Evaluation of strategy control activities of Zoonotic Visceral Leishmaniasis using mathematical modelling

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Optimization model for leishmaniasis control: epidemiological and economical analysis

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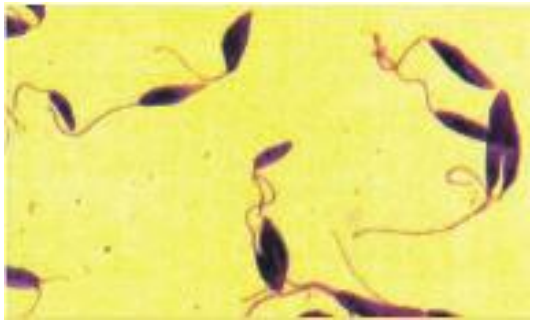
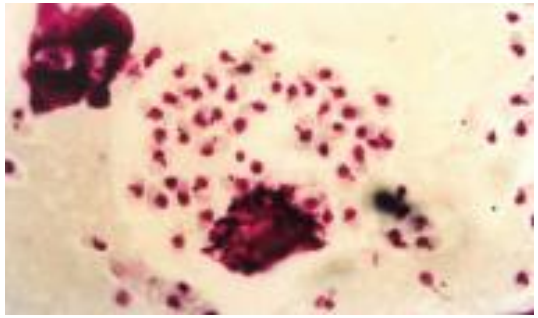
Outline

- Zoonotic visceral leishmaniasis
- The mathematical model
- (Preventive) Control methods
- The optimal control strategy
- Conclusions

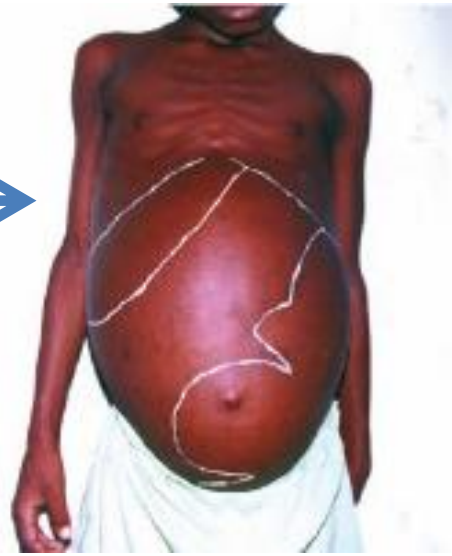
Pathogen: *Leishmania chagasi*

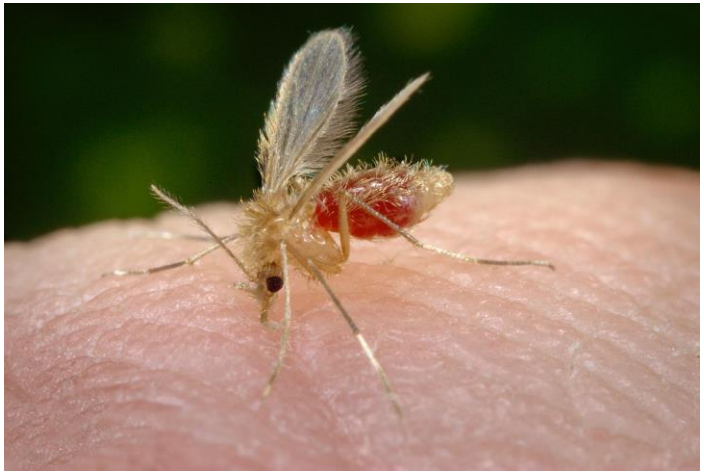


Promastigote form (sandfly)

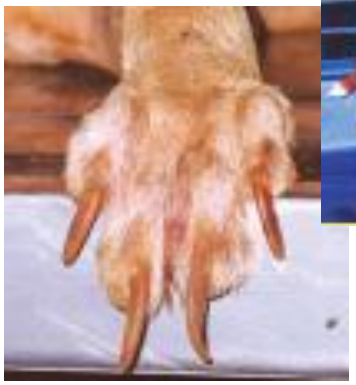


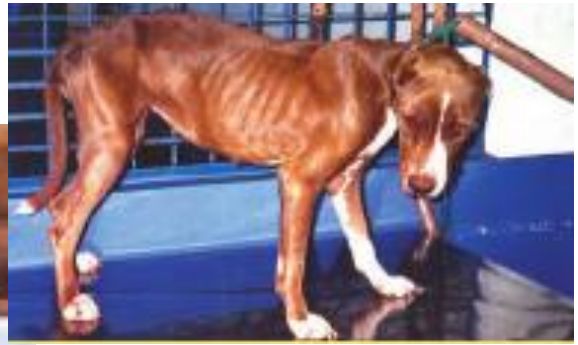
Amastigote form (human and dog)



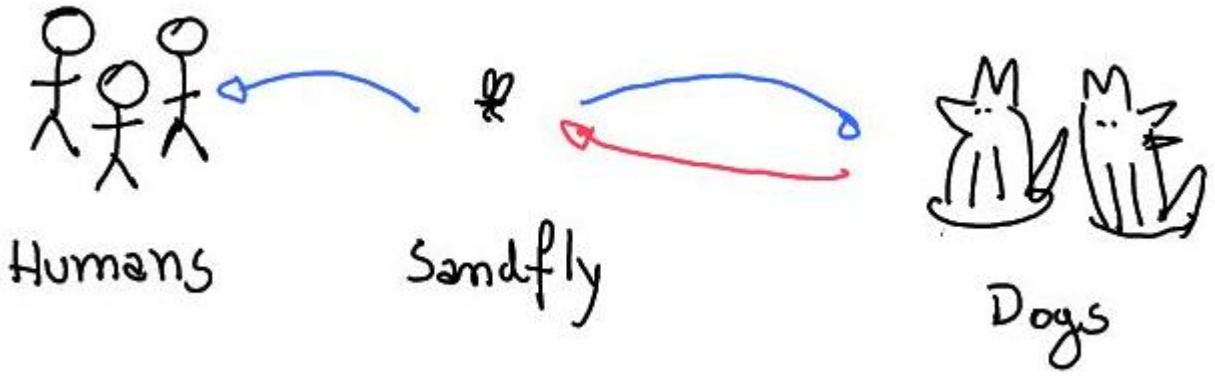


Lutzomyia longipalpis





Zoonotic Visceral Leishmaniasis



- Humans do not infect sandflies but we are infected by them;
- Dogs infect sandflies and are infected by them;
- Infected sandfly transmits the pathogen to humans and dogs when it bites them (the sandfly feeds their blood).

Where and why is this disease important?

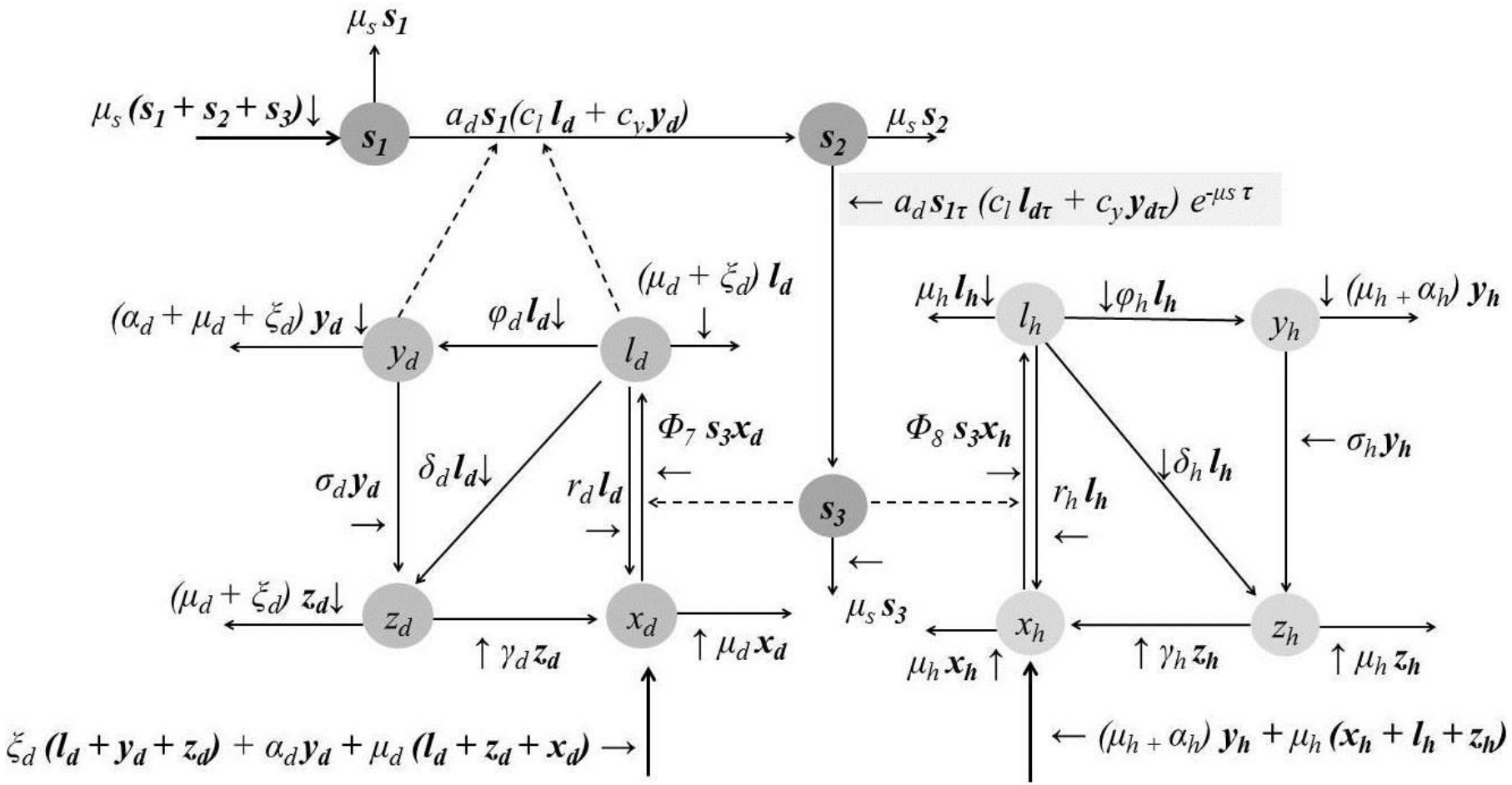
- Brazil
- Although the dog treatment has been allowed since 2018, the Brazilian Ministry of Health has recommended the elimination of infected dogs;
- However, there are researches that conclude the elimination of infected dog is not efficient.

Two stages

1. How could we model the zoonotic VL, in order to analyse this disease dynamics?
2. How could we optimize the control of ZVL, considering an epidemiologic and economic approaches?

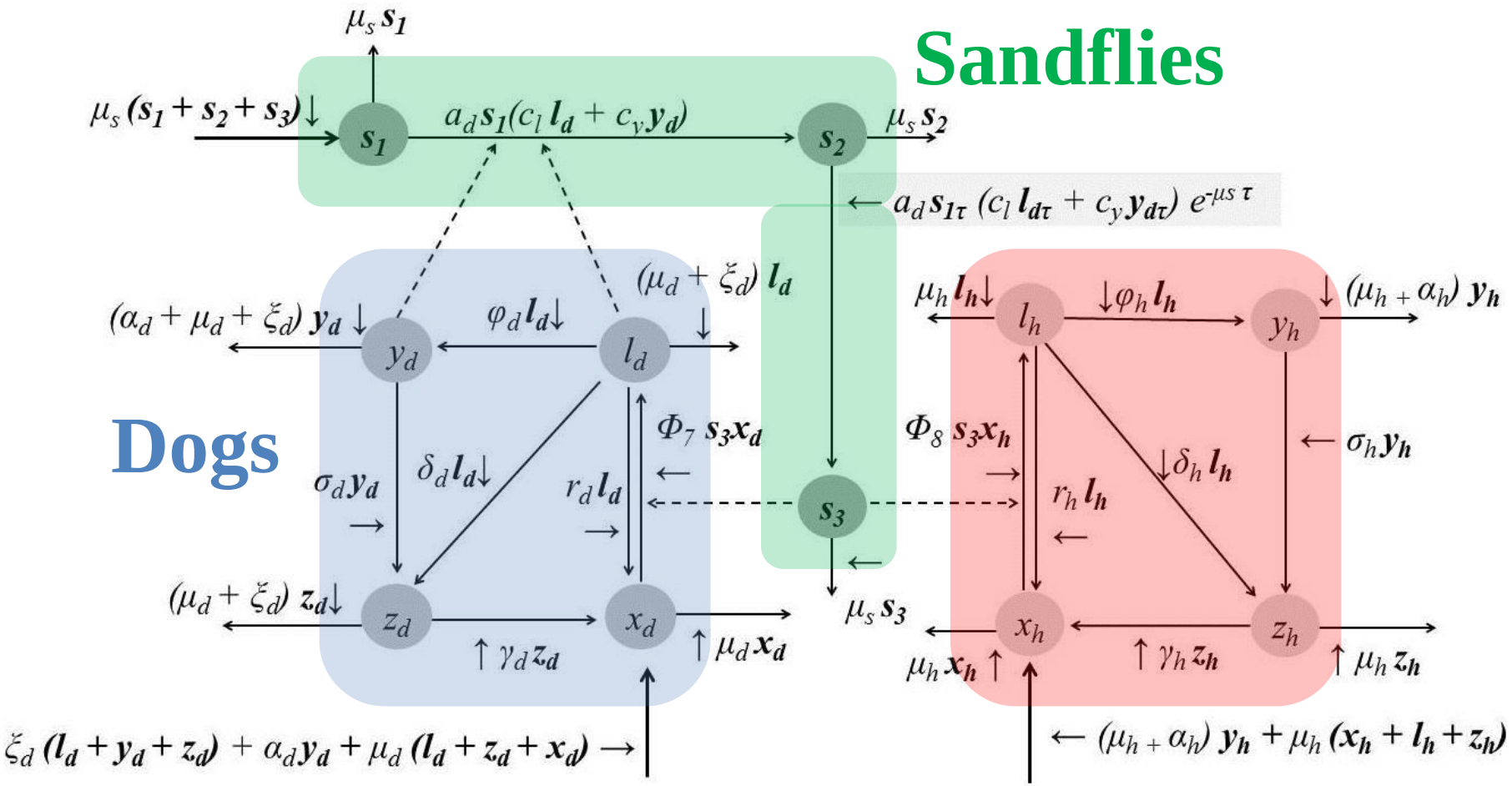
It was considered as reference the Araçatuba city (São Paulo State, Brazil), since there are available reported data and published works about ZVL dynamics in this city.

The compartment model and the flowchart



$$\Phi_7 = b_d a_d m_d \qquad \Phi_8 = b_h a_h m_h$$

The compartment model and the flowchart



$$\Phi_7 = b_d a_d m_d \qquad \Phi_8 = b_h a_h m_h$$

Equations

Human

$$\dot{x_h}(t) = \mu_h\left(l_h(t) + y_h(t) + z_h(t)\right) + r_h l_h(t) + \alpha_h y_h(t) + \gamma_h z_h(t) - b_h a_h m_h(t) s_3(t) x_h(t)$$

$$\dot{l_h}(t) = \left(b_h a_h m_h(t) s_3(t)\right) x_h(t) - (\mu_h + r_h + \delta_h + \varphi_h) l_h(t)$$

$$\dot{y_h}(t) = \varphi_h l_h(t) - (\mu_h + \alpha_h + \sigma_h) y_h(t)$$

$$\dot{z_h}(t) = \delta_h l_h(t) + \sigma_h y_h(t) - (\mu_h + \gamma_h) z_h(t)$$

Let's consider this equation...

Dog

$$\dot{x_d}(t) = (\mu_d + \xi_d)\left(l_d(t) + y_d(t) + z_d(t)\right) + r_d l_d(t) + \alpha_d y_d(t) + \gamma_d z_d(t) - b_d a_d m_d(t) s_3(t) x_d(t)$$

$$\dot{l_d}(t) = \left(b_d a_d m_d(t) s_3(t)\right) x_d(t) - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d) l_d(t)$$

$$\dot{y_d}(t) = \varphi_d l_d(t) - (\mu_d + \alpha_d + \sigma_d + \xi_d) y_d(t)$$

$$\dot{z_d}(t) = \delta_d l_d(t) + \sigma_d y_d(t) - (\mu_d + \gamma_d + \xi_d) z_d(t)$$

Sandfly

$$\dot{s_1}(t) = \mu_s\left(s_2(t) + s_3(t)\right) - a_d\left(c_l l_d(t) + c_y y_d(t)\right) s_1(t)$$

$$\dot{s_2}(t) = a_d\left(c_l l_d(t) + c_y y_d(t)\right) s_1(t) - \mu_s s_2(t) - a_d\left(c_l l_d(t-\tau) + c_y y_d(t-\tau)\right) s_1(t-\tau) e^{-\mu_s \tau}$$

$$\dot{s_3}(t) = a_d\left(c_l l_d(t-\tau) + c_y y_d(t-\tau)\right) s_1(t-\tau) e^{-\mu_s \tau} - \mu_s s_3(t)$$

In Brazil, **Zoonotic Visceral Leishmaniasis is a notifiable disease** (Ministry of Health, Brazil, 2006; Day et al., 2012). Thus, we **assume**:

•A infected human should look for medical treatment when he/she will become clinically ill (y_h);

•Only a fraction of those humans that are clinically ill will be reported to sanitary authorities. The remaining fraction:

- (I) will not look for medical help, even if the clinical symptoms and signs appear; or
- (II) will not be correctly reported in the hospitals.

$$\dot{y}_h(t) = \varphi_h l_h(t) - (\mu_h + \alpha_h + \sigma_h) y_h(t)$$

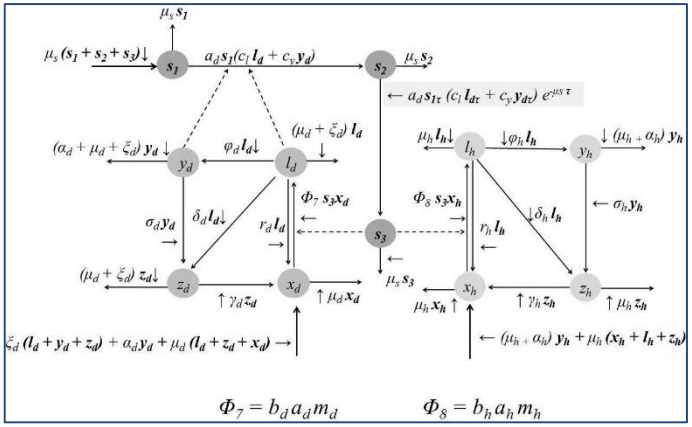
This term means the rate of latent humans who become clinically ill per day. Thus, per day, those amounts of humans are eligible to look for medical help.

$$R(t) = (1 - \eta_h)\varphi_h l_h(t)$$

Daily rate of reported human cases

Only a fraction of those clinically ill humans will be correctly notified to sanitary authorities.

