f\gamma_m A - b\beta_m \frac{H_i}{H} M_s - \mu_m M_s &= 0 \\
b\beta_m \frac{H_i}{H} M_s - (\theta_m + \mu_m)M_e &= 0 \\
\theta_m M_e - \mu_m M_i &= 0 \\
\mu_h H - b\beta_h \frac{M_i}{M} H_s - \mu_h H_s &= 0 \\
b\beta_h \frac{M_i}{M} H_s - (\theta_h + \mu_h)H_e &= 0 \\
\theta_h H_e - (\gamma_h + \mu_h)H_i &= 0.
\end{aligned} \tag{4}$$

To find these solutions, we write all possible variables in terms of exposed mosquitoes, M_e, the parameters of the model, $D = (b\beta_h\theta_m M_e + \mu_h\mu_m M)$ and $K = (\gamma_h + \mu_h)(\theta_h + \mu_h)$:

$$\begin{aligned}
A &= \frac{CM\delta}{\delta M + C(\gamma_m + \mu_a)} \\
M_s &= \frac{CMDKf\delta\gamma_m}{(\delta M + C(\gamma_m + \mu_a))[b^2\beta_m\beta_h\theta_h\theta_m\mu_h M_e + DK\mu_m]} \\
M_i &= \frac{\theta_m}{\mu_m} M_e \\
H_s &= \frac{\mu_m\mu_h HM}{D} \\
H_e &= \frac{b\beta_h\mu_h\theta_m HM_e}{D(\theta_h + \mu_h)} \\
H_i &= \frac{b\beta_h\mu_h\theta_h\theta_m HM_e}{DK}
\end{aligned} \tag{5}$$

with either $M_e = 0$ or

$$M_e = \frac{MCfb^2\delta\gamma_m\beta_m\beta_h\theta_h\theta_m\mu_h - MK(\delta M + C(\gamma_m + \mu_a))(\theta_m + \mu_m)\mu_h\mu_m^2}{b\beta_h\theta_m(\delta M + C(\gamma_m + \mu_a))(\theta_m + \mu_m)[b\beta_m\theta_h\mu_h + K\mu_m]}. \tag{6}$$

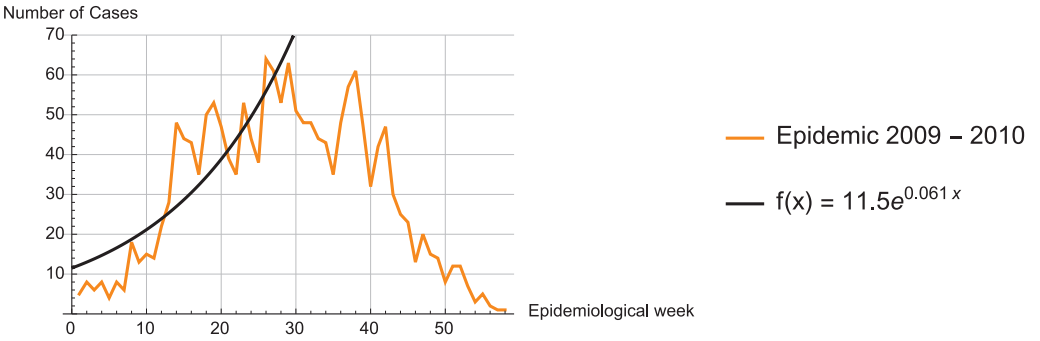

Fig. 4. Exponential growth of dengue cases occurred in Bello in 2010. The orange line shows the number of cases reported during the epidemic of 2009–2010. The black line represents a function that estimates the exponential growth during the early stage of the epidemic (with a correlation coefficient of $R^2 = 0.93$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

If $Me = 0$, then the equilibrium point is

$$P_0 = (A^*, M_s^*, M_e^*, M_i^*, H_s^*, H_e^*, H_i^*) = \left(\frac{\delta MC}{\delta M + C(\gamma_m + \mu_a)}, \frac{f\gamma_m}{\mu_m} A^*, 0, 0, H, 0, 0 \right),$$

where if $M = 0$ (the mosquito population is zero), then the equilibrium point is (0, 0, 0, 0, H, 0, 0), and if $M > 0$, then the equilibrium point is $(A^*, \frac{f\gamma_m}{\mu_m} A^*, 0, 0, H, 0, 0)$. In both cases, these points are termed *disease-free equilibria* because there are no exposed or infectious mosquitoes; then the entire population is susceptible.

When $M_e \neq 0$, there is another equilibrium point, $P_1 = (A, M_s, M_e, M_i, H_s, H_e, H_i)$, where M_e is defined in (6) and the remaining variables are defined in (5). For P_1 to be biologically meaningful, all of its coordinates must be larger than zero, and this will be true if and only if $M_e > 0$.

