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Mathematical modelling for Zoonotic Visceral Leishmaniasis dynamics: A new analysis considering updated parameters and notified human Brazilian data

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ABSTRACT

Brazil is one of the highest endemic countries for Zoonotic Visceral Leishmaniasis: according to the Brazilian Ministry of Health, the annual number of new human cases and deaths due to this disease has been increasing for the last 20 years. In addition, regarding the Americas, the specific relationship between canine and human for Visceral Leishmaniasis dynamics is still not well understood. In this work we propose a new model for Zoonotic Visceral Leishmaniasis, based on the models previously published by Burattini et al. (1998) and Ribas et al. (2013). Herein, we modeled the disease dynamics using a modified set of differential equations from those two authors, considering the same assumptions (inclusion of human, dog and sandfly populations, all constants over time). From this set of equations we were able to calculate the basic reproduction number $\mathscr{R}_0$ and to analyze the stability and sensitivity of the system to the parameters variability. As main result, when the stability of the system is reached, the normalized reporting human cases rate is estimated in *9.12E-08*/day. This estimation is very close to the 2015 report from Araçatuba city, *5.69E-08*/day. We also observed from stability and sensitivity analysis that the activity of sandfly population is critical to introduction and maintenance of Zoonotic Visceral Leishmaniasis in the population. In addition, the importance of dog as source of infection concentrates on latent dog, since it does not show clinical symptoms and signs and, therefore, has a great contribution to disease dissemination. As conclusion, considering the presently ethical issues regarding to elimination of positive dog in Brazil and the highly sensitivity of disease dynamics on sandfly population, we recommend that the sandfly population control should be prioritized.

1. Introduction

Zoonotic Visceral Leishmaniasis is one of the world deadliest and neglected infectious diseases, according to World Health Organization. This disease is endemic in 80 countries worldwide, in which 90% of all cases occur in Bangladesh, Brazil, India, Nepal and Sudan. Thus, about 360 million of people are exposed to risk of infection in the world (Duthie, Raman, Piazza, &

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Reed, 2012; Killick-Kendrick, 2010; Pan American Health Organization, 2001; World Health Organization, 2017). The Zoonotic Visceral Leishmaniasis is a disease of major human and veterinary medical significance that involves a complex interplay between trypanosomatids protozoan from *Leishmania* complex, arthropod vectors (in Brazil, we find the female sandfly *Lutzomyia longipalpis* and *Lutzomyia cruzi*), environmental influence on vector distribution, small companion animal (dog) reservoir of infection and susceptible human populations. In American continent, *Leishmania infantum chagasi* is the most important specie from *Leishmania* complex.

From the last few years, Zoonotic Visceral Leishmaniasis has been emerging within non-endemic areas, mostly because of transportation of dogs from endemic areas and climatic changes with the expansion of the geographical range of the sandfly vector. Thus, the effective control will essentially involve interdisciplinary teams of microbiologists, parasitologists, entomologists, ecologists, epidemiologists, immunologists, veterinarians, public health officers and human physicians (Palatnik-de-Souza & Day, 2011).

Besides the publication of guidelines of Zoonotic Visceral Leishmaniasis control and the investments made in general surveillance activities, the sandfly and the reservoir in urban areas remains among the major challenges for the control activities. These challenges are due to (1) the necessity to better understand the vector behavior in urban environment; (2) the operational and logistic difficulties to carry out activities in sufficient time to obtain good results; and (3) the high costs involved in these activities (Killick-Kendrick, 2010; Maia-Elkhoury, Alves, Souza-Gomes, Sena, & Luna, 2008). In addition, regarding the Americas, the specific relationship between canine and human for Visceral Leishmaniasis dynamics is still not well understood. Thus, the control of the animal reservoir is complex and often needs to combine different ways of interventions. In particular, the Brazilian Control Program recommends a strategy based on canine culling and vector control with insecticide spraying (Ministry of Health, Brazil, 2006; Nunes et al., 2008). Therefore, dog treatment is not recommended, since it is difficult to eliminate the parasitemia from infected dogs (Athanasiou, Saridomichelakis, Kontos, Spanakos, & Rallis, 2013; Ministry of Health, Brazil, 2006). Furthermore, insecticide-impregnated collars for dogs and canine vaccination are not currently recommended as public health control measures (Palatnik-de-Souza & Day, 2011; Romero & Boelaert, 2010).