Model



$$\dot{y_h}(t) = \varphi_h I_h(t) - (\mu_h + \alpha_h + \sigma_h) y_h(t)$$

$$R(t) = (1 - \eta_h)\varphi_h I_h(t)$$

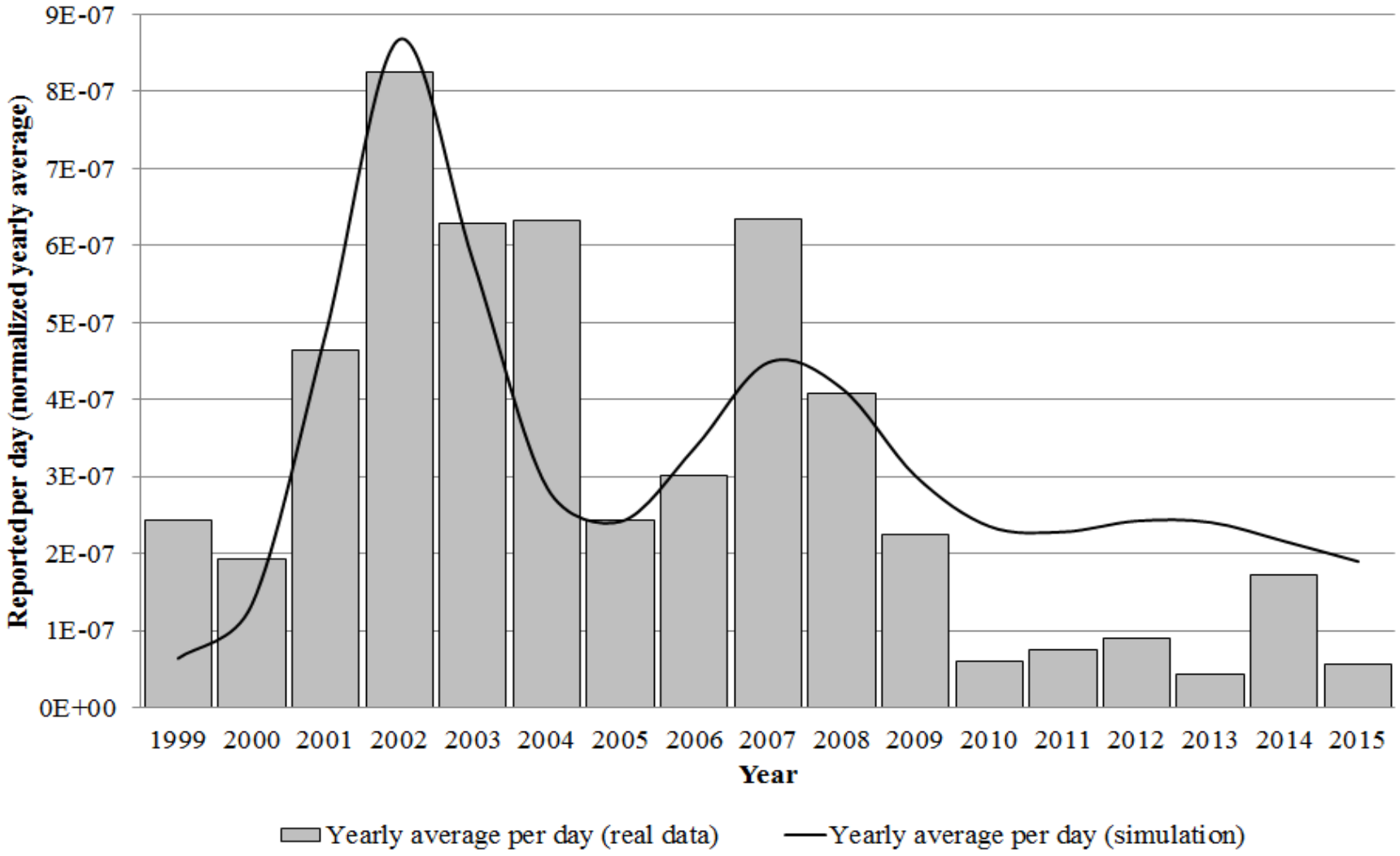
Reported data

Year	Human reported cases per year (CES-SP)	Araçatuba's Human population size (BIGS)	Average of normalized human reported cases per day
1999	15	169303	2.43E-07
2000	12	170296	1.93E-07
2001	29	171289	4.64E-07
2002	52	172768	8.25E-07
2003	40	174399	6.28E-07
2004	41	177823	6.32E-07
2005	16	179717	2.44E-07
2006	20	181598	3.02E-07
2007	42	181371	6.34E-07
2008	27	181143	4.08E-07
2009	15	182204	2.26E-07
2010	4	182365	6.01E-08
2011	5	182526	7.51E-08
2012	6	183441	8.96E-08
2013	3	190536	4.31E-08
2014	12	191662	1.72E-07
2015	4	192757	5.69E-08

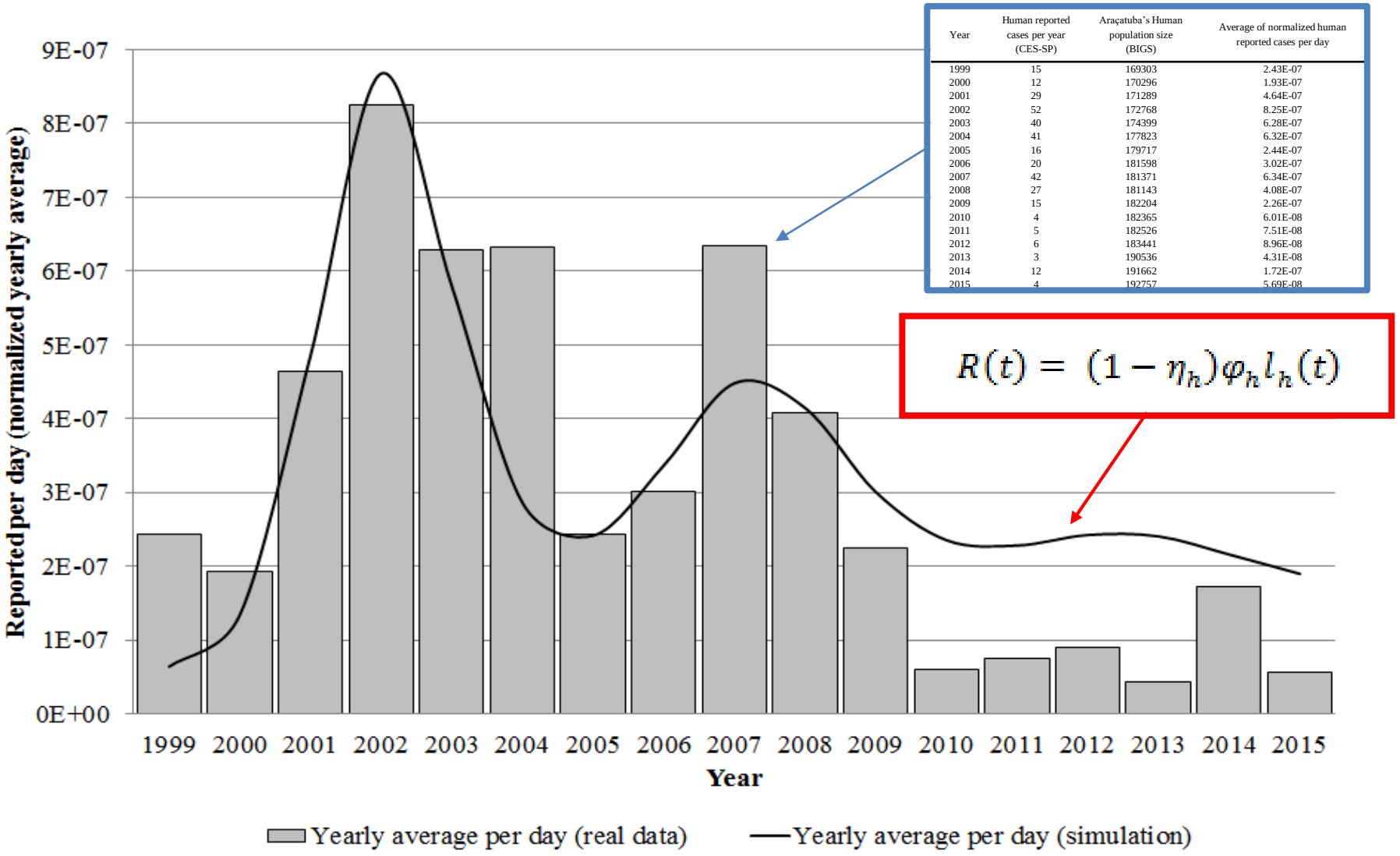
"$R(t)_{Real}$"

The model was fitted according to real data.

Dynamics of reported human cases rate



Dynamics of reported human cases rate



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$$R(t) = (1 - \eta_h)\varphi_h I_h(t)$$

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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.

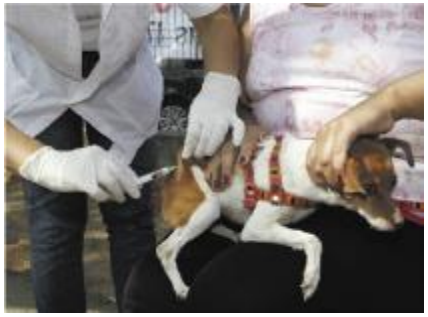
The full work of this first step has already been published.

But, what about the control strategies?

Preventive control methods

Control of sandfly population

Treatment of the dog



Dog vaccination

Inseticide impregnated dog collar

Elimination of infected dog

How could we optimize the control of ZVL, considering an epidemiologic and economic approaches?

Preventive control methods

Control of sandfly population

Treatment of the dog

Dog vaccination

Inseticide impregnated dog collar

Elimination of infected dog

How could we optimize the control of ZVL, considering an epidemiologic and economic approaches?

What are the control strategies rates, considering the economic restrictions?

Here, there are some importante information about Araçatuba city:

Human incidence of cases:
20.18 human cases/year
(average from reported cases data)

The estimation of dog population size in 2016 is around
34,899 dogs

The number of houses in 2016 is around
64,609 houses

Estimated cost for human treatment:
397.25 USD/human

Estimated cost of each control strategy

Calculation details are omitted...

TABLE 8: Summary of average costs for strategy controls and for human patient treatment.

	Meaning	Cost	Cost dimension	Source	Normalized cost (in terms of patient cost)	Normalized cost dimension	Control rate	Control rate dimension
ξ'_d	Elimination of positive dog	170.71	USD/dog	Estimated as Camargo-Neves [31]	0.43	Patient/dog	3.69×10^{-6}	1/day
θ_d	Deltamethrin 4% impregnated dog collar	12.00	USD/dog	Estimated as Camargo-Neves et al. [47]	0.03	Patient/dog	5.25×10^{-5}	1/day
ω_d	Dog treatment with allopurinol and meglumine antimoniate	265.76	USD/dog	Estimated as Miró et al. [45]	0.67	Patient/dog	2.37×10^{-6}	1/day
υ_d	Vaccine	33.00	USD/dog	F. F. Gonzales (Personel communication, 2016)	0.08	Patient/dog	1.91×10^{-5}	1/day
ξ_c	Sandfly population control	23.24	USD × sandfly/(house)^2	Estimated as Camargo-Neves [31]	0.06	Patient × sandfly/(house)^2	1.46×10^{-5}	House/(sandfly × day)
—	Human patient treatment	397.25	USD/patient	Estimated as Akhavan [46]	1.00	Patient/patient	—	—

All strategies would be supported by public health services. Therefore, there would be no charge for population.

(Very quickly) Overview about the flowchart modifications due to the inclusion of control strategies.

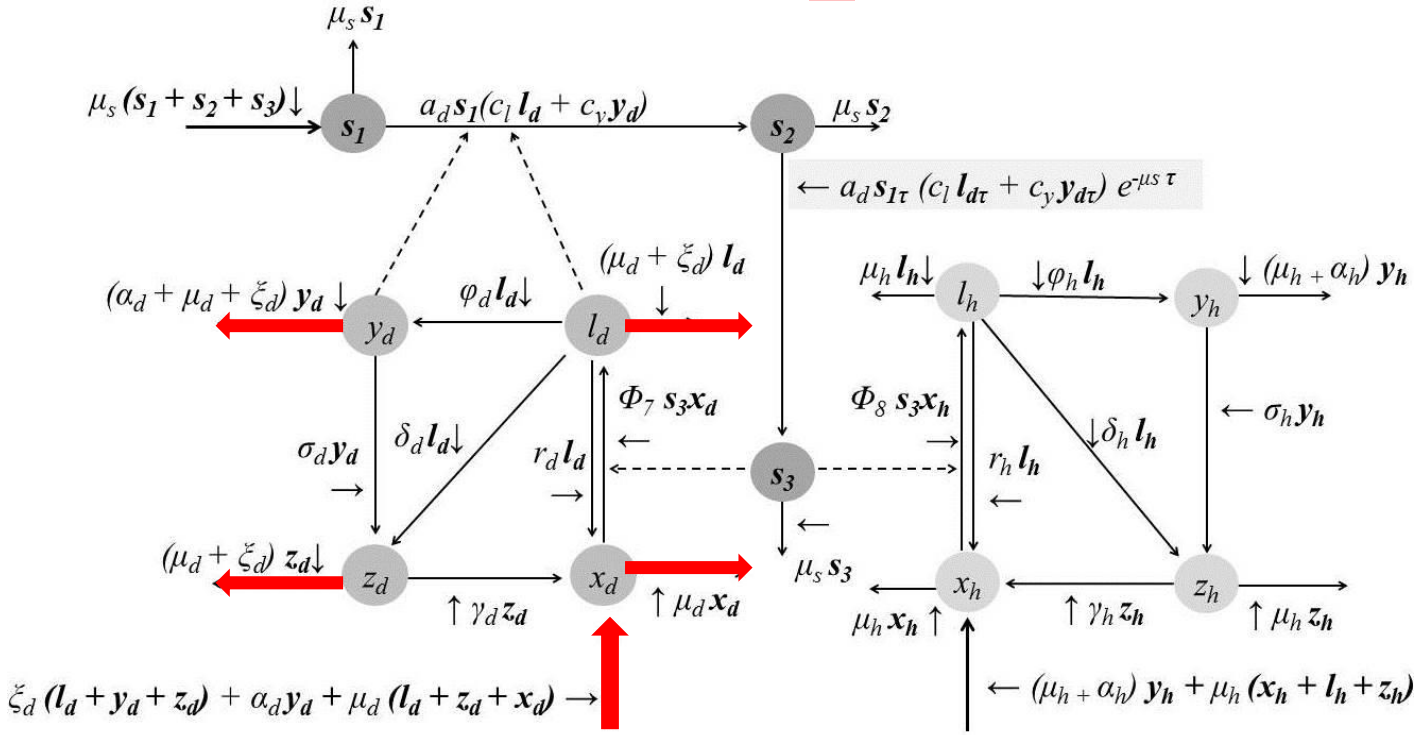
Elimination of positive dogs

$$\dot{x_d}(t) = (\mu_d + \xi_d + \xi'_d)(l_d(t) + y_d(t) + z_d(t)) + r_d l_d(t) + \alpha_d y_d(t) + \gamma_d z_d(t) - b_d a_d m_d(t) s_3(t) x_d(t)$$

$$\dot{l_d}(t) = (b_d a_d m_d(t) s_3(t)) x_d(t) - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d + \xi'_d) l_d(t)$$

$$\dot{y_d}(t) = \varphi_d l_d(t) - (\mu_d + \alpha_d + \sigma_d + \xi_d + \xi'_d) y_d(t)$$

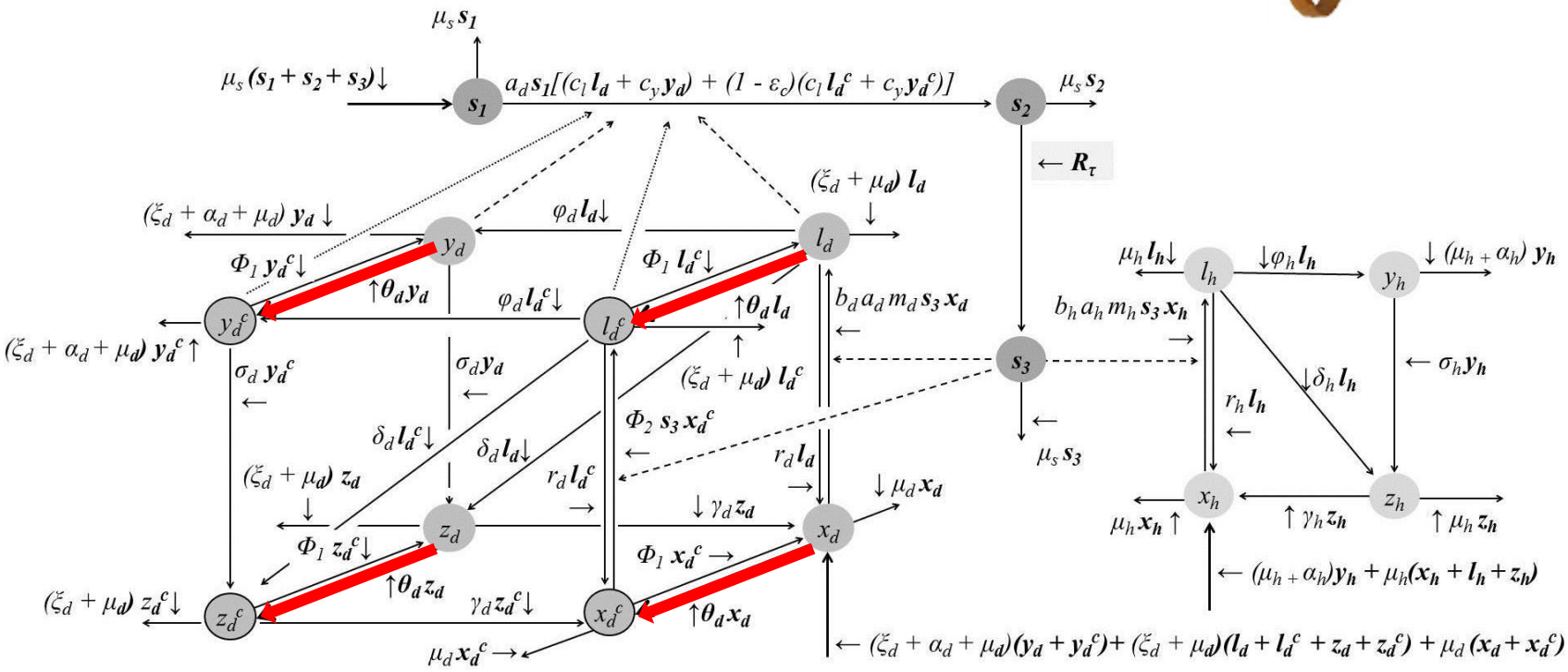
$$\dot{z_d}(t) = \delta_d l_d(t) + \sigma_d y_d(t) - (\mu_d + \gamma_d + \xi_d + \xi'_d) z_d(t)$$