Then, we can write (6) in terms of R_0:

$$M_e = \frac{MCf\delta\gamma_m}{(\delta M + C(\gamma_m + \mu_a))} \cdot \frac{b\beta_m\theta_h\mu_h}{(\theta_m + \mu_m)[b\beta_m\theta_h\mu_h + K\mu_m]} \cdot \frac{R_0 - 1}{R_0}, \tag{7}$$

where

$$R_0 = \frac{b^2\beta_m\beta_h\theta_h\theta_m}{(\theta_m + \mu_m)(\gamma_h + \mu_h)(\theta_h + \mu_h)\mu_m} \cdot \frac{M_s^*}{M}. \tag{8}$$

Therefore, the point of endemic equilibrium, $P_1 = (A, M_s, M_e, M_i, H_s, H_e, H_i)$, exists when $R_0 > 1$. The last coordinate of this point, H_i, which corresponds to the number of infectious humans (5), indicates that the number of cases that may occur after the epidemic has ended without posing a risk to public health. In Bello's case, the values obtained for H_i, from expression in (5), and from ranges established to model parameters (Table 1), ranging between 5 and 20 cases.

As an alternative approach, based on [26,27], we assume that at the beginning of the epidemic, the number of individuals infected with DENV varied exponentially as $H_i \sim H_{i_0} \exp(\Lambda t)$, where Λ represents the infection force. In addition, if we suppose that the numbers of exposed humans and exposed or infectious mosquitoes also followed an exponential trend, we can rewrite R_0 as follows:

$$R_0(\Lambda) = \left(\frac{\Lambda}{\theta_m + \mu_m} + 1 \right) \left(\frac{\Lambda}{\mu_m} + 1 \right) \left(\frac{\Lambda}{\theta_h + \mu_h} + 1 \right) \left(\frac{\Lambda}{\gamma_h + \mu_h} + 1 \right). \tag{9}$$

We calculated the epidemic infection force, Λ, using the reported dengue cases by (DLSB) that occurred from epidemiological weeks 46 in 2009 to weeks 51 in 2010, which showed exponential growth between weeks 1 and 29 in 2010. The mathematical procedures were implemented in the *Mathematica* software suite using the *NonlinearModelFit* method (see Fig. 4).

If we consider that the under-reporting has the same distribution of reported dengue cases, the only change is a vertical displacement of the prevalence curve shape; therefore, the infection force is the same in both scenarios. On the other hand, if under-reporting cases have a different distribution than reported dengue cases, we can not guarantee the same behavior of the infection force.

3. Results

3.1. Size of the epidemic

The upper and lower confidence intervals calculated from the endemic channel indicate that the epidemic began in epidemiological weeks 51 in 2009 and ended in epidemiological weeks 50 in 2010; therefore, this epidemic lasted 52 weeks.

