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Imported and autochthonous cases in the dynamics of dengue epidemics in Brazil

Casos importados e autóctones na dinâmica da epidemia de dengue no Brasil

ABSTRACT

OBJECTIVE: To estimate the basic reproduction number (R_0) of dengue fever including both imported and autochthonous cases.

METHODS: The study was conducted based on epidemiological data of the 2003 dengue epidemic in Brasília, Brazil. The basic reproduction number is estimated from the epidemic curve, fitting linearly the increase of initial cases. Aiming at simulating an epidemic with both autochthonous and imported cases, a "susceptible-infectious-resistant" compartmental model was designed, in which the imported cases were considered as an external forcing. The ratio between R_0 of imported versus autochthonous cases was used as an estimator of real R_0.

RESULTS: The comparison of both reproduction numbers (only autochthonous versus all cases) showed that considering all cases as autochthonous yielded a R_0 above one, although the real R_0 was below one. The same results were seen when the method was applied on simulated epidemics with fixed R_0. This method was also compared to some previous proposed methods by other authors and showed that the latter underestimated R_0 values.

CONCLUSIONS: It was shown that the inclusion of both imported and autochthonous cases is crucial for the modeling of the epidemic dynamics, and thus provides critical information for decision makers in charge of prevention and control of this disease.

DESCRIPTORS: Dengue, epidemiology. Flavivirus Infections, transmission. Risk. Communicable Period. Disease Outbreaks. Epidemiologic Surveillance.

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RESUMO

OBJETIVO: Estimar o número básico de reprodução da dengue (R_0), com base nos casos importados, além dos casos autóctones.

MÉTODOS: O estudo foi feito sobre dados epidemiológicos da epidemia de dengue em Brasília, 2003. O número básico de reprodução é determinado a partir da curva epidêmica, ajustando uma reta ao crescimento inicial do número de casos. Para simular uma epidemia com casos autóctones e importados, foi criado um modelo compartimentado do tipo "suscetíveis-infectados-resistentes". O R_0 real foi estimado pela fração entre R_0 dos casos autóctones e dos importados.

RESULTADOS: A comparação de ambos valores de reprodução (apenas autóctones versus todos os casos) mostrou que considerando todos casos como autóctones, o valor de R_0 foi superior a um, enquanto o R_0 real era inferior a um. O mesmo resultado foi obtido com o conjunto de dados simulando uma epidemia com R_0 fixo. O método foi também comparado a outros, observando-se que estes últimos subestimaram os valores do R_0.

CONCLUSÕES: A inclusão de tanto casos autóctones como os importados é essencial para modelar a dinâmica da epidemia, possibilitando informação crítica aos tomadores de decisão, responsáveis pelo controle da doença.

DESCRITORES: Dengue, epidemiologia. Infecções por Flavivirus, transmissão. Risco. Período de Transmissibilidade. Surtos de Doenças. Vigilância Epidemológica.

INTRODUCTION

Dengue fever has been endemic in Brazil since 1986.[5] Its transmission involves only urban mosquitoes[3] and humans, and many fatal cases occur every year due to epidemics where different serotypes are transmitted.[8]

The quick expansion of vectors and viruses throughout nearly all Brazilian states is facilitated by ever increasing moving and traveling of people in the country. Until recent years in most localities the origin of dengue cases was neither reported nor investigated. To the authors' best knowledge, no study has been published investigating the impact of "imported" cases on the dynamics of the epidemics. The origin of each case in the 2002-2003 epidemics in Brasília was inferred after a detailed survey of the patient's background, taking into account the duration of the incubation phase of the disease. As these data about the most probable origin of these cases were available, we investigated its possible impact on the dynamics of dengue epidemics. We compared its dynamics with the outputs of a simple "susceptible-infectious-resistant" (SIR) model modified in order to include the input of daily numbers of imported cases when estimating the basic reproduction number (R_0).