- **ξ_d' is the "extra" elimination rate;**
- **It is the same flowchart.**

$$\Phi_7 = b_d a_d m_d \qquad \Phi_8 = b_h a_h m_h$$

Deltametrin 4% impregnated dog collar



$$R_\tau = a_d s_1(t - \tau)\,[(c_l l_d(t - \tau) + c_y y_d(t - \tau)) + (1 - \varepsilon_c)(c_l l_d^c(t - \tau) + c_y y_d^c(t - \tau))]\, e^{-\mu_s \tau}$$

$$\Phi_1 = (u_c + \zeta_c) \qquad \Phi_2 = b_d (1 - \varepsilon_c) a_d m_d$$

Deltametrin 4% impregnated dog collar

$$\dot{x_d}(t) = \mathbf{B}(t) + (u_c + \zeta_c)x_d^c(t) + r_d l_d(t) + \gamma_d z_d(t) - \left(\theta_d + b_d a_d m_d s_3(t)\right)x_d(t)$$

$$\dot{l_d}(t) = (u_c + \zeta_c)l_d^c(t) + b_d a_d m_d s_3(t)x_d(t) - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d + \theta_d)l_d(t)$$

$$\dot{y_d}(t) = (u_c + \zeta_c)y_d^c(t) + \varphi_d l_d(t) - (\mu_d + \alpha_d + \sigma_d + \xi_d + \theta_d)y_d(t)$$

$$\dot{z_d}(t) = (u_c + \zeta_c)z_d^c(t) + \delta_d l_d(t) + \sigma_d y_d(t) - (\mu_d + \gamma_d + \xi_d + \theta_d)z_d(t)$$

$$\mathbf{B}(t) = \mu_d\left(1 - x_d(t)\right) + \xi_d\left(1 - x_d(t) - x_d^c(t)\right) + \alpha_d\left(y_d(t) + y_d^c(t)\right)$$

$$\dot{x_d^c}(t) = \theta_d x_d(t) - \left(\mu_d + u_c + \zeta_c + (1 - \varepsilon_c)b_d a_d m_d s_3(t)\right)x_d^c(t) + r_d l_d^c(t) + \gamma_d z_d^c(t)$$

$$\dot{l_d^c}(t) = \theta_d l_d(t) + (1 - \varepsilon_c)b_d a_d m_d s_3(t)x_d^c(t) - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d + u_c + \zeta_c)l_d^c(t)$$

$$\dot{y_d^c}(t) = \theta_d y_d(t) + \varphi_d l_d^c(t) - (\mu_d + \alpha_d + \sigma_d + \zeta_c + u_c + \xi_d)y_d^c(t)$$

$$\dot{z_d^c}(t) = \theta_d z_d(t) + \delta_d l_d^c(t) + \sigma_d y_d^c(t) - (\mu_d + \gamma_d + \zeta_c + u_c + \xi_d)z_d^c(t)$$

$$\dot{s_1}(t) = \mu_s\left(s_2(t) + s_3(t)\right) - a_s\left(\mathbf{I}_d(t) + \mathbf{I}_d^c(t)\right)s_1(t)$$

$$\dot{s_2}(t) = a_s\left(\mathbf{I}_d(t) + \mathbf{I}_d^c(t)\right)s_1(t) - \mu_s s_2(t) - a_s\left(\mathbf{I}_d(t-\tau) + \mathbf{I}_d^c(t-\tau)\right)s_1(t-\tau)e^{-\mu_s\tau}$$

$$\dot{s_3}(t) = a_s\left(\mathbf{I}_d(t-\tau) + \mathbf{I}_d^c(t-\tau)\right)s_1(t-\tau)e^{-\mu_s\tau} - \mu_s s_3(t)$$

$$\mathbf{I}_d(t) = c_l l_d(t) + c_y y_d(t)$$

$$\mathbf{I}_d^c(t) = (1 - \varepsilon_c)\left(c_l l_d^c(t) + c_y y_d^c(t)\right)$$

Dog vaccination

$$\dot{x_d}(t) = \mathbf{B}(t) + r_d l_d(t) + \gamma_d z_d(t) + p_d v_d(t) - (b_d a_d m_d(t) s_3(t) + \varepsilon_v v_d) x_d(t)$$

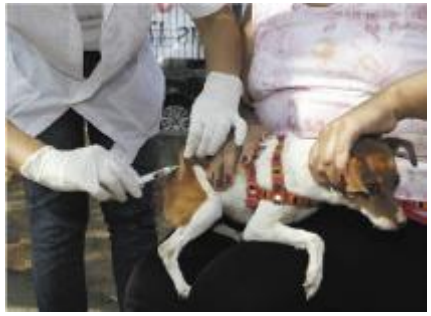
$$\dot{l_d}(t) = b_d a_d m_d(t) s_3(t) x_d(t) - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d) l_d(t)$$

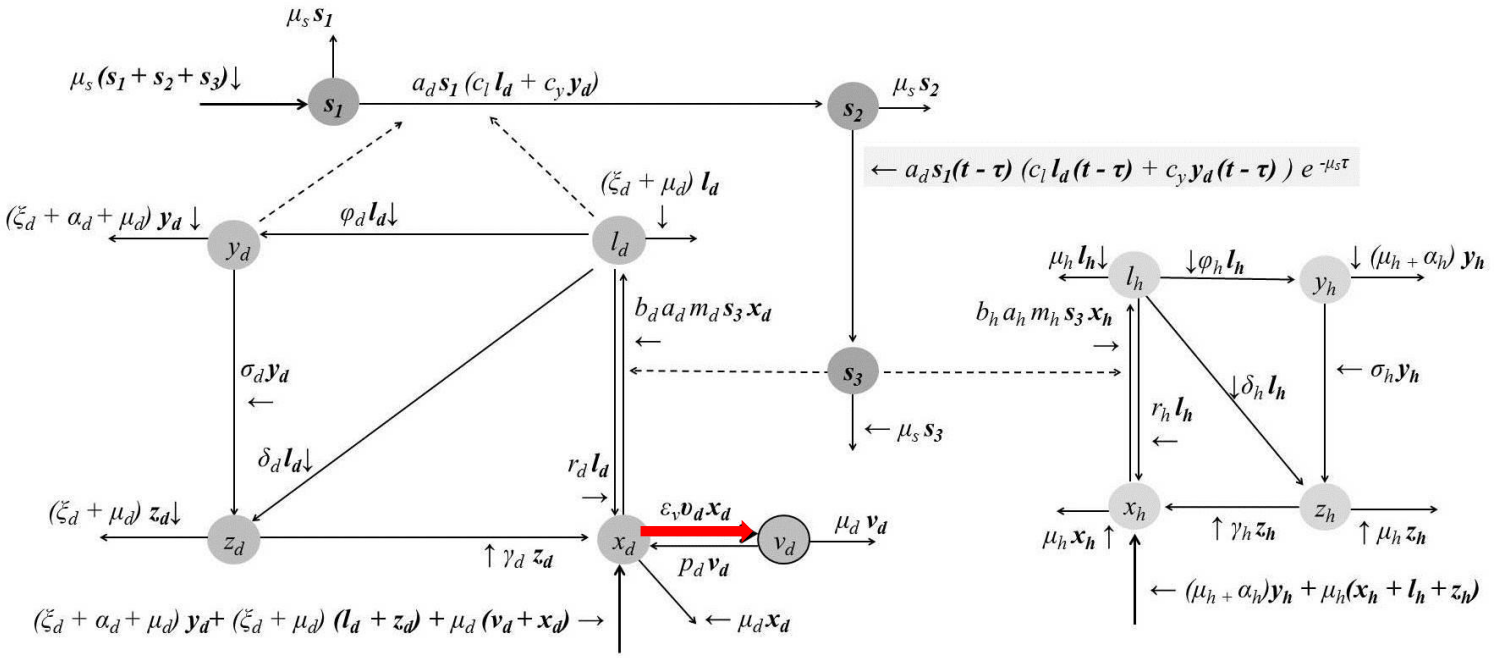
$$\dot{y_d}(t) = \varphi_d l_d(t) - (\mu_d + \alpha_d + \sigma_d + \xi_d) y_d(t)$$

$$\dot{z_d}(t) = \delta_d l_d(t) + \sigma_d y_d(t) - (\mu_d + \gamma_d + \xi_d) z_d(t)$$

$$\dot{v_d}(t) = \varepsilon_v v_d x_d(t) - (p_d + \mu_d + \xi_d) v_d(t)$$

$$\mathbf{B}(t) = (\mu_d + \xi_d)\big(1 - x_d(t)\big) + \alpha_d y_d(t)$$





Dog treatment

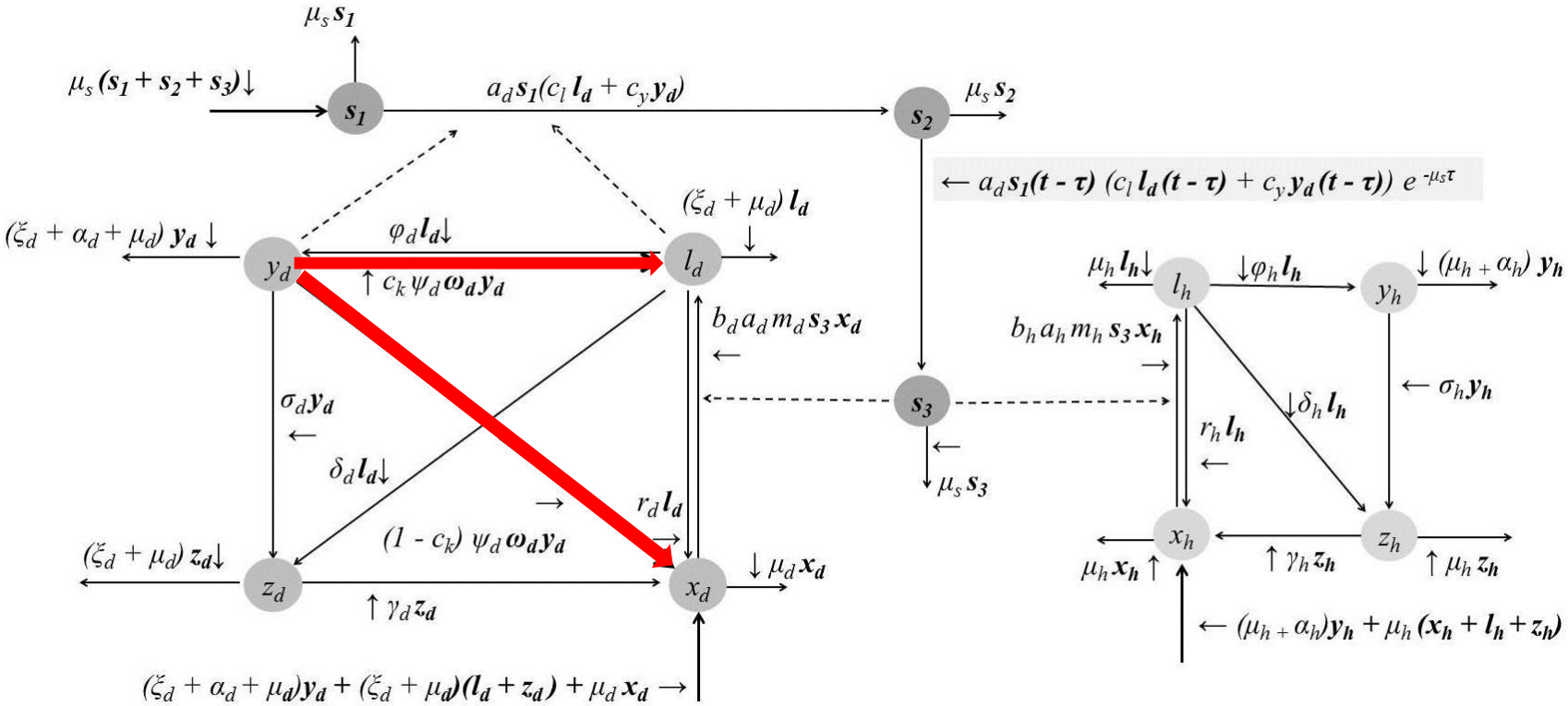
$$\dot{x_d}(t) = \mathbf{B}(t) + (1-c_k)\psi_d\omega_d y_d(t) + r_d l_d(t) + \gamma_d z_d(t) - b_d a_d m_d(t) s_3(t) x_d(t)$$

$$\dot{l_d}(t) = c_k\psi_d\omega_d y_d(t) + b_d a_d m_d(t) s_3(t) x_d(t) - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d) l_d(t)$$

$$\dot{y_d}(t) = \varphi_d l_d(t) - (\mu_d + \alpha_d + \sigma_d + \xi_d + \psi_d\omega_d) y_d(t)$$

$$\dot{z_d}(t) = \delta_d l_d(t) + \sigma_d y_d(t) - (\mu_d + \gamma_d + \xi_d) z_d(t)$$

$$\mathbf{B}(t) = (\mu_d + \xi_d)\big(1 - x_d(t)\big) + \alpha_d y_d(t)$$



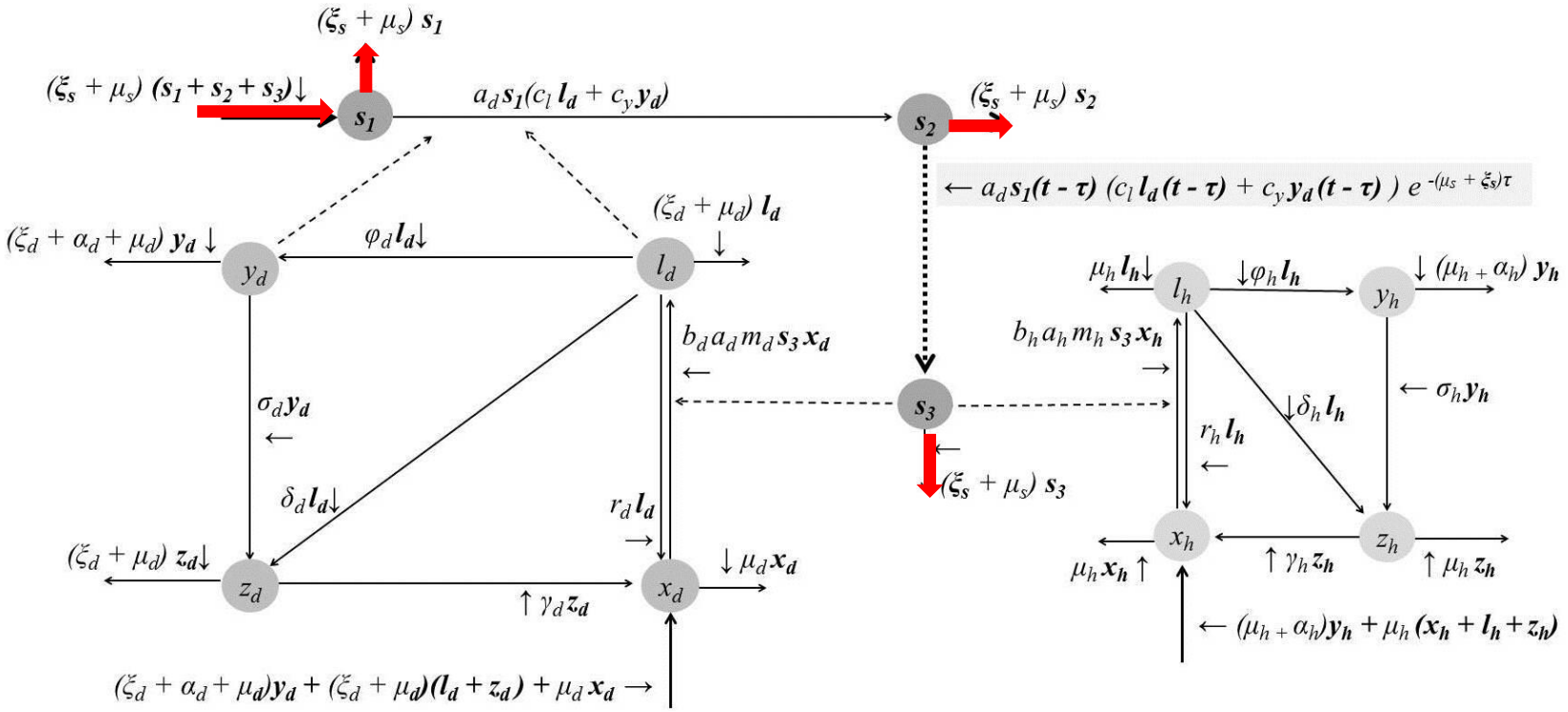
Sandfly population control

$$\dot{s_1}(t) = (\mu_s + \xi_c\, w_{hc}\, m_{h0})\big(s_2(t) + s_3(t)\big) - a_s \mathbf{I}_d(t) s_1(t)$$