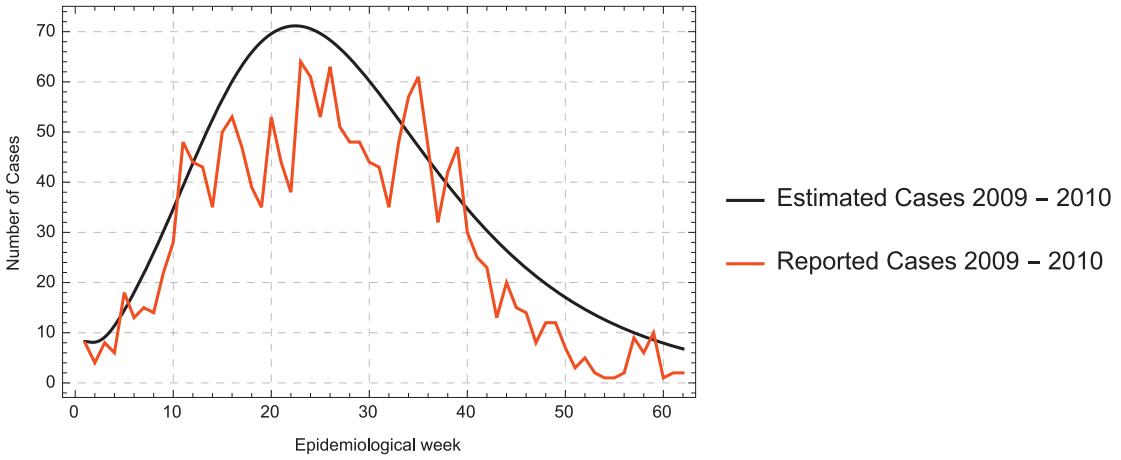

Fig. 5. The model fitted to the real biological data. The red line is the reported cases for the dengue epidemic occurred in Bello in 2010. The black line is the model fit to the real data using the parameter values: $\delta = 65$, $\gamma_m = 0.9$, $\mu_a = 0.13$, $b = 4$, $\mu_m = 0.12$, $\theta_m = 0.6$, $f = 0.5$, $\theta_h = 0.7$, $C = 10{,}000$, $\gamma_h = 1$, $\beta_m = 0.6$, $\beta_h = 0.15$, and $\mu_h = 0.0004$, and the initial conditions $A(0) = 9000$, $M_s(0) = 1{,}199{,}950$, $M_e(0) = 40$, $M_i(0) = 10$, $H_s(0) = 321{,}710$, $H_e(0) = 18$, $H_i(0) = 6$, and $H_r(0) = 81{,}501$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The model defined in (2) is capable of successfully simulating the dengue epidemic that occurred in Bello in 2010 based on biologically significant parameters (see Fig. 5).

3.2. Values and behavior of biological parameters in relationship with the mosquito population of Bello

Mosquitoes from Bello were found to have a hatching rate of between 8 and 24 eggs per day. The fraction of female mosquitoes hatched from all eggs was between 0.42 and 0.55. The transition rate from the aquatic phase to the adult phase was between 0.125 and 0.2. The mortality rate in the aquatic phase was between 0.001 and 0.5, and the mortality rate in the adult phase was between 0.008 and 0.03. All of these parameters were measured per day (Table 1). Additionally, from the maximum risk curve shown in the endemic channel (Fig. 3) as a reference point for determining the beginning of the epidemic, we testing each of the parameters consider in the model (2) to intuit which of them have more influence in the occurrence of new dengue cases, through the model simulations. According to this, we found that the occurrence of new dengue cases in Bello was more sensitive to: the transmission probabilities from human to mosquito and from mosquito to human, β_m and β_h; the biting rate, b; and the mortality rate in the adult phase, μ_m, than to the other parameters over a short period of time; variations of ± 0.25 in the biting rate, ± 0.01 in the mortality rate in the adult phase, and ± 0.05 in the transmission probabilities were sufficient to increase the number of cases above the maximum risk curve in the endemic channel (see Fig. 6). As we mentioned above, this small changes in these parameters may account for the occurrence of an epidemic. Other parameters, such as the oviposition rate, the mortality rate in the aquatic phase, and the fraction of female mosquitoes hatched from all eggs did not demonstrate a significant influence on the number of dengue cases.

Since mathematical tools, we evaluate the sensibility of this parameters by calculating the derivative of the basic reproduction number, R_0, with respect to each one. We observe from expression (8) that:

$$\frac{\partial R_0}{\partial \beta_m} = \frac{1}{\beta_m} R_0, \quad \frac{\partial R_0}{\partial \beta_h} = \frac{1}{\beta_h} R_0, \quad \frac{\partial R_0}{\partial b} = \frac{2}{b} R_0,$$

$$\frac{\partial R_0}{\partial \theta_m} = \frac{\mu_m}{(\theta_m + \mu_m)} R_0, \quad \text{and} \quad \frac{\partial R_0}{\partial \theta_h} = \frac{\mu_h}{(\theta_h + \mu_h)} R_0$$

all these partial derivatives always are positive, i.e. that the parameters β_m, β_h, b, θ_m, and θ_h increase the value of R_0. From ranges considered for each parameter b, θ_m, θ_h, μ_m and μ_h (see Table 1) we have:

$$\frac{\mu_h}{(\theta_h + \mu_h)} < \frac{\mu_m}{(\theta_m + \mu_m)} < \frac{2}{b}.$$

This means that a small change in the biting rate, b, affects more the behavior of R_0 than small change in the transition rate from exposed to infectious mosquitoes, θ_m, and the transition rate from exposed to infectious humans, θ_h as well. If β_m and β_h belong to the interval [0.1, 1], and the biting rate b, satisfied that $b \geq 2$, then we have:

$$\frac{2}{b} \leq \frac{1}{\beta_m} \leq \frac{1}{\beta_h},$$

i.e., a small change in transmission probabilities affects more the behavior of R_0 than a small change in the biting rate. Otherwise, we cannot say which parameter (b, β_m, and β_h) affects more the value of R_0.