Mathematical modeling is a powerful tool to simulate real past situations, to input data from the present and hopefully to forecast future outcomes.[6] It has been widely used to understand the dynamics of infectious diseases.[1] A commonly used family of epidemiological models are the compartmental or "box ones": individuals are grouped in classes according to their immunological status (e.g. SIR models consider the progress in the numbers of susceptible, infectious, and removed immune people).[1] The basic reproduction number (R_0) is an essential parameter to describe the dynamics of an outbreak. It is the number of secondary infections generated by one case when the virus is introduced into a wholly susceptible population and when the probability of contact with the pathogen is homogeneous.[7]

The objective of the present study was to estimate the basic reproduction number (R_0) of dengue fever including both imported and autochthonous cases.

METHODS

Data analyzed refer to the dengue epidemics occurred during 2002–2003 in Brasília, Brazilian Federal District (Figure 1). Brasília is a city situated in Central-West Brazil and has a rather recent history of contact with dengue.[4]

When the number of imported cases is disregarded, the basic reproduction number is generally estimated from the epidemiological curve. At least four different methods for this estimation have been proposed. According

to the classical formula,[1,13,15] $R_0 = ma^2bc\exp(-\mu\tau_e)/\mu\gamma$, where m is the relative density of mosquitoes to humans, a is the daily biting rate of the mosquitoes, b and c are the probabilities of viral transmission from an infected mosquito to a susceptible human, and from an infected human to a mosquito, respectively, μ is the daily mortality rate of the vector, τ_e the extrinsic incubation period, and γ the inverse of the duration of viremia. In the present study, we modified the method used by Massad et al[13] (2001) to estimate the basic reproduction number.[2] Considering that the initial growth of the number of cases is exponential with parameter λ, $R_0 = (1+\lambda/\gamma)(1+\gamma/\mu)\exp(\lambda(\tau_e+\tau_i))$ with τ_i the intrinsic incubation period and the other parameters as above. Then, λ is estimated by a linear least squares fitting of the initial part of the curve of the cumulated number of cases against the daily number of new cases. The number of cases, which was taken into account for the regression of the increase at the beginning of each outbreak (slope λ in Fig. 2 A-D), was chosen to ensure a statistical significance of $p<10^{-4}$.

A simple SIR model is used to characterize the progress of local (autochthonous) cases with continuous influx of exogenous cases (imported). We set S_A, I_A and N_A as susceptible, infectious and cumulative number of autochthonous cases, N as the total susceptible population and I_I and N_I infectious and cumulative numbers of imported cases. The progress of N_I is thus considered as an external forcing.

$$dS_A/dt = -\beta' S_A(I_A + \eta I_I)/(N + N_I)$$

$$dI_A/dt = \beta' S_A(I_A + \eta I_I)/(N + N_I) - \gamma' I_A$$

$$dI_I/dt = \delta N_I/dt - \gamma' I_I$$

The parameter η is introduced to represent the possible differences between the durations of exposure times of autochthonous and imported hosts, the latter arriving at various times of viremia. The basic reproductive rate of autochthonous cases is $R_{0A} = \beta'/\gamma'$ while for imported cases is $R_{0I} = \eta\beta'/\gamma'$. η is thus the ratio between the basic reproductive rate of imported and autochthonous cases. Since the final number of autochthonous cases is far lesser than the whole population, the total number of people can be assumed very large (here N = 100,000) and, as we only consider the initial model behavior, results are independent of N provided it is large enough. The other two parameters (β' and γ') are computed by a fit of the ratio between the cumulative autochthonous cases over the cumulative imported cases in the Nelder-Mead simplex algorithm pre-implemented using MATLAB. Using this index (the ratio between autochthonous and imported cumulative cases) for the fit has yielded results that were more robust to the initial guess than the cumulative number of autochthonous cases. Bootstrap methods were used to estimate confidence intervals and R_0s values were compared to R_0 estimated as if all cases were autochthonous.