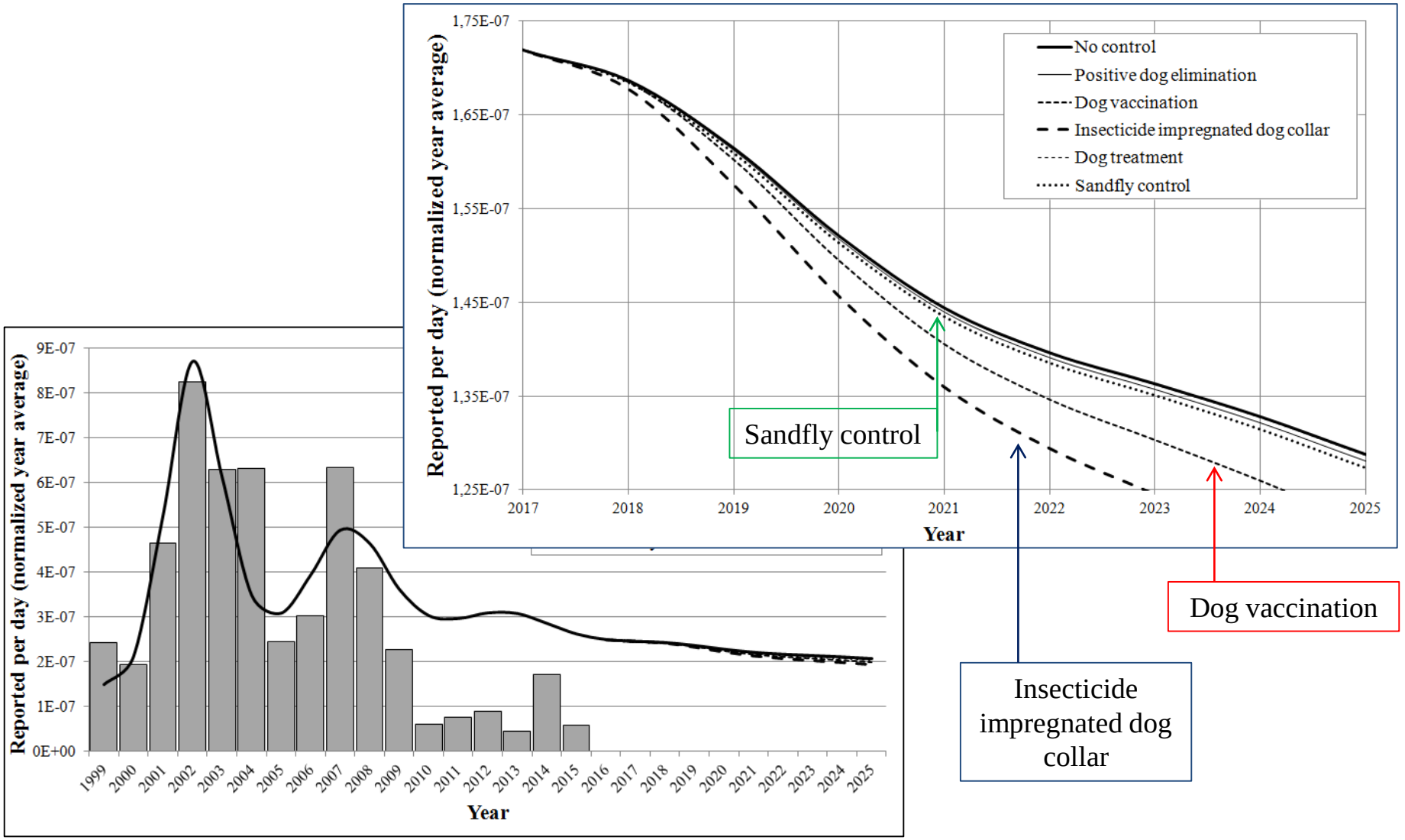
$$\dot{s_2}(t) = a_s \mathbf{I}_d(t) s_1(t) - (\mu_s + \xi_c\, w_{hc}\, m_{h0}) s_2(t) - a_s \mathbf{I}_d(t-\tau) s_1(t-\tau) e^{-(\mu_s + \xi_c\, w_{hc}\, m_{h0})\tau}$$

$$\dot{s_3}(t) = a_s \mathbf{I}_d(t-\tau) s_1(t-\tau) e^{-(\mu_s + \xi_c\, w_{hc}\, m_{h0})\tau} - (\mu_s + \xi_c\, w_{hc}\, m_{h0}) s_3(t)$$

$$\mathbf{I}_d(t) = c_l\, l_d(t) + c_y\, y_d(t)$$



Disease dynamics considering the introduction of control strategies.



Control strategies analysis: the best efficacy and investment result

For each control strategy, we estimated:

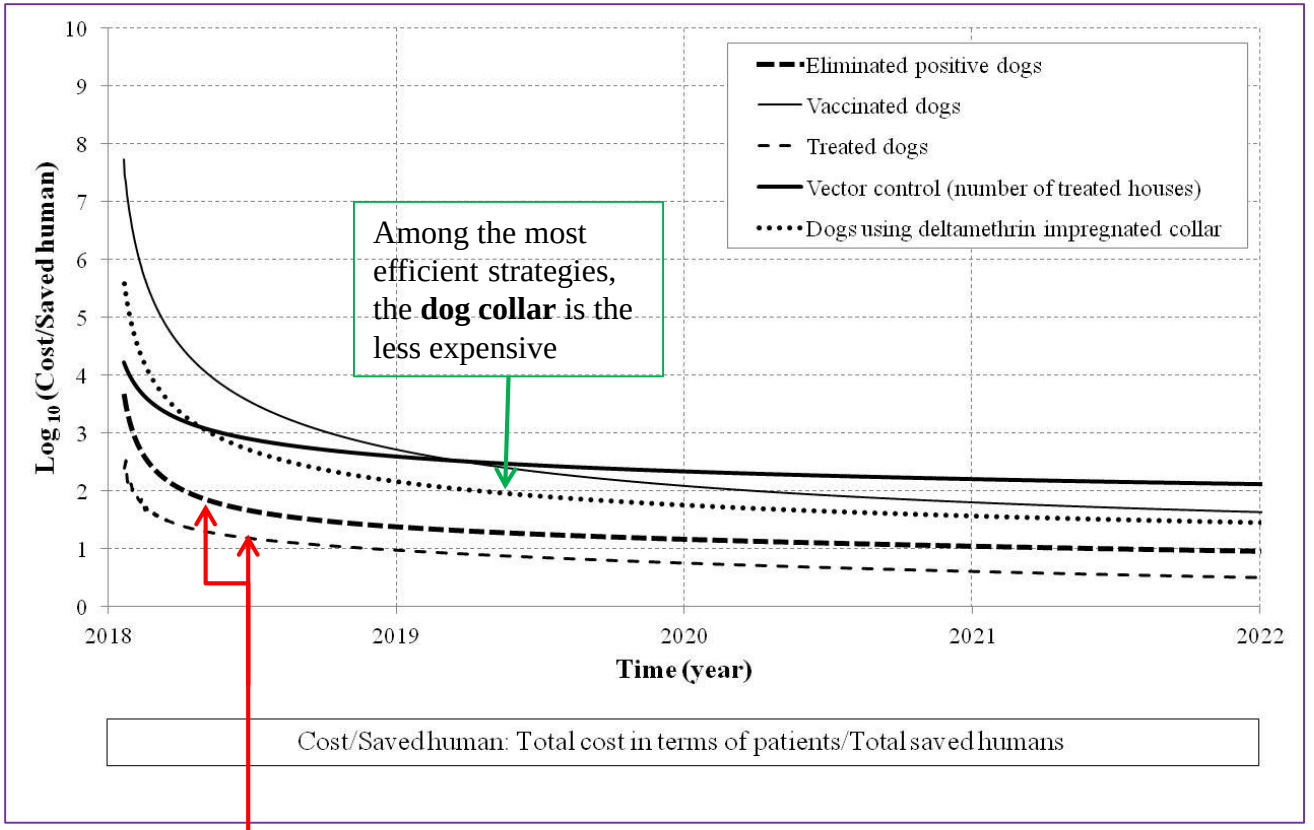
1. The total amount of controlled individuals (dogs or houses);
2. The total of saved human;
3. The cost of investment, normalized by human treatment.

$$\mathfrak{I}_i(t_f) = \frac{T_i(t_f)}{\mathcal{T}^i_{saved}(t_f)}$$ **1** **2**

The ratio of total controlled individuals/total saved humans

$$\mathfrak{C}_i(t_f) = \mathfrak{I}_i(t_f) \times \mathcal{C}_i$$ **3**

Cost of the strategy per saved human



Low cost, but low effect to control ZVL

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Research Article

The Preventive Control of Zoonotic Visceral Leishmaniasis: Efficacy and Economic Evaluation

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Zoonotic Visceral Leishmaniasis (ZVL) is one of the world's deadliest and neglected infectious diseases, according to World Health Organization. This disease is one of major human and veterinary medical significance. The sandfly and the reservoir in urban areas remain among the major challenges for the control activities. In this paper, we evaluated five control strategies (positive dog elimination, insecticide impregnated dog collar, dog vaccination, dog treatment, and sandfly population control), considering disease control results and cost-effectiveness. We elaborated a mathematical model based on a set of differential equations in which three populations were represented (human, dog, and sandfly). Humans and dogs were divided into susceptible, latent, clinically ill, and recovery categories. Sandflies were divided into noninfected, infected, and infective. As the main conclusions, the insecticide impregnated dog collar was the strategy that presented the best combination between disease control and cost-effectiveness. But, depending on the population target, the control results and cost-effectiveness of each strategy may differ. More and detailed studies are needed, specially one which optimizes the control considering more than one strategy in activity.

The full work of this second step has already been published.

Conclusions

• Our results pointed that focusing the control activities on source of infection and on sandfly population is the way to reach the optimal control. This explain the fact that **insecticide impregnated dog collar** was considered the most efficient and cost-effective among the control strategies;

• As each control strategy works in different points of disease maintenance and transmission, it is possible to obtain better results **if considering more than one strategy simultaneously.**

Thank you!

hjunji21@gmail.com

The estimated costs and calculation of control strategy rates

20.18 human cases/year
(average from reported cases data)

397.25 USD/human
(estimated cost for human treatment)

Therefore, per year, the average expanses with human treatment is around:

$20.18 \times 397.25 = 8015$ USD/year
(22 USD/day).

Instead of this 22 USD/day is invested on patient treatments, it would be invested on preventive control strategies…

Araçatuba/SP city in 2016:

- the estimation of dog population is around 34,899 dogs;
- the number of houses is around 64609 houses.

Then, the invested cost:

- per dog
22/34889 = **6.29×10^{-4} USD/(dog × day)**,
- per houses
22/64609 = **3.40×10^{-4} USD/(house × day)**.

What are the control strategies rates, considering the economic restrictions?

As example, if the cost for elimination of one positive dog is 170.71 USD/dog, the maximum rate of elimination dog per day would be:

$6.29 \times 10^{-4}/170.71 = 3.69 \times 10^{-6}$ /day.

Table 8: Summary of average costs for strategy controls and for human patient treatment.

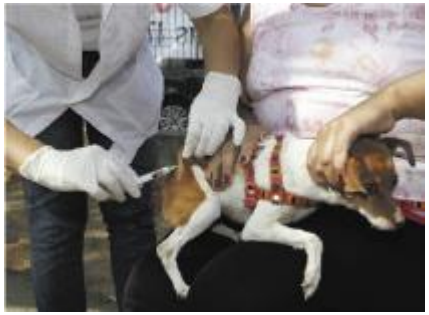
	Meaning	Cost	Cost dimension	Source	Normalized cost (in terms of patient cost)	Normalized cost dimension	Control rate	Control rate dimension
ξ'_d	Elimination of positive dog	170.71	USD/dog	Estimated as Camargo-Neves [31]	0.43	Patient/dog	3.69×10^{-6}	1/day
θ_d	Deltamethrin 4% impregnated dog collar	12.00	USD/dog	Estimated as Camargo-Neves et al. [47]	0.03	Patient/dog	5.25×10^{-5}	1/day
ω_d	Dog treatment with allopurinol and meglumine antimoniate	265.76	USD/dog	Estimated as Miró et al. [45]	0.67	Patient/dog	2.37×10^{-6}	1/day
υ_d	Vaccine	33.00	USD/dog	F. F. Gonzales (Personel communication, 2016)	0.08	Patient/dog	1.91×10^{-5}	1/day
ξ_c	Sandfly population control	23.24	USD × sandfly/(house)^2	Estimated as Camargo-Neves [31]	0.06	Patient × sandfly/(house)^2	1.46×10^{-5}	House/(sandfly × day)
—	Human patient treatment	397.25	USD/patient	Estimated as Akhavan [46]	1.00	Patient/patient	—	—

All strategies would be supported by public health services. Therefore, there would be no charge for population.

Deltametrin 4% impregnated dog collar

Let's assume that those collars are available for inhabitants at local health centers. Thus, we suppose that owners would actively go to health center and acquire the collar for each dog they have. Since we consider all preventive activities are supported by health policies, we can consider that the owner acquire the collar with no charge. If we imagine this simple hypothesis, we conclude that the only additional cost to the health policies is the purchasing of the collar.

Dog vaccination



In our model, we considered that leishmaniasis vaccination would be offered together with rabies vaccine. In other words, we suppose that the rabies vaccination campaign would distribute not only rabies vaccines, but leishmaniasis vaccine too. Since the rabies vaccination campaign has been already included on annual municipality budget, the minimum additional cost to operation of vaccination as control strategy would be only the leishmaniasis vaccine purchasing.

Dog treatment

•Only dogs that present clinical signs and/or symptoms are eligible to be treated;

•We also consider that the dog treatment would be offered by public health policies. Therefore, if the public health services have already included veterinarians in the staff, the minimum additional cost would be the acquisition of the medicine (meglumine antimoniate and allopurinol) and hospital material (for instance, syringes and needles).

Sandfly population control

Sandfly mortality rate

ratio sandfly/human

$$\xi_s = \xi_c \times w_{hc} \times m_{h0}$$

houses to be treated per day and per sandfly

average ratio human/house

Control strategies analysis: the best efficacy and investment result

For each control strategy, we estimated:

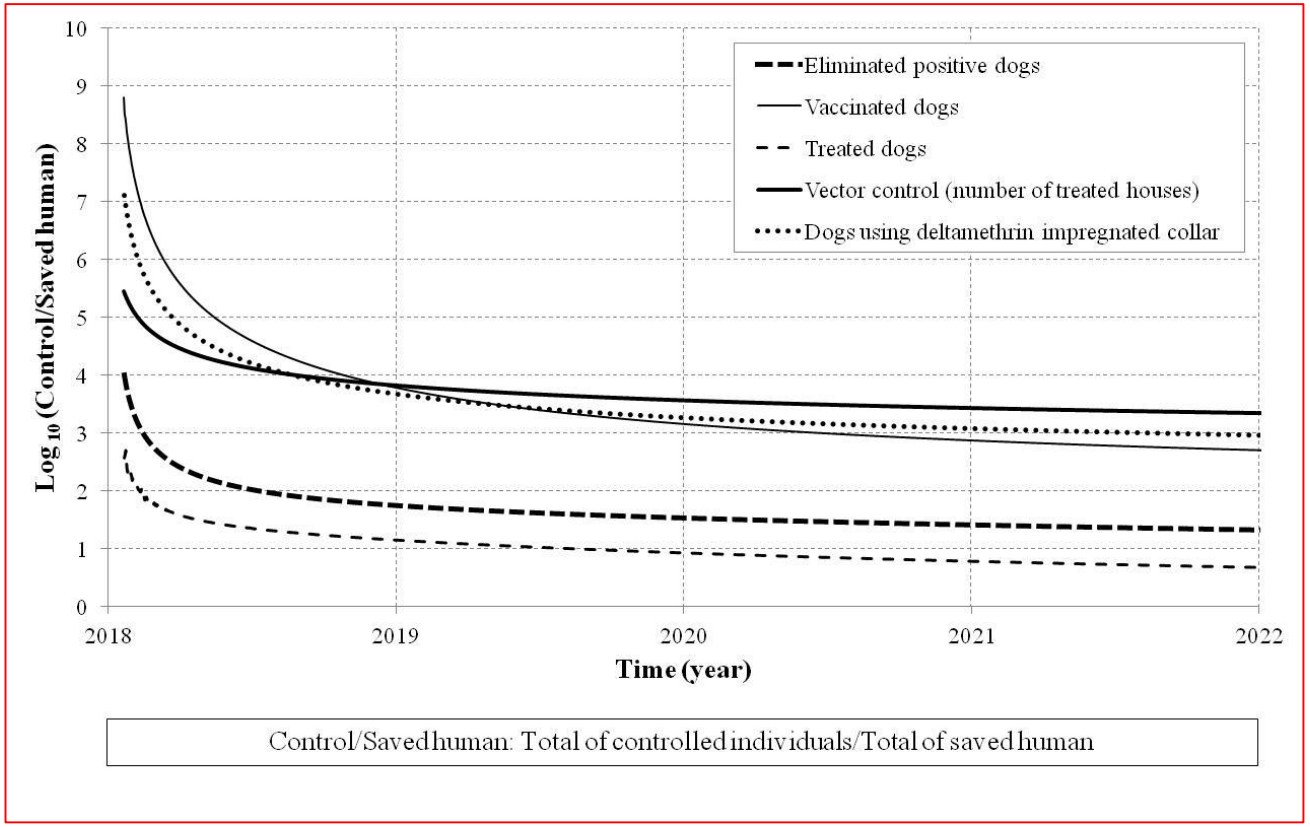
1. The total amount of controlled individuals (dogs or houses);
2. The total of saved human;
3. The cost of investment, normalized by human treatment.

$$\mathfrak{I}_i(t_f) = \frac{T_i(t_f)}{T^i_{saved}(t_f)} \quad (1)\ (2)$$

The ratio of total controlled individuals/total saved humans

$$\mathfrak{C}_i(t_f) = \mathfrak{I}_i(t_f) \times c_i \quad (3)$$

Cost of the strategy per saved human



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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.