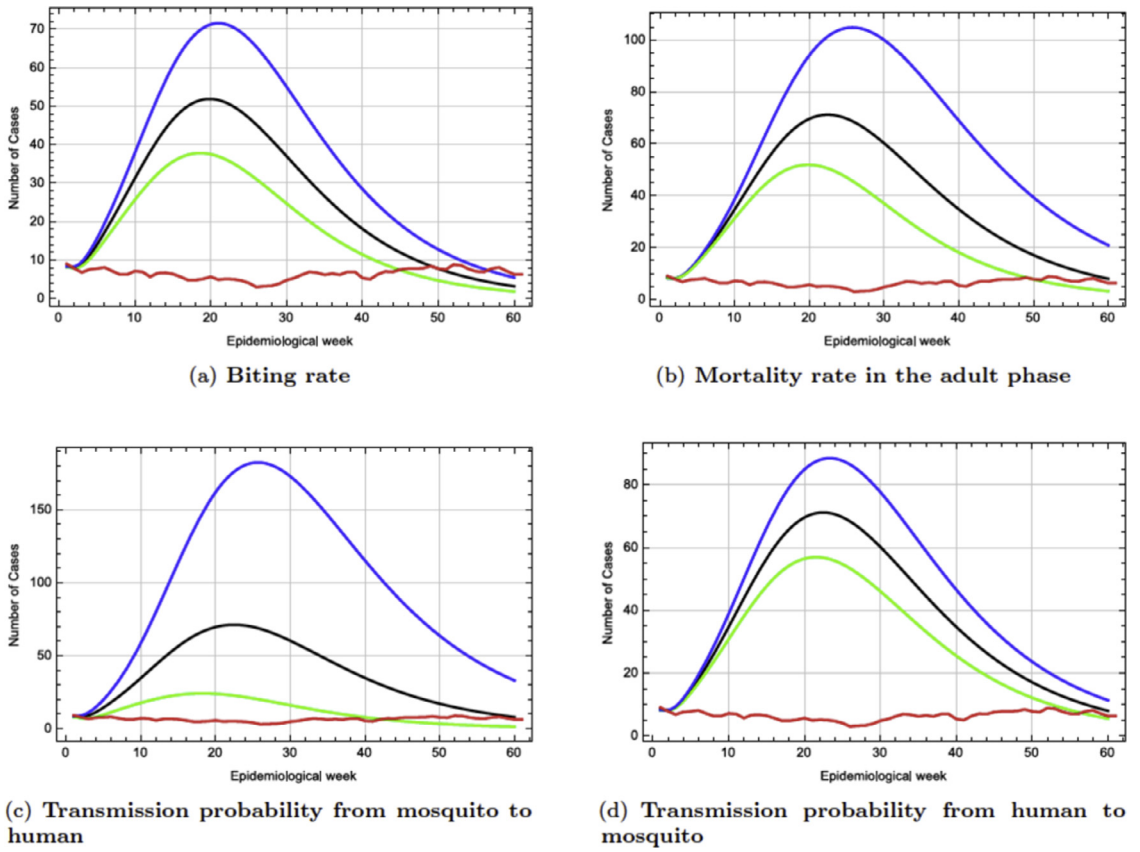

Fig. 6. Changes in the modeled prevalence curve when small changes occur in some parameters. Three different combinations of parameters are shown to evidence that small changes in these cause important changes in the prevalence curve that were modeled. In (a) it is shown a comparison between the maximum risk curve (red line) and the curve obtained by the model simulations when varying the *biting rate* in ± 0.25, (blue line, $b = 4.25$; black line, $b = 4$; green line, $b = 3.75$). (b) show a comparison between the maximum risk curve (red line) and the curve obtained by the model simulations when varying the *mortality rate in the adult phase* in ± 0.01, (blue line, $\mu_m = 0.11$; black line, $\mu_m = 0.12$; green line, $\mu_m = 0.13$). (c) show a comparison between the maximum risk curve (red line) and the curve obtained by the model simulations when varying the *transmission probability from mosquito to human* in ± 0.05, (blue line, $\beta_h = 0.20$; black line, $\beta_h = 0.15$; green line, $\beta_h = 0.10$). (d) show a comparison between the maximum risk curve (red line) and the curve obtained by the model simulations when varying the *transmission probability from human to mosquito* in ± 0.05, (blue line, $\beta_m = 0.65$; black line, $\beta_m = 0.6$; green line, $\beta_m = 0.55$). For all simulations, the other model parameters and initial conditions were set as follow: $\delta = 65$, $\gamma_m = 0.9$, $\mu_a = 0.13$, $\theta_m = 0.6$, $f = 0.5$, $\theta_h = 0.7$, $C = 10{,}000$, $\gamma_h = 1$, $\mu_h = 0.0004$, $A(0) = 9000$, $M_s(0) = 1{,}199{,}950$, $M_e(0) = 40$, $M_i(0) = 10$, $H_s(0) = 321{,}710$, $H_e(0) = 18$, $H_i(0) = 6$, and $H_r(0) = 81{,}501$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