RESULTS

In the case of the 2003 dengue epidemic in Brasília, the imported cases were included, and the modified model fitted when only autochthonous cases were considered (Figure 3B), as well when autochthonous cases were divided by the daily numbers of imported cases (Figure 3A). The comparison of R_0 estimated using the method above (when the number of imported cases is unknown or disregarded) with R_0 estimated when

Table 1. Estimates of the initial slope of the fitted curve (λ) and R_0 with standard error, according to various methods, for the epidemics in Brasília (Federal District), Belém (Northern Brazil) and Fortaleza (Northeastern Brazil).

Methods for estimating R_0	$\lambda \pm 1$ standard deviation	First doubling time of the number of cases[12]	Initial exponential phase of the number of cases[13]	Fitting of the SIR model on the initial slope of accumulated cases plotted against the daily number of cases
Belém, 1996–1997	0.05 ± 0.008	1.3 ± 0.06 (0.13)	1.95 ± 0.17 (0.58)	4.12 ± 0.87 (2.33)
Brasília, 2000	0.12 ± 0.01	1.72 ± 0.10 (0.31)	3.78 ± 0.30 (1.6)	22.89 ± 5.27 (21.35)
Brasília, 2001	0.11 ± 0.001	1.66 ± 0.009 (0.19)	3.48 ± 0.02 (1.17)	18.15 ± 0.42 (12.37)
Brasília, 2001*	0.076 ± 0.008	1.45 ± 0.07 (0.18)	2.56 ± 0.21 (0.90)	8.00 ± 1.69 (5.66)
Fortaleza, 2001	0.024 ± 0.002	1.14 ± 0.01 (0.04)	1.42 ± 0.03 (0.20)	2.03 ± 0.11 (0.50)
Fortaleza, 2002	0.059 ± 0.02	1.35 ± 0.16 (0.24)	2.14 ± 0.46 (0.95)	5.17 ± 2.66 (4.76)
Fortaleza, 2003	0.015 ± 0.008	1.09 ± 005 (0.07)	1.25 ± 0.14 (0.24)	1.56 ± 0.37 (0.56)
SIR-simulated epidemic with R0 = 8.0**	0.073 ± 0.006	1.44 ± 0.12 (0.37)	2.49 ± 0.16 (0.28)	7.43 ± 1.20 (1.21)

* In the case of the 2001 Brasília epidemic, calculations have also been done considering the total number of cases as if their imported vs. autochthonous nature were unknown, thus allowing the comparison with the method which includes imported cases.
** The SIR epidemic have been obtained by simulation, and served as control with fixed value of R_0. Between parenthesis are the standard error when variation was added to the model parameters. The following values were taken from McBride & Bielefeldt-Ohmann[14] (2000): $\mu = 0.1 \pm 0.05$; infectious viremic period = 6 ± 1 days; $\gamma = 0.166 \pm 0.027$; $\tau_i = 5 \pm 1$ days; $\tau_e = 10 \pm 2$ days.