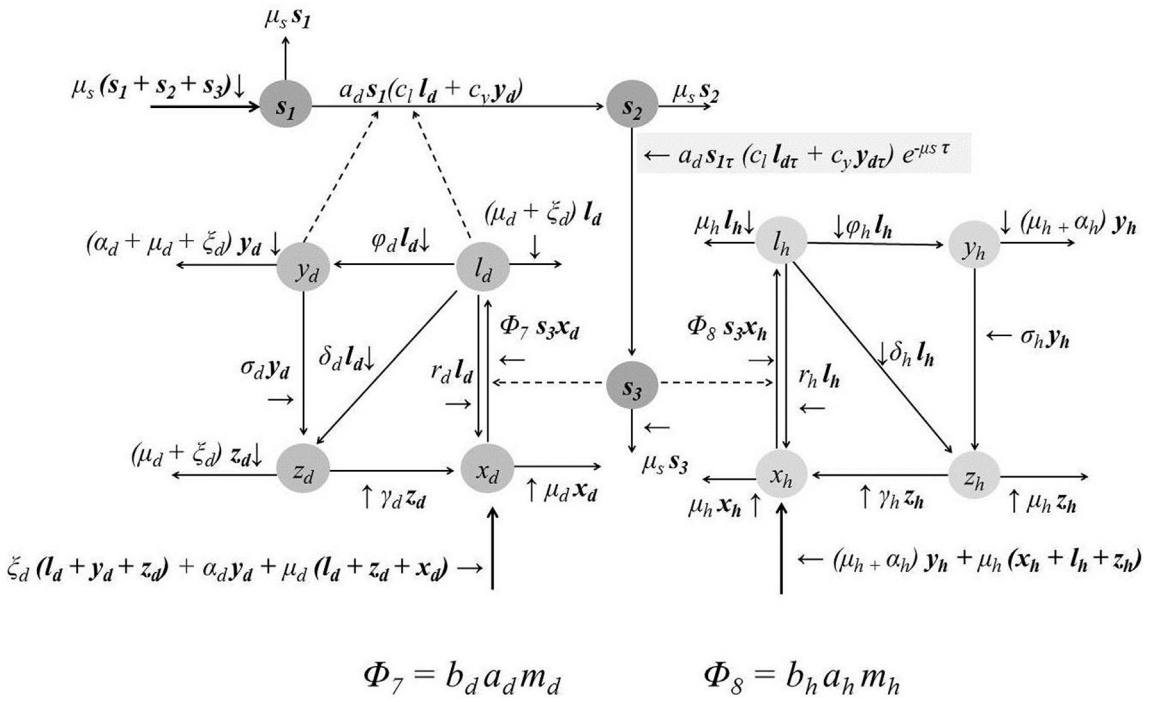
The flowchart and compartment model (Fig. 1) and the set of differential equations describing the model's dynamics (System 1) are presented as following.

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

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.



$$\Phi_7 = b_d a_d m_d \qquad \Phi_8 = b_h a_h m_h$$

Fig. 1. The compartment model and the flowchart. Note that only dogs are source of infection and sandflies transmits the *Leishmania* sp. to both, dogs and humans.

Let now $X_h(t)_h$ be the total number of susceptible individuals in the human population. In an infinitesimal time interval dt, $X_h(t)$ varies as follows:

The infected flies are able to bite on any category of human population. Thus, only a fraction of the infected bites are on uninfected individuals: $a_h S(t)dt\, s_3\,(t) x_h(t)$, where $x_h(t)$ is the fraction of uninfected humans. But, a fraction b_h of $a_h S(t)dt\, s_3\,(t) x_h(t)$ becomes latent, so X_h diminishes by $b_h a_h S(t)dt\, s_3\,(t) x_h(t)$;

Simultaneously, $r_h L_h(t)dt + \gamma_h Z_h(t)dt$ individuals, latent and immune, revert to the susceptible condition, and $\mu_h X_h(t)dt$ die by natural causes other than the disease.

We must add an entrance term, due to natality, which we choose to be $\alpha_h Y_h(t)dt + \mu_h N_h(t)dt$, where α_h is the disease-induced mortality rate, $Y_h(t)$ is the number of infected humans (clinically ill humans), and $N_h(t)$ is the total number of humans needed to maintain a constant population (where $N_h(t) = X_h(t) + L_h(t) + Y_h(t) + Z_h(t)$, with $L_h(t)$ as the number of latent humans and $Z_h(t)$ as the number of recovered humans).

Thus we have:

$$dX_h(t) = \alpha_h Y_h(t)dt + \mu_h N_h(t)dt - b_h a_h S(t)dt\, s_3\,(t) x_h(t) + r_h L_h(t)dt + \gamma_h Z_h(t)dt - \mu_h X_h(t)dt \tag{2}$$

Dividing this equation by $N_h(t)dt$ and calling $S(t)/N_h(t) = m_h$, we get the first equation of System (1).

Observe that m_h is a function time-dependent: $m_h(t)$. This expression is the simplest way to simulate the changings on sandfly population size dynamics between 1999 and 2015.

We can apply the same process in order to obtain the equation for the dynamic of susceptible dogs (x_d). However, observe from Table 1 that the ratio sandfly:dog depends on the ratio sandfly:human and on the ratio human:dog: $m_d = x_h(t) \times w_{dh}$. Although all the populations are constant, if we consider the real number of individuals, we expect more humans than dogs. Thus, if the sandfly population is constant, we have different values for m_d and m_h.

The last three equations of system 1 refer to the flies. When infected, a fly remains in a latent stage for a period of time τ. This time corresponds to the extrinsic incubation period of the parasite inside the vector fly. Numerically it lasts for about half the life expectancy of the flies.

Let S_1 be the number of susceptible flies. In an infinitesimal period of time dt, $(a_s(L_d(t) + Y_d(t)/N_d(t))dt)\, S_1(t)$ bites due to uninfected flies occur on latent and infected dogs (humans are not considered to be infective for flies; see Tesh (1995)). A fraction c_l and c_y of the flies (who bites latents and clinically ill dogs, respectively) becomes latently infected as a result. Therefore, we have:

$$dS_1(t) = \mu_s(S_2(t) + S_3(t))dt - a_s(c_l l_d(t) + c_y y_d(t))S_1(t)dt \tag{3}$$

Table 1
Parameters adopted in our model. The indexes h, d and s stand for humans, dogs and sandflies, respectively.

Parameter	Meaning	Value	Dimension	Source
μ_h	Natural mortality rate	3.67×10^{-5}	1/day	Brazilian Institute of Geography and Statistics, Brazil (2013)
α_h	Kalazar specific lethality	6.31×10^{-3}	1/day	World Health Organization (2017)
a_h	Average daily biting rate	2.00×10^{-1}	human/(sandfly × day)	Epidemiological Surveillance Direction, Santa Catarina State, Brazil (2008)
$m_h(t)$	Vector density per host (time-dependent)	*Variable*	sandfly/human	Fitted
w_{hc}	Ratio human:house	3	human/house	Brazilian Institute of Geography and Statistics, Brazil (2013)
b_h	Proportion of infective bites	1.00×10^{-2}	dimensionless	Molineaux and Gramiccia (1980)
r_h	Spontaneous recovery rate	5.48×10^{-4}	1/day	Badaró et al. (1986)
γ_h	Loss of immunity rate	5.48×10^{-4}	1/day	Kault and March (1991)
δ_h	Latent recovery rate	1.10×10^{-2}	1/day	Bardaró et al. (1986)
φ_h	Inverse of incubation period	4.00×10^{-4}	1/day	Pearson and Souza (1990)
σ_h	Recovery rate to immunes	2.50×10^{-3}	1/day	Ministry of Health, Brazil (2006)
η_h	Proportion of unreported cases	0.705	dimensionless	Maia-Elkhoury, Carmo, Sousa-Gomes, and Mota (2007)
μ_d	Natural mortality rate	2.28×10^{-4}	1/day	http://www.sciencedirect.com/science/article/pii/S0960982213004132 Selman, Nussey, and Monaghan (2013)
α_d	Kalazar specific lethality	1.81×10^{-3}	1/day	Lanotte, Rioux, Perieres, and Vollhardt (1979)
a_d	Average daily biting rate	2.00×10^{-1}	dog/(sandfly × day)	Epidemiological Surveillance Direction, Santa Catarina State, Brazil (2008)
w_{dh}	Ratio human:dog for Araçatuba/SP city	10/1.8	human/dog	Andrade, Queiroz, Perri, and Nunes (2008)
$m_d(t)$	Vector density per host	$w_{dh} \times m_h(t)$	sandfly/dog	–
φ_d	Inverse of incubation period	3.78×10^{-4}	1/day	Greene (2011)
b_d	Proportion of infective bites	1.00×10^{-2}	dimensionless	Molineaux and Gramiccia (1980)
r_d	Spontaneous recovery rate	2.74×10^{-4}	1/day	Lanotte et al. (1979)
γ_d	Loss of immunity rate (recovery to susceptible)	2.74×10^{-3}	1/day	Kault and Marsh (1991)
σ_d	Recovery rate from clinically ill to immunes	9.04×10^{-4}	1/day	Lanotte et al. (1979)
δ_d	Latent recovery rate	8.22×10^{-3}	1/day	Lanotte et al. (1979)
ξ_d	Dog elimination rate	3.36×10^{-4}	1/day	Camargo-Neves (2004)
μ_s	Natural mortality rate	5.00×10^{-2}	1/day	Ministry of Health, Brazil (2006)
τ	Extrinsic incubation period	7	day	Neva and Sacks (1990)
a_S	Average daily biting rate (on dogs)	2.00×10^{-1}	1/day	Estimated as Epidemiological Surveillance Direction, Santa Catarina State, Brazil (2008)
c_l	Probability of latent dog to infect the sandfly	0.385	dimensionless	Laurenti et al. (2013)
c_y	Probability of clinically ill dog to infect the sandfly	0.247	dimensionless	Laurenti et al. (2013)

Dividing by $S(t) = S_1(t) + S_2(t) + S_3(t)$ and by dt, we get the equation for non-infected sandflies ($s_1(t)$).

Basically, we adopted different mathematical techniques for dogs and humans in latency stage and for sandflies in latency stage because there are differences between their biological characteristics. In the case of human and dogs, once they are in the incubation period, this latency time usually presents an exponential distribution (in average approach). That's why we chose modelling this incubation process using a latent compartment instead of a delay term. On the other hand, the incubation process regarding to sandflies is biologically different from humans and dogs. When a sandfly is infected with *leishmania* parasite, this sandfly becomes infective only after a constant latent period (Bocharov & Rihan, 2000). Therefore, in this case, it is much more feasible using delay term to model sandfly population dynamics instead of latent compartments. In addition, the infected dogs get infective in an exponential fasion whereas the sandflies get infective immediately after the extrinsic incubation period τ elapses.

Although this is a brief but detailed description about the non-infected categories equations (that is, x_h, x_d and s_1), we can note that each term of our system equation has a biological meaning. The meaning of each term is in agreement with the parameter in which is together with.

Although Zoonotic Visceral Leishmaniais (ZVL) is a disease that causes immunological damages (and, therefore potencialize the probability of co-infections), those co-infections were possible and lethal only because of primary leishmaniasis infection. Thus, we considered that ZVL - infected individuals die because of the ZVL infection.

2.1. The positivity and boundedness of the solutions

We argue about the positivity and boundeness of the solutions considering the proof provided by Burattini et al. (1998), which our model was based on.

An important point about system (1) is that positivity is preserved. Thus, given positive initial conditions, the variables remain non-negative.

Firstly, let us consider the equations for sandfly population dynamics (that is, the equations for s_1, s_2 and s_3). Observe that the term $a_s(c_l l_d(t) + c_y y_d(t))$ is always positive in those three equations. However, it may appear at first sight that positivity is not preserved by system (1), because if $s_2(t) = 0$ in the equation for $s_2(t)$, the delayed term $a_s(c_l l_d(t-\tau) + c_y y_d(t-\tau))s_1(t-\tau)e^{-\mu_s \tau}$ could be non-zero. But, we can demonstrate that if $s_2(t)$ becomes zero, then this delayed term (which is a term of removal from the compartment s_2) must necessarily be zero. Also, observe that the equations for susceptible category (in both human and dog populations) can be rewrite as (4):

$$\begin{aligned} \dot{x_h}(t) &= \mu_h(1 - x_h(t)) + r_h l_h(t) + \alpha_h y_h(t) + \gamma_h z_h(t) - b_h a_h m_h(t) s_3(t) x_h(t) \\ \dot{x_d}(t) &= (\mu_d + \xi_d)(1 - x_d(t)) + r_d l_d(t) + \alpha_d y_d(t) + \gamma_d z_d(t) - b_d a_d m_d(t) s_3(t) x_d(t) \end{aligned} \tag{4}$$

As $0 < x_i(t) < 1$ $(i = h, d)$, those susceptible categories can never become negative. As a consequence, the other categories $l_i(t)$, $y_i(t)$ and $z_i(t)$ can never become negative. In addition if $0 < s_1(t) < 1$ for some t it will never become negative afterwards. Note also that if $s_3(t) > 0$ for some t it Will also never become negative since $a_s(c_l l_d(t) + c_y y_d(t)) > 0$.

Let now $a_s(c_l l_d(t') + c_y y_d(t'))s_1(t')e^{-\mu_s(t-t')}dt'$ be the proportion of flies which become infected between t' and $t' + dt'$ and have survived for the period $t - t' \leq \tau$. This expression is positive and is a fraction of the total latent flies.

Note that the proportion of latent flies is the sum of $a_s(c_l l_d(t') + c_y y_d(t'))s_1(t')e^{-\mu_s(t-t')}$ in t', from $t - \tau$ to t, that is:

$$s_2(t) = \int_{t-\tau}^{t} a_s(c_l l_d(t') + c_y y_d(t'))s_1(t')e^{-\mu_s(t-t')}dt' \tag{5}$$

Therefore, if $s_2(t) = 0$ then $n(t', t) = 0$ for all t'. Now, replacing t' by $t - \tau$ in $a_s(c_l l_d(t') + c_y y_d(t'))s_1(t')e^{-\mu_s(t-t')}dt'$, we have that if $s_2(t) = 0$, then $a_s(c_l l_d(t-\tau) + c_y y_d(t-\tau))s_1(t-\tau)e^{-\mu_s \tau} = 0$.

Once the positivity of the solutions was proven, we can discuss about the boundedness of the solutions. Here in, we will consider a similar approach as that one presented by Cai, Lashari, Jung, Okosun, and Seo (2013). Thus, it can be shown that the region Ω given by (6):

$$\begin{aligned} \Omega = \Big\{ &(x_h(t), l_h(t), y_h(t), x_d(t), l_d(t), y_d(t), s_1(t), s_3(t)) \in \mathbb{R}_+^8 : \ 0 \leq x_h(t) + l_h(t) + y_h(t) \leq 1, \ 0 \leq x_d(t) + l_d(t) + y_d(t) \\ &\leq 1, \ 0 \leq s_1(t) + s_3(t) \leq 1 \Big\} \end{aligned} \tag{6}$$

is positively invariant with respect to system (1). Thus, every solution of (1), with initial conditions in Ω remains there for $t > 0$. Therefore, it is sufficient to consider the dynamics of the flow generated by (1) in Ω. In this region the model can be considered as been epidemiologically and mathematically well posed.

3. The reported cases

In Brazil, Zoonotic Visceral Leishmaniasis is a notifiable disease (Ministry of Health, Brazil, 2006; Day et al., 2012). Thus, we can assume:

- A infected human should look for medical treatment when he/she will become clinically ill (y_h);
- Only a fraction of those humans that are clinically ill will be reported to sanitary authorities. The remaining fraction (I) will not look for medical help, even if the clinical symptoms and signs appear; or (II) will not be correctly reported in the hospitals.

Now, let's see again the equation for $y_h(t)$ in system (1):

$$\dot{y_h}(t) = \varphi_h l_h(t) - (\mu_h + \alpha_h + \sigma_h) y_h(t) \tag{7}$$

The term $\varphi_h l_h(t)$ from (7) means the rate of latent humans who become clinically ill per day. Thus, per day, those amounts of humans are eligible to look for medical help. However, only a fraction $(1 - \eta_h)$ of those clinically ill humans will be correctly notified to sanitary authorities. Therefore, the daily rate of reported human cases is defined by equation (8):

$$R(t) = (1 - \eta_h)\varphi_h l_h(t) \tag{8}$$

The Centre of Epidemiological Surveillance of São Paulo State (CES-SP) (2016) is the institution who administrates the data about ZoonoticVisceral Leishmaniasis in São Paulo State. In order to validate our model, we decided to use the data of human reported cases from the municipality of Araçatuba (São Paulo State – Brazil) as reference, because it is an endemic city for this disease. Those data are presented in Table 2 and are available on Centre of Epidemiological Surveillance of São Paulo State website (Centre of Epidemiological Surveillance of São Paulo State, Brazil, 2016).

Note that we have the total of reported cases per year. Thus, since our time scale is *day*, we estimated an average of human reported cases per day for each year (dividing the total from each year by 365). Finally, we also have to consider that our model works with normalized population (all three populations are constant). Thus, as a last step, we have to divide each rate of human reported cases per day by the official population size of Araçatuba municipality. The population size of Araçatuba municipality is available on Brazilian Institute of Geography and Statistics (BIGS) website (Brazilian Institute of Geography and Statistics, Brazil, 2016).

In order to fit and compare our results to real data, we also calculated a normalized average of reported cases per day from each 365 days of simulation. This simulation was run considering 60 years and the obtained curve was fitted by simple handling along the time-axis (for instance, we could assume the initial day $t_0 = 1$ as the first day of 1970 or 1980, depending on how best the simulated curve fits on the real data). Thus, we could obtain the yearly average of reported human cases per day and compare it to the real yearly average provided by CES-SP (Table 2).

4. The basic reproduction number ($\mathscr{R}_o$)

According Anderson and May (2010), the Disease Free Equilibrium (DFE) state means the state in which there is no disease in the population. Also, there are no infected individuals, even latent ones.

The basic reproduction number, denoted $\mathscr{R}_o$, is 'the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual'. If $\mathscr{R}_o < 1$, then on average an infected individual produces less than one new infected individual over the course of its infectious period, and the infection cannot grow. Conversely, if $\mathscr{R}_o > 1$, then each infected individual produces, on average, more than one new infection, and the disease can invade the population (van den Driessche & Watmough, 2002).

In order to estimate the $\mathscr{R}_o$ of our model, we applied the method presented by van den Driessche and Watmough (2002). Here, we will avoid any mathematical demonstration regarding to Driessche & Watmough method, since this is not the focus of this work. However, the idea is to calculate the relationship between the parameters that causes instability to the trivial solution of system (1), which represents the absence of disease in the populations considered. That is, we studied the stability of the solution $x_i = 1, l_i = 0, y_i = 0, z_i = 0$ (where $i = h, d$) and $s_1 = 1, s_2 = 0, s_3 = 0$. If this solution turns out to be stable, that is, when $\mathscr{R}_o < 1$, the disease cannot invade the population (Burattini et al., 1998). We strongly suggest the reader to see all the details in their publication (see van den Driessche and Watmough (2002) in the references list).

Herein, we remark that the Driessche & Watmough method was not developed for delay differential equations. Thus, we refer to Burattini et al. (1998) and Wei (2004) to explain about the delayed terms. Since this system contains a time delay in the population of flies, the linearization around the trivial solution is not straightforward. Basically, the $\mathscr{R}_o$ analysis is a particular case of stability analysis on free-disease state condition. In the case of delayed term in our system, we need to consider two Jacobian Matrices separately: one is the usual Jacobian (for term without delay) and the other one is the Jacobian

Table 2
Human reported cases in Araçatuba municipality: average of the normalized rate per day for each year.