For the others parameters, μ_m and γ_h, we have:

$$\frac{\partial R_0}{\partial \mu_m} = -\frac{1}{(\theta_m + \mu_m)}\left(2 + \frac{\theta_m}{\mu_m}\right)R_0 \quad \text{and} \quad \frac{\partial R_0}{\partial \gamma_h} = -\frac{1}{(\gamma_h + \mu_h)}R_0.$$

These partial derivatives always are negative, thus the parameters μ_m and γ_h decrease the value of R_0. Moreover, we observe that from ranges considered for each these parameters:

$$\frac{1}{(\gamma_h + \mu_h)} < \frac{1}{(\theta_m + \mu_m)}\left(2 + \frac{\theta_m}{\mu_m}\right),$$

i.e., that R_0 is more sensitive to small changes in mortality rate in the adult phase, μ_m, than small changes in recovery rate γ_h.

3.3. Initial conditions of the model

The initial conditions for susceptible, exposed and infectious mosquito populations (1,199,950, 40 and 10, respectively) and initial conditions for susceptible, exposed and infectious human populations (321,710, 18, and 6, respectively) were all relevant when fitting the model (Fig. 7).

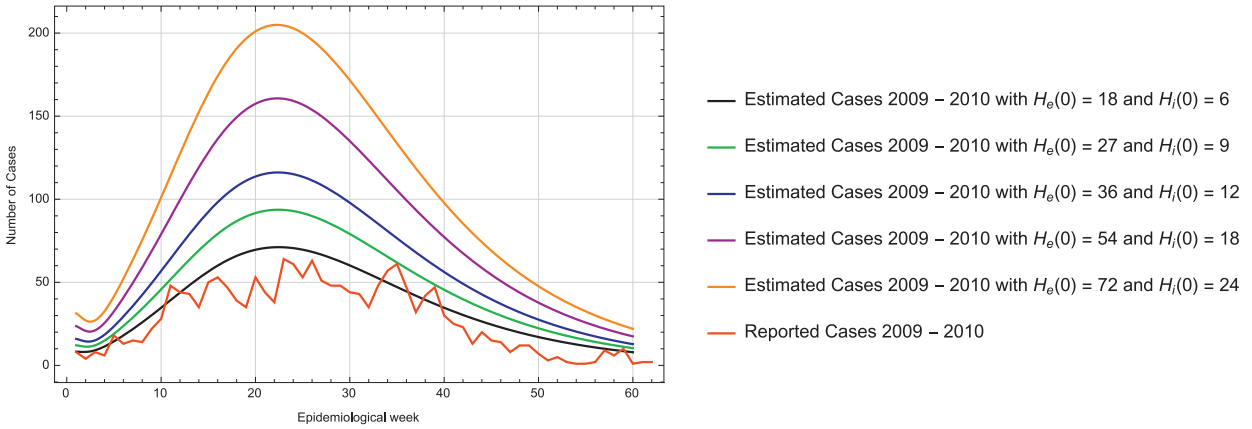

Fig. 7. Changes in prevalence curve when taking into account the under-reporting. The red line is the reported cases for the dengue epidemic occurred in Bello in 2010. The black line is the model fit to the real data. The green line shows an increase of 50% in the initial conditions of exposed and infectious humans. The blue line shows an increase of 100% in the initial conditions of exposed and infectious. The purple line shows an increase of 200% in the initial conditions of exposed and infectious humans. The orange line shows an increase of 300% in the initial conditions of exposed and infectious humans. For all simulations the parameters and initial conditions used in the model were: $\delta = 65$, $\gamma_m = 0.9$, $\mu_a = 0.13$, $b = 4$, $\mu_m = 0.12$, $\theta_m = 0.6$, $f = 0.5$, $\theta_h = 0.7$, $C = 10{,}000$, $\gamma_h = 1$, $\beta_m = 0.6$, $\beta_h = 0.15$, $\mu_h = 0.0004$, $A(0) = 9000$, $M_s(0) = 1{,}199{,}950$, $M_e(0) = 40$, $M_i(0) = 10$, $H_s(0) = 321{,}710$, and $H_r(0) = 81{,}501$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.4. Basic reproductive number and infection force

The R_0 value for Bello was found to range between 1.5 and 2.7, indicating that each reported case of dengue was able to produce more than one new case, as evidenced by the exponential growth observed between weeks 1 and 29 in 2010. The infection force was $\Lambda = 0.061$, that refers to rate (exponential) at which new infections of DENV are produced.