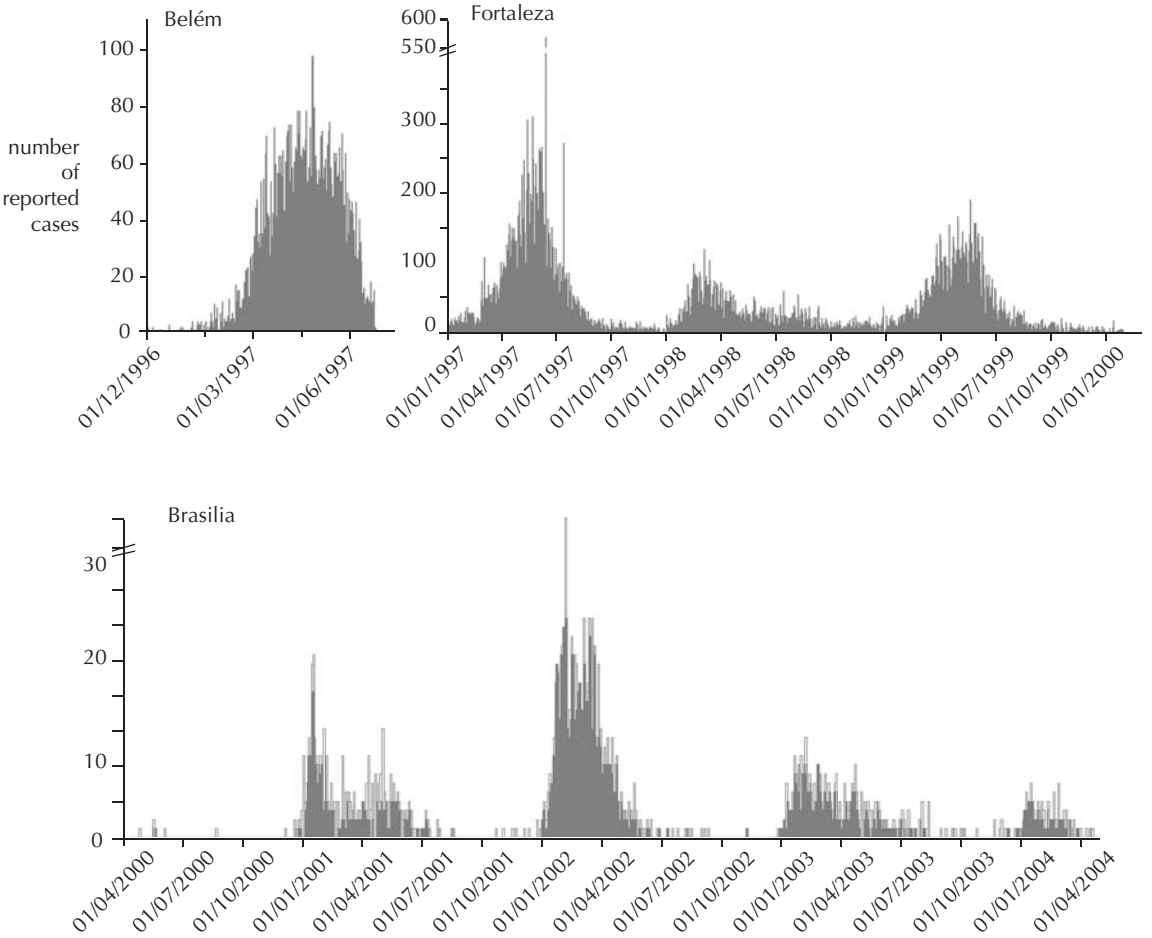

Figure 1. Daily numbers of dengue fever cases during the epidemics in Brazil. (A) Belém, Northern Brazil, 1996–1997, (B) Brasília, Federal District, 2001–2003, and (C) Fortaleza, Northeastern Brazil, 2001–2003.

exogenous cases are explicitly included is striking. In the first case, R_0 is far greater than one, indicating eco-epidemiological conditions favorable to local transmission of the virus. In the second case, the local R_0 (estimated for autochthonous transmission) is clearly lower than one. The results of the comparison between the three methods are shown in Table 1, for different epidemics and for a SIR-simulated one with pre-defined $R_0 = 8.0$. Besides great variability between the epidemics, the R_0 values estimated by the method here described are always greater than those obtained using other methods. Furthermore, this method is the only one that provides a correct estimation of the R_0 of the SIR-modeled epidemic. Figure 4 shows an almost linear relationship between R_{0aut} and R_{0imp}, when the former is set under one. Thus, under such assumptions, it becomes evident that in case of an epidemic, the reproduction number due to imported cases cannot be above 0.45 and that if the reproduction number due to autochthonous cases is near one, the latter becomes negligible.

DISCUSSION

The methods used by Marques et al[12] (1994) and Massad et al[13] (2001) systematically underestimated R_0, probably because they failed to consider the whole delay between two successive cases (viremia, and intrinsic and extrinsic incubation periods). The differences between the R_0 values obtained for different epidemics (Table 1) reflect various eco-epidemiological conditions influencing hidden parameters (such as mosquito density, effective exposure rates between hosts and vectors[10]).