Year	Human reported cases per year (CES-SP)	Araçatuba's Human population size (BIGS)	Average of normalized human reported cases per day
1999	15	169303	2.43E-07
2000	12	170296	1.93E-07
2001	29	171289	4.64E-07
2002	52	172768	8.25E-07
2003	40	174399	6.28E-07
2004	41	177823	6.32E-07
2005	16	179717	2.44E-07
2006	20	181598	3.02E-07
2007	42	181371	6.34E-07
2008	27	181143	4.08E-07
2009	15	182204	2.26E-07
2010	4	182365	6.01E-08
2011	5	182526	7.51E-08
2012	6	183441	8.96E-08
2013	3	190536	4.31E-08
2014	12	191662	1.72E-07
2015	4	192757	5.69E-08

for delayed terms only. We suggest the reader to see Burattini et al. (1998) and Wei (2004), in order to understand how to handle delayed differential equations for $\mathscr{R}_o$ analysis.

We will suppress all steps of the calculation and present the final equation for $\mathscr{R}_o$. Thus, we get (Equation (9)):

$$\mathscr{R}_0(t) = \frac{m_d(t)a_d a_s b_d e^{-\mu_s \tau}\left(c_l(\sigma_d + \alpha_d + \mu_d + \xi_d) + c_y \varphi_d\right)}{(r_d + \delta_d + \varphi_d + \mu_d + \xi_d)(\sigma_d + \alpha_d + \mu_d + \xi_d)\mu_s} \tag{9}$$

It is possible to observe that equation (9) splits naturally into two terms: the contributions to $\mathscr{R}_o$ from latent dog population and clinically ill dog population. Thus, we have system (10):

$$\begin{aligned} \mathscr{R}^l_{od}(t) &= \frac{w_{dh} m_h(t) a_d a_s b_d e^{-\mu_s \tau} c_l}{(r_d + \delta_d + \varphi_d + \mu_d + \xi_d)\mu_s} \\ \mathscr{R}^y_{od}(t) &= \frac{w_{dh} m_h(t) a_d a_s b_d e^{-\mu_s \tau} c_y \varphi_d}{(r_d + \delta_d + \varphi_d + \mu_d + \xi_d)(\sigma_d + \alpha_d + \mu_d + \xi_d)\mu_s} \end{aligned} \tag{10}$$

Let's explain biologically the meaning of $\mathscr{R}_o$ in a similar approach as that one presented by Burattini et al. (1998). Given a population in a DFE state, someone could ask if the introduction of a small amount of infective individuals would start an epidemic outbreak. Once this epidemic appears, it eventually would converge to an endemic equilibrium state (that is, equilibrium with the disease). In this case, if $\mathscr{R}_0 > 1$, even a small amount of infective individuals would start an epidemic, which it would be in a endemic level different from zero. However, observe that the expression from equation (9) includes 2 components, $\mathscr{R}^l_{od}$ e $\mathscr{R}^y_{od}$ (system (10)). As an example, once a small amount of latent dogs (l_d) is introduced, if $\mathscr{R}^l_{od} > 1$ the epidemic would be installed due to the introduction of those small amount of latent dogs. The same idea occurs if we consider clinically ill dogs (y_d), since $\mathscr{R}^y_{od} > 1$. And, if the introduced individuals are from different subpopulations, the epidemic would be installed if the sum of the all $\mathscr{R}_o$ contributions is more than 1. In other words, we should have $\mathscr{R}^l_{od} + \mathscr{R}^y_{od} = \mathscr{R}_o > 1$.

5. Fitting the ratio Human:Sandflies ($m_h(t)$) and model dynamics

Previously, we demonstrated by Equation (9) that $\mathscr{R}_o$ depends on the parameter $m_d(t)$ (dog/sandfly ratio). But, we can assume that dog population size is related to human population's habits and culture (Beck, 1973; Molineaux & Gramiccia, 1980). Therefore, we can estimate the human:sandfly ratio if we consider the human:dog ratio (w_{dh}) for the municipality of Araçatuba. According to Andrade et al. (2008) this ratio was estimated as $w_{dh} = 10/1.8$ *human/dog*. As consequence, we have $m_d(t) = m_h(t) \times w_{dh}$.

Once we need to fit the $m_h(t)$ value for our model and considering we are interesting to understand the disease dynamic, we can consider the relation between $m_h(t)$ and $\mathscr{R}_o$ according to Equation (9). In this case we have to suppose $\mathscr{R}_o > 1$. Thus, we obtain:

$$\mathscr{R}_0 > 1 \therefore m_h(t) > \frac{(r_d + \delta_d + \varphi_d + \mu_d + \xi_d)(\sigma_d + \alpha_d + \mu_d + \xi_d)\mu_s}{w_{dh} a_d^2 b_d e^{-\mu_s \tau}\left(c_l(\sigma_d + \alpha_d + \mu_d + \xi_d) + c_y \varphi_d\right)} \tag{11}$$

where numerically we need $m_h(t) > 0.74$ *sandfly/human*.

The real data provided in Table 2 suggests that the incidence was not constant along those years in which the data was collected (1999–2015). One reasonable hypothesis is the climate changings that have been occurring for the last years (Massad, Coutinho, Lopez, & da Silva, 2011). Thus, since the sandfly population dynamics depends on climate and geographical conditions, we can include this idea in our model by fitting $m_h(t)$ as time-function. It is not the scope of this paper to model the sandfly population dynamics according to climatic and geographic variations. Therefore, we will assume that a simple function for $m_h(t)$, that can fit the simulation data to the real data, should include those climatic and geographic variabilities.

Let's consider the following function for $m_h(t)$:

$$m_h(t) = m_{h0} + \left(\frac{t e^{-\left(L + \frac{t}{K_1}\right)}}{K_1}\right)\left(A + B\sin\left(\frac{2\pi t}{T}\right)\right) \quad \lim_{t \to +\infty} m_h(t) = m_{h0} \tag{12}$$

The parameter values for (12) are in Table 3. Biologically, we can suppose that sandfly population reaches stability and oscillations decrease overtime. Thus, note that for $t \to +\infty$ we have $m_h(t)$ trending to m_{h0}.

Although the ratio shows an oscillating behavior over time, we remind that $m_h(t)$ is the ratio sandfly/human. In other words, in our model, the absolute size of sandfly population is time dependent. However, we normalized our system. Once the

Table 3
Parameter values for (12) and their biological meaning.

Parameter	Meaning	Value	Dimension	Source
m_{h0}	Vector density per host (baseline value)	0.75	sandfly/human	Fitted
A	Vector density per host	3.4	sandfly/human	Fitted
B	Vector density per host	8.3	sandfly/human	Fitted
L	Linear constant	3.0	dimensionless	Fitted
K_1	Proportionality constant	3.5×365	day	Fitted
T	Sandfly population dynamics period	5.5×365	day	Fitted

population is normalized, we can assume $s_1(t) + s_2(t) + s_3(t) = 1$ (that is, the sum of proportions of each category in the sandfly population is always equals to 1). Thus, in a proportional approach, all three populations (humans, dogs, and vectors) can be considered constants.

Let's consider the equilibrium condition, that is, $\lim_{t \to +\infty} m_h(t) = m_{h0}$. If we substitute the parameters that compose the $\mathscr{R}_o$ expressions in (9) and (10), we obtain $\mathscr{R}^l_{od} \cong 0.96$ and $\mathscr{R}^y_{od} \cong 0.07$. Therefore, the sum of those two values provides us the total contribution from those two classes of dogs, $\mathscr{R}_o = \mathscr{R}^l_{od} + \mathscr{R}^y_{od} \cong 1.03$. The difference between $\mathscr{R}^l_{od}$ and $\mathscr{R}^y_{od}$ values could be explained by the skin integrity of the infected dogs. In other words, the clinically ill dogs (y_d) usually present skin lesions and the skin of a dog from this category is more damaged than that one from a latent dog (l_d). Because of this, we can suppose that the sandflies are less probable to acquire available parasites from dogs of y_d category. On the other hand, the opposite occurs with the latent dog, since their skins are heathier than the clinically ill dog's skin (Laurenti et al., 2013).

6. Stability analysis

Mathematically, our model is a nonlinear delay differential equation system. It is very usual to model the dynamics of natural phenomena using nonlinear systems, because most of them are ruled by nonlinear behavior. However, in opposition to linear systems, the dynamics of nonlinear systems commonly are not simple and they may appear chaotic. Thus, because of the behavior of nonlinear differential systems, it is useful to study the stability of this system. Herein, we follow the method describe by Wei (2004).

A nonlinear system is considered stable when the variable's derivatives are zero ($\dot{f}(t) = 0, f(t)$ is the vector of variables). When the stability is reached, the variables assume constant values, and they are the fixed points of the system. In order to determine how stable the system is when it reaches the fixed points, we need to obtain the Jacobian Matrix (J_0, as the usual Jacobian Matrix, and J_τ, for the time-delayed terms) of the system and calculate its values on the fixed points. Following, we calculate the eigenvalues λ of the determinant below (Equation (13)).

$$det\left|J_0 + e^{-\lambda\tau}J_\tau - \lambda I\right| = 0 \tag{13}$$

where I is the identity matrix. If all eigenvalues λ has negative real part, the equilibrium of the system at the fixed point is stable. On the other hand, if there is at least one eigenvalue λ with positive real part, the system at the fixed point is unstable.

Basically, our model is composed by three populations, but the human population dynamics is directly dependent on the sandfly population dynamics. On the other hand, the sandfly and dog populations are mutually dependent. Since the human population does not interfere on dog or sandfly dynamics, we do not need to include the humans' equations in the fixed point calculation (the humans' population fixed points will naturally be solved once we obtain s_3^* fixed point). Thus, we would work with seven equations only.

We also have to consider that the populations are constants: $x_d(t) + l_d(t) + y_d(t) + z_d(t) = 1$ and $s_1(t) + s_2(t) + s_3(t) = 1$. If we use those two conditions, we are allowed to eliminate one differential equation of each population by substituting one category of each population by the respective condition. For convenience, we adopted $z_d(t) = 1 - (x_d(t) + l_d(t) + y_d(t))$ and $s_2(t) = 1 - (s_1(t) + s_3(t))$. Thus, we obtain the following system (14), reduced to five equations.

$$\begin{aligned}
\dot{x_d}(t) &= -\Xi x_d(t) - El_d(t) - Fy_d(t) - \beta s_3(t)x_d(t) + \Xi \\
\dot{l_d}(t) &= \beta s_3(t)x_d(t) - Gl_d(t) \\
\dot{y_d}(t) &= \varphi_d l_d(t) - Hy_d(t) \\
\dot{s_1}(t) &= -\mu_s s_1(t) - C_1 l_d(t)s_1(t) - D_1 y_d(t)s_1(t) + \mu_s \\
\dot{s_3}(t) &= -\mu_s s_3(t) + C_2 l_{d\tau}(t)s_{1\tau}(t) + D_2 y_{d\tau}(t)s_{1\tau}(t)
\end{aligned} \tag{14}$$

where the terms with the index τ are the time-delayed terms. The meaning of each parameter is in Table 4.

Before obtain the Jacobian Matrices J_0 and J_τ, we need to linearize system (14) around the fixed points, applying Taylor series for differential equation systems (Fiedler-Ferrara & Prado, 1995). Thus, considering the expansion until the first order terms, we have system (15).

Table 4
Parameter meanings for (14). All parameters are real positive values.

Parameter	Meaning
Ξ	$\mu_d + \xi_d + \gamma_d$
β	$b_d\, a_d\, m_d$
C_1	$a_s\, c_l$
C_2	$a_s\, c_l \exp(-\mu_s \tau)$
D_1	$as\, c_y$
D_2	$a_s\, c_y \exp(-\mu_s \tau)$
E	γ_d - r_d
F	γ_d - α_d
G	$\mu_d + \xi_d + r_d + \delta_d + \varphi_d$
H	$\mu_d + \xi_d + \alpha_d + \sigma_d$

$$\begin{aligned}
\dot{\widetilde{x_d}}(t) &= -(\Xi - \beta s_3^*)\widetilde{x_d}(t) - E\widetilde{l_d}(t) - F\widetilde{y_d}(t) - \beta x_d^* \widetilde{s_3}(t) \\
\dot{\widetilde{l_d}}(t) &= \beta s_3^* \widetilde{x_d}(t) - G\widetilde{l_d}(t) + \beta x_d^* \widetilde{s_3}(t) \\
\dot{\widetilde{y_d}}(t) &= \varphi_d \widetilde{l_d}(t) - H\widetilde{y_d}(t) \\
\dot{\widetilde{s_1}}(t) &= -C_1 s_1^* \widetilde{l_d}(t) - D_1 s_1^* \widetilde{y_d}(t) - \left(\mu_s + C_1 l_d^* + D_1 y_d^*\right)\widetilde{s_1}(t) \\
\dot{\widetilde{s_3}}(t) &= -\mu_s \widetilde{s_3}(t) + C_2 s_{1\tau}^* \widetilde{l_{d\tau}}(t) + D_{2\tau} s_{1\tau}^* \widetilde{y_{d\tau}}(t) + \left(C_2 l_{d\tau}^* + D_2 y_{d\tau}^*\right)\widetilde{s_{1\tau}}(t)
\end{aligned} \tag{15}$$

where the terms with index τ refer to time-delay terms, the star '*' refers to fixed points and the tilde '~' indicates the first order approximation for the distances between the variable's value and the fixed points, for instance $\tilde{f}(t) = f(t) - f^*$. Therefore, the tilde marked variables describe the local behavior of solutions close to fixed point and it help us to understand how the system progresses when the initial conditions (in this case, we suppose the trivial solution as initial conditions) are lightly disturbed from the equilibrium state (Fiedler-Ferrara & Prado, 1995).

Numerically, once reached the equilibrium state, the time-delayed terms have the same value as the usual terms. That is, $l_d^* = l_{d\tau}^*,\ y_d^* = y_{d\tau}^*,\ s_1^* = s_{1\tau}^*$.

The following steps depend on which fixed point we are evaluating. Let us start from the Disease Free Equilibrium (DFE) state. Following, we analyze the Endemic Equilibrium (EE) state.

6.1. Stability of Disease Free Equilibrium (DFE)

Our model is considered in DFE state if we consider the trivial solution for fixed points: $x_d^* = s_1^* = 1$ and $l_d^* = y_d^* = s_3^* = 0$. If we substitute those fixed points on system (15), we can uncoupled the equation for $\widetilde{x_d}$ and $\widetilde{s_1}$ from the remained system, since those two variables disappear on the other three equations. Therefore, the system we need to analyze is (16).

$$\begin{aligned}
\dot{\widetilde{l_d}}(t) &= -G\widetilde{l_d}(t) + \beta \widetilde{s_3}(t) \\
\dot{\widetilde{y_d}}(t) &= \varphi_d \widetilde{l_d}(t) - H\widetilde{y_d}(t) \\
\dot{\widetilde{s_3}}(t) &= -\mu_s \widetilde{s_3}(t) + C_2 \widetilde{l_{d\tau}}(t) + D_{2\tau} \widetilde{y_{d\tau}}(t)
\end{aligned} \tag{16}$$

And, applying (13) on system (16), we obtain (17).

$$\begin{aligned}
det\left|J_0 + e^{-\lambda\tau} J_\tau - \lambda I\right| &= det\begin{vmatrix} -(G+\lambda) & 0 & \beta \\ \varphi_d & -(H+\lambda) & 0 \\ C_2 e^{-\lambda\tau} & D_2 e^{-\lambda\tau} & -(\mu_s+\lambda) \end{vmatrix} \\
&= 0 \therefore \lambda^3 + (G+H+\mu_s)\lambda^2 + (H\mu_s + GH + G\mu_s)\lambda + GH\mu_s - (\varphi_d D_2 + C_2(H+\lambda))\beta\, e^{-\lambda\tau} = 0
\end{aligned} \tag{17}$$

equation (17) is the characteristic equation of fixed points of the system. This equation is very similar to usual polynomial equations, exception to exponential terms $e^{-\lambda\tau}$. This kind of equation is classified as quasi-polynomials and, in opposition to polynomial equations, they usually have infinite solutions in the complex plane. Because of this natural difficult to handle quasi-polynomial equations, we adopted the approximation $e^{-\lambda\tau} \cong 1 - \lambda\tau$. Once substituting the exponential terms by this approximation, we obtain a third order polynomial equation. Finally, using the numerical values from Table 1 on Table 4, we were able to calculate the eigenvalues λ from (17): $\lambda_1 = 1.90E-04,\ \lambda_2 = -3.83E-03,\ \lambda_3 = -6.22E-02$. Since we had at least one eigenvalue greater than 0, we conclude that when the system is on DFE state, the equilibrium is unstable.

6.2. Stability of endemic equilibria (EE) and backward bifurcation

The stability analysis of the Endemic Equilibrium (EE) is exactly the same process. However, in this case, all fixed points are non-zero. Therefore, we are not able to simplify the system as we did before, because the all five equations will be coupled among them. For this analysis, we have to consider the non-trivial fixed points: $x_d^* \cong 9.80E-01$, $I_d^* \cong 5.43E-03$, $y_d^* \cong 6.26E-04$, $s_1^* \cong 9.91E-01$ and $s_3^* \cong 6.27E-03$. Thus, we have to analyze system (10) with their five equations.

Applying (13) on (15), we obtain (18).

$$det\left|J_0 + e^{-\lambda\tau}J_\tau - \lambda I\right| = det\begin{vmatrix} -(\Xi+\beta s_3^*+\lambda) & -E & -F & 0 & -\beta x_d^* \\ \beta s_3^* & -(G+\lambda) & 0 & 0 & \beta x_d^* \\ 0 & \varphi_d & -(H+\lambda) & 0 & 0 \\ 0 & -C_1 s_1^* & -D_1 s_1^* & -\left(\mu_s + C_1 I_d^* + D_1 y_d^* + \lambda\right) & 0 \\ 0 & C_2 e^{-\lambda\tau} & D_2 e^{-\lambda\tau} & \left(C_2 I_d^* + D_2 y_d^*\right)e^{-\lambda\tau} & -(\mu_s+\lambda) \end{vmatrix} = 0$$

$$\therefore (\Xi+\beta s_3^*+\lambda)(G+\lambda)(H+\lambda)\left(\mu_s + C_1 I_d^* + D_1 y_d^* + \lambda\right)(\mu_s+\lambda) - \beta^2\varphi_d D_1\left(C_2 I_d^* + D_2 y_d^*\right)x_d^* s_3^* s_1^* e^{-\lambda\tau} = 0. \tag{18}$$

Considering the approximation $e^{-\lambda\tau} \cong 1-\lambda\tau$, we found the following values for eigenvalue λ: $\lambda_1 = -2.09E-04$, $\lambda_2 = -3.30E-03$, $\lambda_3 = -3.76E-03$, $\lambda_4 = -5.00E-02$, $\lambda_1 = -6.23E-02$. We observed all eigenvalues have negative values. Therefore, the Endemic Equilibrium state of this system is stable.