3.5. Other relationships between parameters

We identified an inverse relationship between the probabilities β_m and β_h, which was inferred from mathematical and biological considerations. From the mathematical point of view was inferred equating the two expressions obtained for R_0, (8) and (9):

$$R_0(\Lambda) \cdot \frac{\mu_m(\gamma_h + \mu_h)(\theta_h + \mu_h)(\theta_m + \mu_m)}{b^2\theta_m\theta_h} = \beta_m\beta_h k,$$

where $k = \frac{M_s^*}{M}$. From a biological point of view it must meet that $k \leq 1$, otherwise have been more susceptible mosquitoes than the total population. Thus β_h must meet the following restriction:

$$R_0(\Lambda) \cdot \frac{\mu_m(\gamma_h + \mu_h)(\theta_h + \mu_h)(\theta_m + \mu_m)}{b^2\theta_m\theta_h\beta_m} \geq \beta_h.$$

Based on this information, we can estimate appropriate values of these probabilities in order to fit the model for dengue epidemic occurred in Bello in 2010.

4. Discussion

We developed a model for the dengue epidemic occurred in 2010 in Bello based on ordinary differential equations, which were fit to local biological data. This is the first work in which an experimental assay has been designed to obtain real data regarding to the local mosquito population to better fit the applied model. Several mathematical models have previously been developed, taking into account several considerations such as a variable human population [13], effects of vector control on dengue transmission [15], and the existence of multiple serotypes [14]; a more detailed review is provided in [28]. However, despite the good fitting results obtained with these models, all of them used data from the literature. Although it may be mathematically possible to fit a model to reality using different (arbitrary) parameter values, this does not imply that the parameters used have any real meaning for the reality that they are attempting to simulate. In fact, when data from the Bello epidemic were used to run the various models from the literature, [12,28-30], none of them performed well, for this reason, we consider that it is very important to use local parameters relevant to the study area. Finally, it was necessary to fit the models using the local data from the municipality.

The *Ae. aegypti* populations from Bello have biological parameters that differ from those of other locations, and these differences can affect the model results. In this case, we observed differences in several of the parameters from Bello with respect to the parameters used to build the models used for Salvador (Brazil) [31]; the mortality rate in the adult phase, μ_m

was lower in the Bello mosquitoes, the transition rate from the aquatic phase to the adult phase, γ_m was higher in the Bello mosquitoes, the oviposition rate and the mortality rate in the aquatic phase had larger ranges for the Bello mosquitoes, and the range of the fraction of female mosquitoes hatched from all eggs f, was lower for the Bello mosquitoes. It is evident that the ranges of these parameters used in the previous models are incompatible with the parameter values for Bello (see Table 1).

We determined realistic initial conditions for the studied epidemic based on the information available for the municipality. These values are important for identifying the initial state of development of an epidemic; indeed, this model is very sensitive to the initial conditions. For other compartmental models, hypothetical initial conditions are considered for the fitting of a model to a real epidemic of interest, but the results of these models are not realistic compared with the true characteristics of epidemics in the studied cities [32,33].

An important value for epidemic characterization is R_0. In Bello, the dengue epidemic in 2010 had an R_0 value of 1.5–2.7, which seems low compared with values for other epidemics that occurred in cities such as Salvador (Brazil) in 1995–1996, where R_0 was between 2.77 and 3.7, and in 2002, where R_0 was between 2.5 and 3.3. However, in Bello, this value was sufficient to produce the worst epidemic ever recorded in this location. For this reason, it is necessary to estimate other important parameters of the local dengue epidemiology, such as vector competence, which can be specific to each endemic zone [34].

To mathematically characterize the occurrence of the dengue epidemic in Bello in 2010, we used two methodologies: the endemic channel and the R_0 value. Using the endemic channel, we were able to detect atypical behavior of dengue cases occurrence, which allowed identify the initial conditions for the exposed and infectious human populations. This methodology is generally employed by health authorities for risk detection. The second methodology consisted of calculating R_0 via two methods: (a) analysis of the equilibrium points of (2) to determine when the coordinate of the endemic equilibrium point P_1 corresponding to the number of exposed mosquitoes became greater than zero (8) and (b) calculation of the infection force, (which can be interpreted as the rate (exponential) at which new infectious of DENV are produced). The equilibrium points define zones in the parameter space with epidemiological meaning, which, in turn, define values to which all trajectories could converge [35]; from the endemic point P_1, we found that the number of cases that could safely occur after the conclusion of an epidemic oscillates between 5 and 20, which is consistent with the results of the endemic channel built for Bello. This important value has not been calculated in previous works in which mathematical models have been used to describe dengue epidemics. The infection force can be used to calculate R_0 from real data, and it is a measure of the rate of increase of an epidemic. For the Bello epidemic, a value of $\Lambda = 0.061$ was found, which is relatively low compared with other epidemics around the world [26,31]. This value indicates, in some sense, the severity of an epidemic and could help to identify the main parameters involved in such an event, with the purpose of mitigating them to prevent future epidemics.