In this work we propose a new model for Zoonotic Visceral Leishmaniasis, based on the models previously published by Burattini, Coutinho, Lopez, and Massad (1998) and Ribas, Zaher, Shimozako, and Massad (2013). In this new model we updated most of parameters, calculated the new $\mathscr{R}_0$ value and analyzed the stability and sensitivity of the system. Then, we discussed the disease dynamics based on those mathematical analyses and addressed the critical points that benefit the introduction and maintenance of this disease in the population.

2. The model

We used a mathematical model that is an adaptation of the one proposed by Burattini et al. (1998). In our model, we assume:

1. A human and a dog population, with the biological vector transmitting the infection within and between the two populations;
2. Those three populations (humans, dogs, and vectors) are constants;
3. Both human (indexed as h) and dog (indexed as d) populations are divided into four categories: susceptible (x_h and x_d), infected but without noticeable disease (l_h and l_d) (i.e., "latent"), clinically ill (y_h and y_d), and recovered immunes (z_h and z_d). On the other hand, the vector population is divided into three categories: noninfected, infected but not infective, and infective individuals, denoted as s_1, s_2, and s_3, respectively.

The flowchart and compartment model (Fig. 1) and the set of differential equations describing the model's dynamics (System 1) are presented as following.

$$
\begin{aligned}
x_h(t) &= \mu_h(l_h(t)+y_h(t)+z_h(t)) + r_h l_h(t) + \alpha_h y_h(t) + \gamma_h z_h(t) - b_h a_h m_h(t) s_3(t) x_h(t)\\
l_h(t) &= (b_h a_h m_h(t) s_3(t)) x_h(t) - (\mu_h + r_h + \delta_h + \varphi_h) l_h(t)\\
y_h(t) &= \varphi_h l_h(t) - (\mu_h + \alpha_h + \sigma_h) y_h(t) z_h(t) = \delta_h l_h(t) + \sigma_h y_h(t) - (\mu_h + \gamma_h) z_h(t)\\
x_d(t) &= (\mu_d + \xi_d)(l_d(t) + y_d(t) + z_d(t)) + r_d l_d(t) + \alpha_d y_d(t) + \gamma_d z_d(t) - b_d a_d m_d(t) s_3(t) x_d(t)\\
l_d(t) &= (b_d a_d m_d(t) s_3(t)) x_d(t) - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d) l_d(t)\\
y_d(t) &= \varphi_d l_d(t) - (\mu_d + \alpha_d + \sigma_d + \xi_d) y_d(t) z_d(t) = \delta_d l_d(t) + \sigma_d y_d(t) - (\mu_d + \gamma_d + \xi_d) z_d(t)\\
s_1(t) &= \mu_s(s_2(t) + s_3(t)) - a_d(c_l l_d(t) + c_y y_d(t)) s_1(t)\\
s_2(t) &= a_d(c_l l_d(t) + c_y y_d(t)) s_1(t) - \mu_s s_2(t) - a_d(c_l l_d(t-\tau) + c_y y_d(t-\tau)) s_1(t-\tau) e^{-\mu_s \tau}\\
s_3(t) &= a_d(c_l l_d(t-\tau) + c_y y_d(t-\tau)) s_1(t-\tau) e^{-\mu_s \tau} - \mu_s s_3(t)
\end{aligned}
\tag{1}
$$

The definition, biological meaning, and values of each of parameter are described in Table 1.

A brief description of system (1) should clarify their meaning.

Let S be the total number of sandflies. The number of bites inflicted in the human host population in an infinitesimal time interval dt is $a_h S(t) dt$, where a_h is the biting rate on humans. The number of bites inflicted by infected flies is $a_h S(t) dt\, S_3(t)/S(t) = a_h S(t) dt\, s_3(t)$, where $S_3(t)$ is the number of infected flies.