The mathematical condition to observe the backward bifurcation in our model (when $\mathscr{R}_0 < 1$) is the existence of two positive real solutions. Thus, when the equilibrium points were calculated considering System 14 and Table 4, we obtain the following $\mathbf{s_3}$ solutions (we suppressed the full calculations):

$$\begin{aligned} \mathbf{s}_{3(\mathbf{I})} &= -\frac{\Xi HG}{(H(E+G)+F\varphi_d)\beta} \\ &= -\frac{(\mu_d+\xi_d+\gamma_d)(\mu_d+\xi_d+\alpha_d+\sigma_d)}{((\mu_d+\xi_d+\sigma_d)(\mu_d+\xi_d+\delta_d+\varphi_d)+\alpha_d(\mu_d+\xi_d+\delta_d)+\gamma_d(\mu_d+\xi_d+\sigma_d+\varphi_d)+\alpha_d\gamma_d)} \times \frac{(\mu_d+\xi_d+r_d+\delta_d+\varphi_d)}{b_d a_d w_{hc} m_h} \\ \mathbf{s}_{3(\mathbf{II})} &= \frac{\Xi((C_2H+D_2\varphi_d)\beta - HG\mu_s)}{((C_1H+D_1\varphi_d)\Xi+(H(E+G)+F\varphi_d)\mu_s)\beta} \\ &= \frac{\left((c_l(\mu_d+\xi_d+\alpha_d+\sigma_d)+c_y\varphi_d)b_d a_d a_s w_{hc} m_h e^{-\mu_s\tau} - (\mu_d+\xi_d+\alpha_d+\sigma_d)(\mu_d+\xi_d+r_d+\delta_d+\varphi_d)\mu_s\right)}{\left((c_l(\mu_d+\xi_d+\alpha_d+\sigma_d)+c_y\varphi_d)(\mu_d+\xi_d+\gamma_d)a_s+(H(E+G)+F\varphi_d)\mu_s\right)} \times \frac{(\mu_d+\xi_d+\gamma_d)}{b_d a_d w_{hc} m_h} \end{aligned} \tag{19}$$

From Table 1, we have all parameter values and all of them are real positive values. Therefore, for $\mathbf{s}_{3(\mathbf{I})}$ we will always have a negative solution, since there is a minus signal in front of the $\mathbf{s}_{3(\mathbf{I})}$ expression. On the other hand, for $\mathbf{s}_{3(\mathbf{II})}$ we found that the positivity depends on numerical values for numerator, since the denominator is already positive (from $\mathbf{s}_{3(\mathbf{I})}$ we observed $H(E+G)+F\varphi_d > 0$ in denominator). Therefore, the existence of should obey the following condition:

$$\left(c_l(\mu_d+\xi_d+\alpha_d+\sigma_d)+c_y\varphi_d\right)b_d a_d a_s w_{hc} m_h e^{-\mu_s\tau} > (\mu_d+\xi_d+\alpha_d+\sigma_d)(\mu_d+\xi_d+r_d+\delta_d+\varphi_d)\mu_s \tag{20}$$

In our model, we have only one physical solution for s_3. Thus, there is no occurrence of backward bifurcation in our system.

7. Sensitivity analysis

The precise of the results of mathematical and computational models of biological systems is directly dependent of how certain the parameters are. Such parameters are usually estimated from experimental approaches. In some situations, we have some parameters subject to uncertainty due to the lack of complete information about their source (Adhikari & Supakankunti, 2010). Thus, the presence of uncertainty in the experimental data may lead to uncertainties on the estimated parameters. Consequently, the uncertain parameters can propagate their uncertainties onto mathematical models' results (Vuolo, 1996). Even when a parsimonious approach is followed during model building, available knowledge of phenomena is often incomplete, and experimental measures are lacking, ambiguous, or contradictory. So the question of how to address uncertainties naturally arises as part of the process. Uncertainty and sensitivity analysis techniques help to assess and control these uncertainties. Uncertainty analysis is performed to investigate the uncertainty in the model output that is

generated from uncertainty in parameter inputs. Sensitivity analysis naturally follows uncertainty analysis as it assesses how variations in model outputs can be apportioned, qualitatively or quantitatively, to different input sources (Marino, Hogue, Ray, & Kirschner, 2008).

Table 5
Equilibrium state values and the set of parameters that are most sensitive for each variable in the non-trivial equilibrium state.

	Disease Free Equilibrium State (Trivial Equilibrium Point)	Disease Equilibrium State (Nontrivial Equilibrium Point)	Parameter set related to human population, in which the variable is sensitive (on EE state)	Parameter set related to dog population, in which the variable is sensitive (on EE state)	Parameter set related to sandfly population, in which the variable is sensitive (on EE state)
x_h	1.0	9.84E-01	-	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l
l_h	0.0	7.73E-04	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l
y_h	0.0	3.50E-05	-	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l
z_h	0.0	1.47E-02	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l
x_d	1.0	9.80E-01	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l, c_y
l_d	0.0	5.43E-03	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l, c_y
y_d	0.0	6.26E-04	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l, c_y
z_d	0.0	1.37E-02	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l, c_y
s_1	1.0	9.91E-01	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l, c_y
s_2	0.0	2.63E-03	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l, c_y
s_3	0.0	6.27E-03	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l, c_y
Rep [1/day]	0.0	9.12E-08	μ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l
$\mathscr{R}^l_{0d}$	-	9.58E-01	φ_h	w_{dh}, δ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l
$\mathscr{R}^y_{0d}$	-	7.09E-02	-	μ_d, α_d, w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_h, b_d, a_s,a_d, m_{h0}, μ_s, τ, c_y
$\mathscr{R}_0$	-	1.03E+00	φ_h	w_{dh}, δ_d, φ_d, σ_d, ξ_d	b_d, a_d, a_s,m_{h0}, μ_s, τ, c_l, c_y

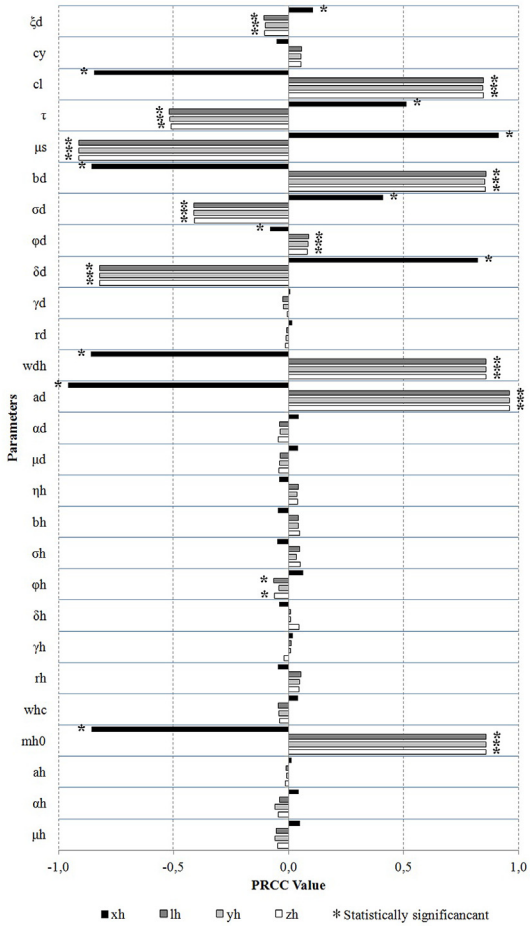


Fig. 2. PRCC values in respect to human population categories. Parameters that are significant, ($p < 0.05$) are marked with a star.

In this study, we used the Latin Hypercube Sampling (LHS) as uncertainty analysis and Partial Rank Correlation Coefficient (PRCC) as index for sensitivity analysis. It is not the focus of this paper to show the mathematical demonstration of those techniques. So, we strongly recommend to the reader to see Marino et al. (2008) for more information.

We analyzed the parameters sensitivity in the nontrivial equilibrium (Endemic Equilibrium) state. As we presented in (7), when $t \to +\infty$ we have $m_h(t)$ trending to m_{h0}. Thus, we are able to calculate the equilibrium points. Once we obtain the equilibrium points expressions, we can use them to evaluate their sensitivity to the parameters. We evaluated the sensitivity considering a range of $\pm 1\%$ of each parameter value.

In Table 5 we present a summary of the sensitivity analysis. Figs. 2–5 we graphically illustrate the relation between variable sensitivity and parameters.

From this sensitivity analysis method, we obtained some interesting results. This method allows us to check if some variable is sensitive for any parameter of the system, even if this parameter is not directly related to a specific population. This characteristic is different from that one presented by Burattini et al. (1998), in which was found a relationship between the parameter and variable are from the same population. However, we have to stress that Burattini et al. (1998) did not used the same sensitivity analysis method as here.

From Table 5, we observed that all variables listed in this table are sensitive for most of parameters related to sandfly population dynamics. In particular, the parameters that compose the force of infection - b_d, a_d and m_{h0} - resulted in high correlation with the variables (Figs. 2–5). This dominance of parameters related to sandfly population in the Zoonotic Visceral Leishmaniasis dynamics sensitivity suggests how dependent from the contact between sandfly and dog is. This fact may be very useful for planning activities regarding to sandfly population control.

We also observed that there are some parameters related to dog population in which the model is sensitive - w_{dh}, δ_d, φ_d, σ_d, and ξ_d. Those, exception of σ_d, are all related to l_d category. According to Laurenti et al. (2013), the latent dog has greater probability to infect sandflies than the clinically ill dogs. Thus, we are able to better understand why w_{dh}, δ_d, φ_d and ξ_d are sensitive for our model, since those parameters model l_d category dynamics. When any variation on those parameter values

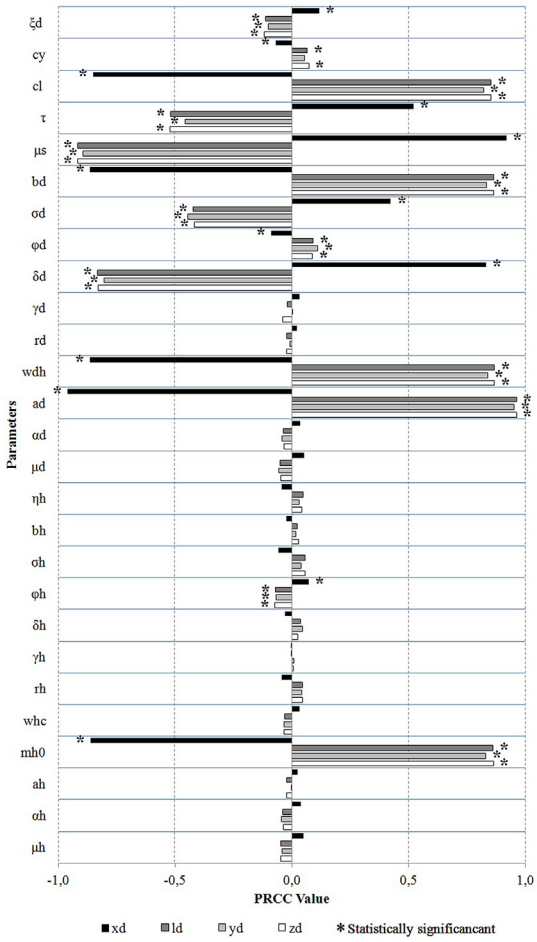


Fig. 3. PRCC values in respect to dog population categories. Parameters that are significant, ($p < 0.05$) are marked with a star.

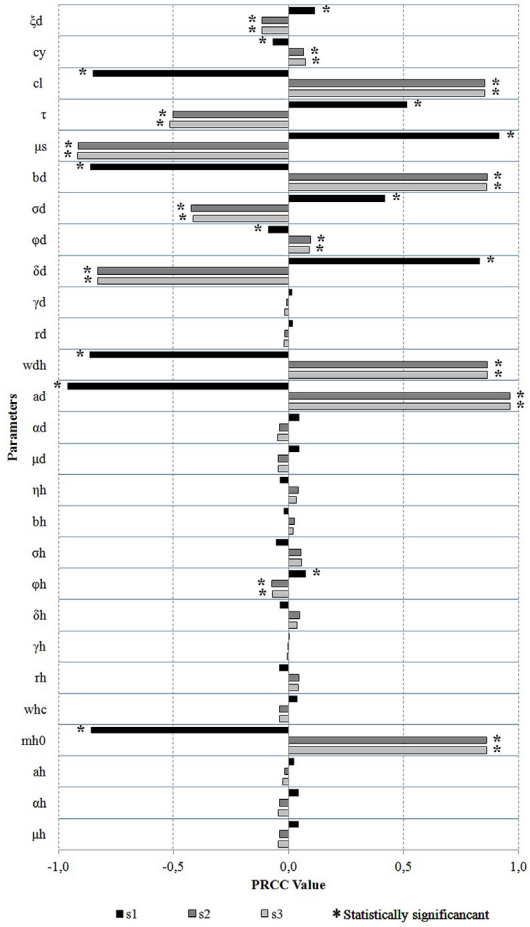


Fig. 4. PRCC values in respect to sandfly population categories. Parameters that are significant, ($p < 0.05$) are marked with a star.

occurs, we are directly handling on the main category that composes the real source of infection. On the other hand, the parameter σ_d and ξ_d are related to y_d category, but the model is not so sensitive as that one related to l_d category, since the contribution of y_d as source of infection is lower than l_d.

Numerical simulation

Finally, in order to analyze the dynamics of our model, we simulated our set of equations from (1) considering the parameters on Table 1. We focused on human reported rate, since we can use the real data as reference. Figs. 6 and 7 illustrate the reported human cases rate and the sandflies per human ratio dynamics (yearly average).

First of all, we need to make some comments about Figs. 5 and 6. First of all, although we based our modelling on the previous studies published by Burattini et al. (1998) and Ribas et al. (2013), our results are clearly different from them, in special, because we not only made changes on model, but also we used different parameter values. In addition, our approach is different, since we focus on incidence rate (human reported cases per day), instead of prevalence.

In order to compare our results, we were able to find some descriptions about some demographic characterization of those populations regarding to Zoonotic Visceral Leishmaniasis (see the endemic equilibrium states from Table 5). For instance, our sum of latent (l_d) and recovery (z_d) dog was around 1.91E − 02 and the sum of latent (l_d) and clinically ill (y_d) dogs was around 6.06E − 03. On the other hand, Cabral et al. (1998) found that the sum of density of latent and recovered dogs was around 0.50 and Quinnell et al. (2001) found the density of 0.579 for the sum of latent and clinically ill dogs. Observe that our densities values are very different from those other authors. However, we remark that those works were not developed at Araçatuba/SP city. In addition, in Brazil the distribution of zoonotic visceral leishmaniasis is not homogeneus. Thus, we can find states with no human reported cases for 2012 year (as Rio Grande do Sul State) (Brasil, 2015). This non-homogeneus distribution is related to geographic featuring and climate changes, in which probably has influenced on the sandfly population dynamics. Therefore, this is one of the arguments to explain the discrepancy regarding to our result and the real data.

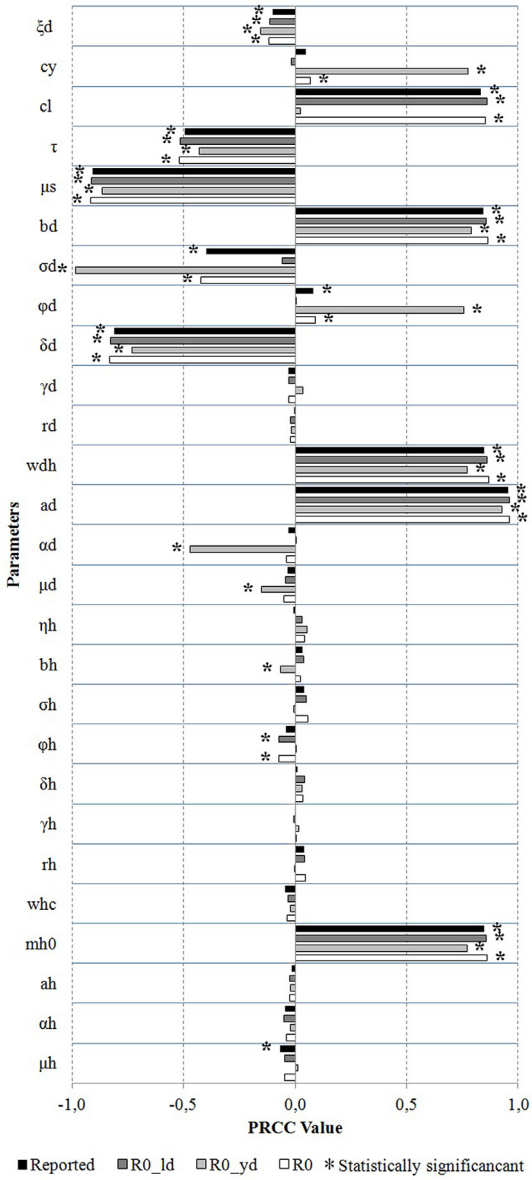


Fig. 5. PRCC values in respect to reported cases rate and $\mathscr{R}_0$. Parameters that are significant, ($p < 0.05$) are marked with a star.

Discussion

The model presented in this article provided a new and interesting view about Zoonotic Visceral Leishmaniasis transmission dynamics among humans, dogs and sandflies population. Although the first work developed by our research group about this disease dynamics addresses from 1998 (Burattini et al., 1998), in this paper we included some new approaches. Herein, we not only updated most of parameters, but also analyzed the reported human cases rate dynamics and evaluated the model's sensitivity for parameters using LHS and PRCC as uncertainty and sensitivity analysis, respectively.