The probabilities of dengue transmission (human to mosquito and mosquito to human) were assumed to be constant and equal; however, we found an expression that allowed us to determine the values of the probabilities of transmission from human to mosquito, β_m and from mosquito to human, β_h in terms of the ratio of the susceptible mosquito population to the entire mosquito population. Although these parameters cannot be experimentally determined for ethical reasons, this expression allows them to be calculated, in any research study, such that they have biological meaning with respect to the particular epidemiological situation of the area of interest based on the local vector competence and capacity, the genetics of the serotypes in circulation, and the genetic background of the human population.

Despite the fact that four dengue serotypes could be circulating in Bello in 2010 [36], we could not account for the effects of these multiple serotypes because the data provided by the relevant entities are not classified according to serotype and are missing information. This absence of information also makes it possible to incorrectly evaluate the size of the susceptible human population during the epidemic, because an infection by any dengue serotype results in permanent immunity to that serotype but appears to provide only temporary cross-immunity to the other serotypes [23]. Thus, it is necessary to improve the manner in which the relevant information is collected to allow these considerations to be included in the model and improve its ability to represent reality.

In summary, our model represents a pioneering effort to produce an epidemic model with biological meaning; however, it will also be necessary to consider other specific parameters to improve the accuracy of the model, implement the model in other eco-epidemiological scenarios using the proper biological information, and translate it into an endemic model with predictive power that can to help to prevent cases of dengue infection and diminish the impact of the virus on human populations.

Acknowledgments

Funding for the research was provided jointly by Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología Francisco José de Caldas, COLCIENCIAS, Universidad EAFIT and Universidad de Antioquia (Project: 111556933531). We give special thanks to Dr. Lourdes Esteva from UNAM (Universidad Autónoma de México) for providing valuable contributions and knowledge on this subject.

References

[1] S.S. Whitehead, J.E. Blaney, A.P. Durbin, B.R. Murphy, Prospects for a dengue virus vaccine, Nat. Rev. Microbiol. 5 (7) (2007) 518–528.
[2] K. Clyde, J.L. Kyle, E. Harris, Recent advances in deciphering viral and host determinants of dengue virus replication and pathogenesis, J. Virol. 80 (23) (2006) 11418–11431.