Except for the viremic period in infected people, these parameters vary with climatic factors, mainly temperature and relative humidity, which affect vector survival and virus extrinsic cycle. Other factors may influence R_0 but are generally not addressed due to unavailability of relevant data such as the degree of urbanization and social structure,[11] transmission history and/or immune status of human population. The human population is no more fully susceptible in most Brazilian cities, and the

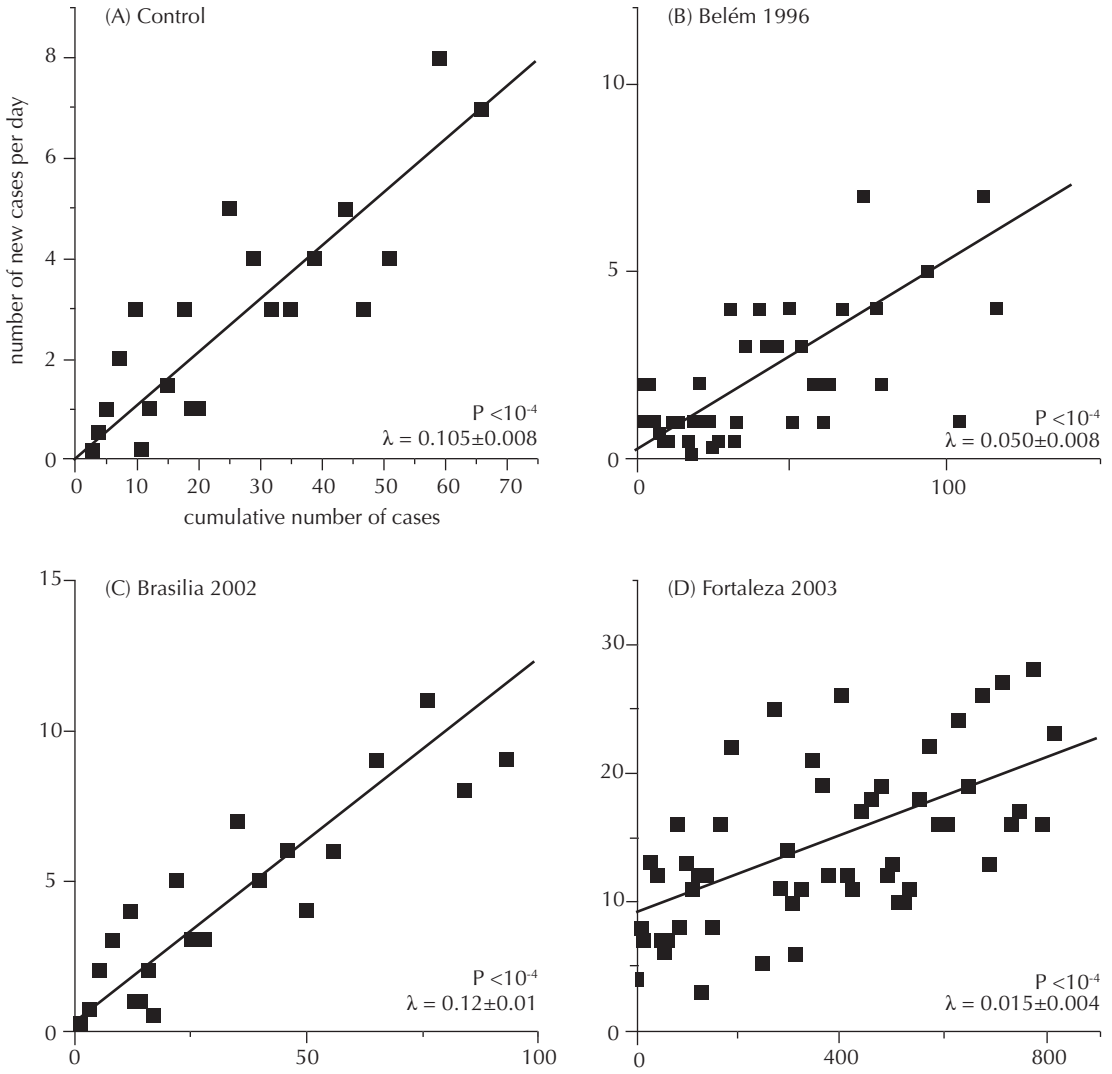

Figure 2. Estimation of R_0 including only the autochthonous cases or the total number of cases when the number of imported ones was not known. (A) Simulated epidemic, obtained by the SIR model where R_0 was set at 8.4 (see methods), (B) Belém (Northern Brazil) 1996 epidemic, (C) Brasília (FD), 2002 epidemic, and (D) Fortaleza (Northeastern Brazil), 2003 epidemic. The number of cumulative cases used to estimate R_0 was chosen for p<10-4; λ is the slope of the regression curve.

case of Belém (Northern Brazil) was an exception since the 1997–1998 epidemic was the first in this city.[16] In the cases of Brasília and Fortaleza (Northeastern Brazil) epidemics, where dengue transmission is known since 1997 and 1986, respectively,[4,a] our R_0 values are thus probably underestimated. As illustrated by Keeling & Grenfell[9] (2000), assumptions about case distribution are rarely met in natural situations, and the assumption of homogeneity of contact is also generally not met, as it has been previously shown that cases are often aggregated inside and around the houses of the first cases. This may also contribute to underestimating R_0 values. An unknown proportion of cases remain undetected as they are asymptomatic or are diagnosed as other fever-causing diseases. This fact makes the determination of the number of cases uncertain but not the estimation of R_0 if we postulate that it is independent of the intensity of symptoms. A similar, or even more serious difficulty is the number of uncharacterized imported cases, which may negatively affect the estimation of R_0 and thus invalidate any decision about prevention and control. This clearly implies that dengue epidemics may occur even when local ecological conditions are unfavorable, as was probably the case in Brasília in 2003. This is

[a] Degallier N, Hervé J-P, Travassos da Rosa APA, Travassos da Rosa ES, Vasconcelos PFC, Monteiro HAO, Sá Filho G, Travassos da Rosa JFS. Entomological studies on dengue fever vectors in Brazil: the epidemics of Boa Vista, Roraima, 1982, Niterói, Rio de Janeiro, 1986, and Ceará State, 1986, 1994. In: Travassos da Rosa APA, Vasconcelos PFC, Travassos da Rosa JFS. *An overview of arbovirology in Brazil and neighbouring countries.* Belem, Pará: Instituto Evandro Chagas; 1998. p.261-71.