[3] J.G. Rigau-Pérez, Severe dengue: the need for new case definitions, Lancet Infect. Dis. 6 (5) (2006) 297–302.
[4] D.J. Gubler, Dengue and dengue hemorrhagic fever, Clin. Microbiol. Rev. 11 (3) (1998) 480–496.
[5] R.-f. Qi, L. Zhang, C.-w. Chi, Biological characteristics of dengue virus and potential targets for drug design, Acta Biochim. Biophys. Sin. 40 (2) (2008) 91–101.
[6] J.L. Kyle, E. Harris, Global spread and persistence of dengue, Ann. Rev. Microbiol. 62 (2008) 71–92.
[7] S. Banu, W. Hu, C. Hurst, S. Tong, Dengue transmission in the asia-pacific region: impact of climate change and socio-environmental factors, Trop. Med. Int. Health 16 (5) (2011) 598–607.
[8] M.A. Johansson, F. Dominici, G.E. Glass, et al., Local and global effects of climate on dengue transmission in puerto rico, PLoS Negl. Trop. Dis. 3 (2) (2009) e382.
[9] M.A. Johansson, D.A. Cummings, G.E. Glass, Multiyear climate variability and dengue–el nino southern oscillation, weather, and dengue incidence in Puerto Rico, Mexico, and Thailand: a longitudinal data analysis, PLoS Med. 6 (11) (2009) e1000168.
[10] H.W. Hethcote, The mathematics of infectious diseases, SIAM Rev. 42 (4) (2000) 599–653.
[11] W.O. Kermack, A.G. McKendrick, A contribution to the mathematical theory of epidemics, in: Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences, 115, The Royal Society, 1927, pp. 700–721.
[12] L. Esteva, C. Vargas, Analysis of a dengue disease transmission model, Math. Biosci. 150 (2) (1998) 131–151.
[13] L. Esteva, C. Vargas, A model for dengue disease with variable human population, J. Math. Biol. 38 (3) (1999) 220–240.
[14] L. Esteva, C. Vargas, Coexistence of different serotypes of dengue virus, J. Math. Biol. 46 (1) (2003) 31–47.
[15] H.M. Yang, C.P. Ferreira, Assessing the effects of vector control on dengue transmission, Appl. Math. Comput. 198 (1) (2008) 401–413.
[16] V.H. Peña-García, O. Triana-Chávez, A.M. Mejía-Jaramillo, F.J. Díaz, A. Gómez-Palacio, S. Arboleda-Sánchez, Infection rates by dengue virus in mosquitoes and the influence of temperature may be related to different endemicity patterns in three colombian cities, Int. J. Environ. Res. Public Health 13 (7) (2016) 734.
[17] S. Arboleda, A.T. Peterson, et al., Mapping environmental dimensions of dengue fever transmission risk in the Aburrá valley, Colombia, Int. J. Environ. Res. Public Health 6 (12) (2009) 3040–3055.
[18] J.C. Castrillón, J.C. Castaño, S. Urcuqui, Dengue en Colombia, diez años de evolución, Rev. Chil. Infectol. 32 (2) (2015) 142–149.
[19] H. Yang, M. Macoris, K. Galvani, M. Andrighetti, D. Wanderley, Assessing the effects of temperature on dengue transmission, Epidemiol. Infect. 137 (08) (2009) 1179–1187.
[20] M. Bortman, Elaboración de corredores o canales endémicos mediante planillas de cálculo, Pan Am. J. Public Health 5 (1999) 1–8.
[21] C. Gomez, J.E. Rabinovich, C. Machado-Allison, Population analysis of culex pipiens fatigans wied. (diptera: Culicidae) under laboratory conditions, J. Med. Entomol. 13 (4–5) (1977) (453–463).
[22] World Health Organization, Regional Guidelines on Dengue/DHF Prevention and Control, Regional Publication 29. World Health Organization, 1999.
[23] World Health Organization, Dengue: Guías Para el Diagnóstico, Tratamiento, Prevención yControl, World Health Organization, 2009.
[24] S. Bhatt, P.W. Gething, O.J. Brady, J.P. Messina, A.W. Farlow, C.L. Moyes, J.M. Drake, J.S. Brownstein, A.G. Hoen, O. Sankoh, et al., The global distribution and burden of dengue, Nature 496 (7446) (2013) 504–507.
[25] J. Heesterbeek, K. Dietz, The concept of ro in epidemic theory, Stat. Neerl. 50 (1) (1996) 89–110.
[26] C. Favier, N. Dégallier, M.G. Rosa-Freitas, J.-P. Boulanger, J. Costa Lima, J.F. Luitgards-Moura, C.E. Menkès, B. Mondet, C. Oliveira, E. Weimann, et al., Early determination of the reproductive number for vector-borne diseases: the case of dengue in brazil, Trop. Med. Int. Health 11 (3) (2006) 332–340.
[27] E. Massad, F. Coutinho, M. Burattini, M. Amaku, Estimation of R_0 from the initial phase of an outbreak of a vector-borne infection, Trop. Med. Int. Health 15 (1) (2010) 120–126.
[28] R.C. Reiner, T.A. Perkins, C.M. Barker, T. Niu, L.F. Chaves, A.M. Ellis, D.B. George, A. Le Menach, J.R. Pulliam, D. Bisanzio, et al., A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970–2010, J. R. Soc. Interface 10 (81) (2013) 20120921.
[29] S. Side, S.M. Noorani, A sir model for spread of dengue fever disease (simulation for South Sulawesi, Indonesia and Selangor, Malaysia), World J. Model. Simul. 9 (2) (2013) 96–105.
[30] H.-M. Wei, X.-Z. Li, M. Martcheva, An epidemic model of a vector-borne disease with direct transmission and time delay, J. Math. Anal. Appl. 342 (2) (2008) 895–908.
[31] S.T.R.d. Pinho, C.P. Ferreira, L. Esteva, F. Barreto, V.M. e Silva, M. Teixeira, Modelling the dynamics of dengue real epidemics, Philos. Trans. R. Soc. A Math. Phys. Eng. Sci. 368 (1933) (2010) 5679–5693.
[32] T. Sardar, S. Rana, S. Bhattacharya, K. Al-Khaled, J. Chattopadhyay, A generic model for a single strain mosquito-transmitted disease with memory on the host and the vector, Math. Biosci. 263 (2015) 18–36.
[33] A. Pandey, A. Mubayi, J. Medlock, Comparing vector–host and sir models for dengue transmission, Math. Biosci. 246 (2) (2013) 252–259.
[34] L. Urdaneta-Marquez, A.-B. Failloux, Population genetic structure of aedes aegypti, the principal vector of dengue viruses, Infect. Gen. Evol. 11 (2) (2011) 253–261.
[35] J. LaSalle, Stability theory for ordinary differential equations, J. Differ. Equ. 4 (1) (1968) 57–65.
[36] J.C. Padilla, D.P. Rojas, R.S. Gómez, Dengue en Colombia: Epidemiología de la Reemergencia a la Hiperendemia, Guías de Impresión Ltda., 2012.