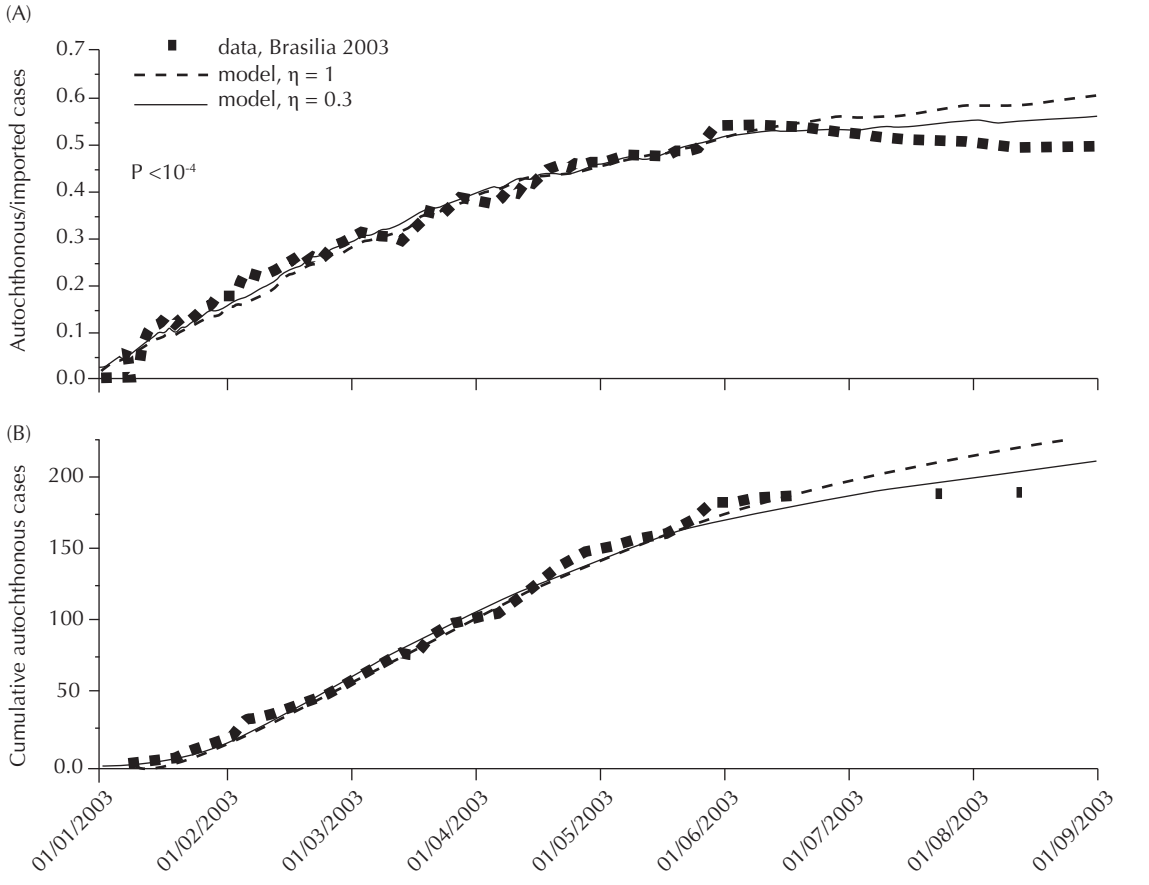

Figure 3. Fitting of the modified SIR model (with imported cases included) with the initial cumulative curve of daily numbers of autochthonous cases (B), and daily ratio of autochthonous / imported cases (A) in Brasília, DF, 2003. Best-fit model was obtained with $\gamma = 0.04$ and $\beta = 0.015$ for $\eta = 1$ and with $\gamma = 0.07$ and $\beta = 0.048$ for $\eta = 0.3$ (η is the ratio between the basic reproductive rate of imported cases and the rate of autochthonous cases).

the first report emphasizing this aspect. Taking into account the imported *vs*. autochthonous nature of each diagnosed case will allow a better evaluation of the risk of dengue transmission or epidemic. Health authorities involved with dengue monitoring and prevention should develop and strengthen their methods to determine the imported or autochthonous origin of the cases. Future studies should incorporate these data in models, along with the yet missing entomological field data. As the populations of arthropod vectors are much influenced by climatic factors, it may thus be possible to link the dynamics of outbreaks to climatic factors through the underlying R_0 and vectorial capacity.

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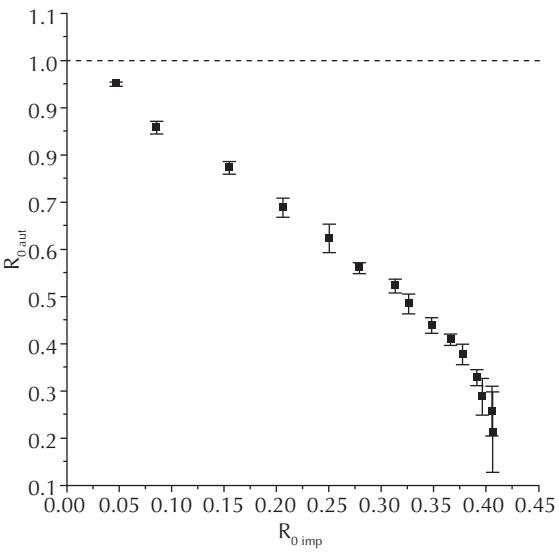

Figure 4. Relationships between imported and autochthonous cases during the 2002 epidemic in Brasília, FD, Brazil. R_{0I} and R_{0A} were both set below one, with $R_{0I} \leq R_{0A}$, and the R_{0A}/R_{0I} ratio was set at various values from 1 to 0.2. Error bars represents the 0.95 confidence interval.

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