In our model we considered only dog population as source of infection, whereas Burattini et al. (1998) considered that the sandfly can acquire the protozoan from both human and dog populations. This explains why only dog population (in particular, latent and clinically ill dogs) composes the $\mathscr{R}_0$ expressions (9) and (10). Once splitting this expression, we have the numerical result that latent dog contribution ($\mathscr{R}^l_{0d} \cong 0.96$) is greater than clinically ill contribution ($\mathscr{R}^y_{0d} \cong 0.07$). We obtained this result due to the assumptions we adopted (the fraction of sandflies that become infected when bite a latent dog was $c_l = 0.385$ and a clinically ill dog was $c_y = 0.247$). This result addresses how important the latent dogs are for maintenance and introduction of Zoonotic Visceral Leishmaniasis into population. Also, if we consider that latent dogs are visually healthy, it is very difficult to detect them. Thus, latent dogs stay free to act as source of infection (Ministry of Health, Brazil, 2006).

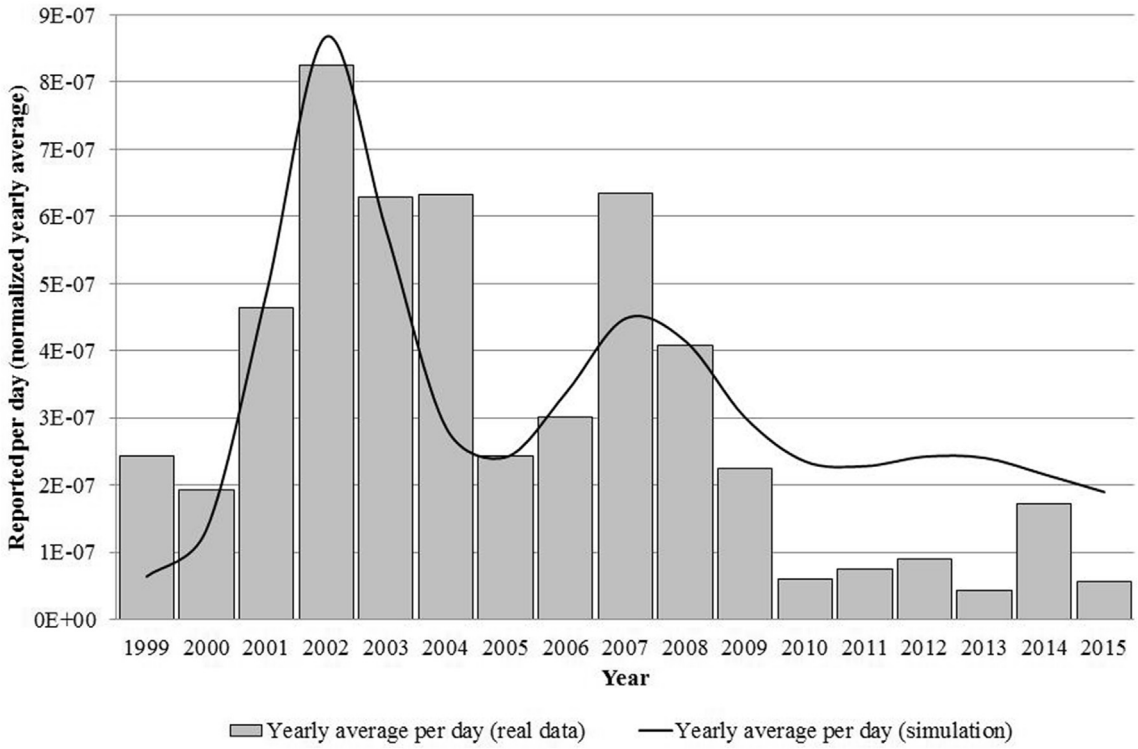


Fig. 6. Dynamics of reported human cases rate. The available real data are from 1999 to 2015 (bars) and our model was fitted for the same period (line). Observe that the real data shows three peaks that decrease over time: 2002, 2007 and 2014. Source: CES-SP and BIGE.

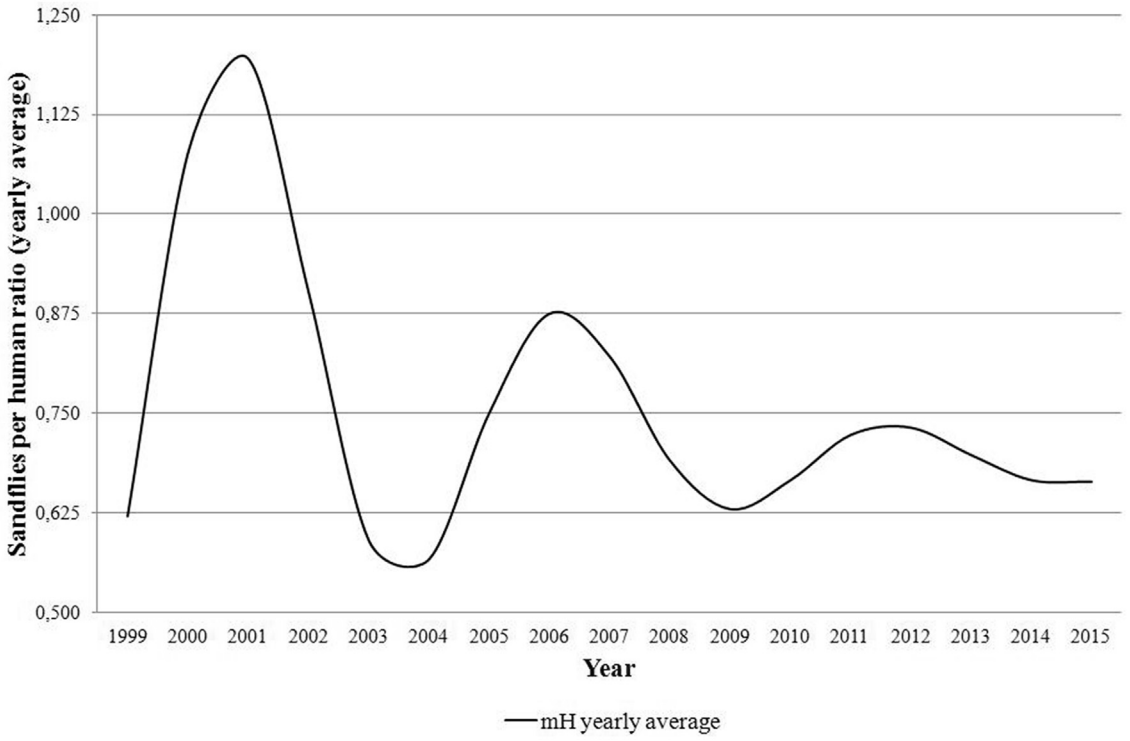


Fig. 7. Dynamics of sandflies per human ratio. This curve was obtained from simulation of equation (5). Observe that there is a cycle and the peaks decrease over time. This curve becomes stable according to time progress.

In our model we could estimate the proportion of the individuals in each stage of disease dynamic. This evaluation is very important, since latent individuals (humans and dogs) are difficult to detect. In particular, the contribution of latent dog to disease maintenance is greater than the clinically ill one. Furthermore, here we estimated the reported human cases rate for our model in the equilibrium state $9.12E-08$/day. This value is at the same order of magnitude of the 2015 normalized yearly average reported rate (Table 2).

The real importance of reporting human cases of Zoonotic Visceral Leishmaniasis was well illustrated by Killick-Kendrick (2010). They highlighted that the key to reach the Visceral Leishmaniasis control is education. Although education was not considered in our model but we see that public health education and epidemiological surveillance system are very close and work together. As example, infected people that neglected the visceral Leishmaniasis provide unreported cases of this disease. As consequence, few cases are reported and the control programs are undervalued. Thus, if we know the proportion of unreported cases, we could evaluate the efficacy of the surveillance service. Finally, this can indirectly influence the control programs, since the strengthening of the surveillance system capacity is essential to avoid the underreporting of human cases and to follow-up the infection behavior in canine and human population. Strong surveillance will certainly contribute to improve data quality for decision-makers in this complex scenario (Romero & Boelaert, 2010; Maia-Elkhoury et al., 2007).

Classically, Zoonotic Visceral Leishmaniasis transmission is intensified when the prevalence on dog population is high and there is sandly population available. However, all mathematical analysis on our model provided us a better understanding about how dog and sandfly populations influence on disease dynamics. In particular, we observed that the model is highly sensitive to sandfly population parameters and this is related to our findings on stability analysis, in which the Disease Free Equilibrium state is broken when some infective sandfly is introduced. We can also observe the importance of sandfly population on this dynamics when we compare Figs. 6 and 7, where $m_h(t)$ dynamics over time clearly influence on human reported cases curve. At the same time, our $\mathscr{R}_0$ calculation showed that it depends on dog (latent and clinically ill categories) and sandfly populations. The sensitivity analysis also indicated that parameters related to latent and clinically ill dog dynamics have some influence on disease dynamics. But, sandfly population is more important than dog population regarding to disease dissemination.

The recent work published by Zhao et al. (2016), although it showed some similar conclusions to that one provided by our model, it also presented some important differences. Firstly, there are some differences on adopted assumptions. For instance, Zhao et al. (2016) assumed that all recovered dogs are always under treatment. In our model, we considered that a dog can become naturally recovered (Table 1). In addition, Zhao et al. (2016) considered that there is a migration rate regarding to sandfly population. In our model we did not include this assumption (Fig. 1).

Although both models were elaborated from a classical compartmental model approach (SEIR model), we have some differences. Mathematically, Zhao et al. (2016) modeled the disease dynamics in a simplest way, since they considered fewer parameters and did not applied delay terms for sandfly population dynamics. This structural difference explains the differences regarding to results. As example, in our model it was not found the coexistence among DFE and EE state. Therefore, according to our model, the phenomenon of backward bifurcation (which Zhao et al. (2016) have proven in their work) was not presented. On the other hand, Zhao et al. (2016) have proven the existence of backward bifurcation in their model.

Finally, Zhao et al. (2016) demonstrated mathematically the optimal control based on their model. Although we did not develop a deep optimal control analysis, our sensitivity analysis also allowed us to conclude that the control strategy should focus on sandfly population, since our system was very sensitive to parameters related sandfly population dynamics (Table 5 and Figs. 2–5). On the other hand, our model was able to represent the trend pattern of ZVL in a Brazilian city (Araçatuba, SP), since we obtained the real data and, therefore, it allowed us to fit our simulated results to real data (Fig. 6).

In this work, we presented a new model for Zoonotic Visceral Leishmaniasis, considering only dogs as source of infection, different probabilities of infecting sandflies for latent and clinically ill dogs and updated parameters. Since our analysis pointed that the introduction and maintenance of this disease is related to sandfly population and latent and clinically ill dogs, the preventive control activities should be focused on them. In special, 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. The evaluation of preventive activities on Zoonotic Visceral Leishmaniasis control is in our upcoming works.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HJS and EM were responsible for study design and planning. HJS and JW conducted the mathematical analysis. HJS conducted model simulations. HJS, JW and EM contributed to results interpretation and discussion. HJS contributed to writing the manuscript. All authors read and approved the final version of the manuscript.

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Research Article

The Preventive Control of Zoonotic Visceral Leishmaniasis: Efficacy and Economic Evaluation

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Zoonotic Visceral Leishmaniasis (ZVL) is one of the world's deadliest and neglected infectious diseases, according to World Health Organization. This disease is one of major human and veterinary medical significance. The sandfly and the reservoir in urban areas remain among the major challenges for the control activities. In this paper, we evaluated five control strategies (positive dog elimination, insecticide impregnated dog collar, dog vaccination, dog treatment, and sandfly population control), considering disease control results and cost-effectiveness. We elaborated a mathematical model based on a set of differential equations in which three populations were represented (human, dog, and sandfly). Humans and dogs were divided into susceptible, latent, clinically ill, and recovery categories. Sandflies were divided into noninfected, infected, and infective. As the main conclusions, the insecticide impregnated dog collar was the strategy that presented the best combination between disease control and cost-effectiveness. But, depending on the population target, the control results and cost-effectiveness of each strategy may differ. More and detailed studies are needed, specially one which optimizes the control considering more than one strategy in activity.

1. Introduction

Zoonotic Visceral Leishmaniasis (ZVL) 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 [1–4]. The ZVL 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 sandflies *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 species from *Leishmania* complex.

From the last few years, ZVL has been emerging within nonendemic 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 [5].

Besides the publication of guidelines of ZVL control and the investments made in general surveillance activities, the sandfly and the reservoir in urban areas remain 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 [2, 6].

Usually, health is not analyzed as an economical activity. However, economical analysis in health studies is important for comprehension of health polices dynamics and trends. From those results, it is possible to obtain arguments and support to organize and supervise health polices programs. In short, economic health expresses the universal desire of reaching the best investment, not only in terms of clinical effectiveness, but also in terms of approaching cost-effectiveness about healthcare procedures [7, 8].

Marinho et al. [9] observed that there are few studies that analyzed the economical impact on visceral leishmaniasis considering social and collective approach. In addition, there are several difficulties to develop economical analysis of visceral leishmaniasis transmission due to (I) the interval of time between the intervention and epidemiological impact or/and (II) the difficulty to relate the intervention activities to the resulting impact. Considering those difficulties and still open-questions about ZVL dynamics and impact, the use of mathematical models should become a very interesting alternative of analysis.

Some deterministic models have been published in literature and all of them analyze the dynamic of this disease and make any evaluation of strategies controls. In particular, since 1998 our research group has been working on ZVL modeling. Burattini et al. [10] worked on a mathematical model to visceral leishmaniasis where both humans and dogs were considered source of infection. Later, Ribas et al. [11] developed a model, based on Burattini et al. [10], which was restricted to LVZ and some preventive control strategies were also considered. Newly, an original article was published by Shimozako et al. [12], where they reviewed the model published by Burattini et al. [10] and not only updated some parameters but also provided a more complete mathematical analysis. In this most recent paper, we were able to fit the model to real data from Araçatuba/SP city (Brazil), carrying out a very robust model and results. And, besides those models published by our research team, we also have other researchers who published mathematical models for LVZ, as Zhao et al. [13], in which their model differs from ours by the adopted mathematical structure and the presence of backward bifurcation.

Even though the result from mathematical model indicates epidemiological availability for visceral leishmaniasis control, we should evaluate carefully the practical and economical viability. In this case, regarding public health, the disease control activities should work considering the best cost-effectiveness, since the available resources are limited. We also know that it is important to be aware of the time-response and applicability-practicality conditions. In other words, it is necessary to be careful with investment time and method application relationship and the respective expected result [5, 14–17].

In this work we propose an evaluation of five ZVL control strategies (positive dog elimination, insecticide impregnated dog collar, dog vaccination, dog treatment, and sandfly population control), by mathematical modeling. This mathematical model was based on the previous models published by Burattini et al. [10] and Ribas et al. [11]. We studied the impact of those control strategies on human and dog population by approaching the epidemiological control and cost-effectiveness. Then, we discussed the most efficient control strategies and how they act on visceral leishmaniasis epidemiological chain.

2. The Model

We used a mathematical model that is an adaptation of the one proposed by Burattini et al. [10]. 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) being constants;

(3) both human (indexed as h) and dog (indexed as d) populations being 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 recovering 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 (Figure 1) and the set of differential equations describing the model's dynamics (system (1)) are presented as shown in Figure 1 and are as follows:

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

$$\dot{s_3}(t) = a_s\left(c_l l_d(t-\tau) + c_y y_d(t-\tau)\right) s_1(t-\tau)\, e^{-\mu_s \tau} - \mu_s s_3(t). \quad (1)$$

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 $a_h S(t)dtS_3(t)/S(t) = a_h S(t)dts_3(t)$, where $S_3(t)$ is the number of infected flies.

Let now $X_h(t)_h$ be the total number of susceptible individuals in the human population. In an infinitesimal time interval dt, $X_h(t)$ varies as follows:

(i) The infected flies are able to bite on any category of human population. Thus, only a fraction of the infected bites are on uninfected individuals: $a_h S(t)dts_3(t)x_h(t)$, where $x_h(t)$ is the fraction of uninfected humans. But, a fraction b_h of $a_h S(t)dts_3(t)x_h(t)$ becomes latent, so X_h diminishes by $b_h a_h S(t)dts_3(t)x_h(t)$.

(ii) Simultaneously, $r_h L_h(t)dt + \gamma_h Z_h(t)dt$ individuals, latent and immune, revert to the susceptible condition, and $\mu_h X_h(t)dt$ die by natural causes other than the disease.

(iii) We must add an entrance term, due to natality, which we choose to be $\alpha_h Y_h(t)dt + \mu_h N_h(t)dt$, where α_h is the disease-induced mortality rate, $Y_h(t)$ is the number of infected humans (clinically ill humans), and $N_h(t)$ is the total number of humans needed to maintain a constant population (where $N_h(t) = X_h(t) + L_h(t) + Y_h(t) + Z_h(t)$, with $L_h(t)$ as the number of latent humans and $Z_h(t)$ as the number of recovering humans).

Thus we have

$$dX_h = \alpha_h Y_h(t)\,dt + \mu_h N_h(t)\,dt - b_h a_h S(t)\,dts_3(t)\,x_h(t) + \left(r_h L_h(t)\,dt + \gamma_h Z_h(t)\,dt\right) - \mu_h X_h(t)\,dt. \quad (2)$$

Dividing this equation by $N_h(t)dt$ and calling $S(t)/N_h(t) = m_h$, we get the first equation of system (1).

Observe that m_h is a time-dependent function: $m_h(t)$. This expression is the simplest way to simulate the changes on sandfly population size dynamics between 1999 and 2015.

We can apply the same process in order to obtain the equation for the dynamic of susceptible dogs (x_d). However, observe from Table 1 that the sandfly : dog ratio depends on the sandfly : human ratio and on the human : dog ratio: $m_d = m_h(t) \times w_{dh}$. Although all the populations are constant, if we consider the real number of individuals, we expect more humans than dogs. Thus, if the sandfly population is constant, we have different values for m_d and m_h.

The last three equations of system (1) refer to the flies. When infected, a fly remains in a latent stage for a period of time τ. This time corresponds to the extrinsic incubation period of the parasite inside the vector fly. Numerically it lasts for about half the life expectancy of the flies.

Let S_1 be the number of susceptible flies. In an infinitesimal period of time dt, $(a_S(L_d(t) + Y_d(t)/N_d(t))dt)S_1(t)$ bites due to uninfected flies occur on latent and infected dogs (humans are not considered to be infective for flies; see Tesh [18]). A fraction, c_l and c_y, of the flies (that bites latent and clinically ill dogs, resp.) becomes latently infected as a result. Therefore, we have

$$dS_1(t) = \mu_s\left(S_2(t) + S_3(t)\right)dt - a_S\left(c_l l_d(t) + c_y y_d(t)\right) S_1(t)\,dt. \quad (3)$$

Dividing by $S(t) = S_1(t) + S_2(t) + S_3(t)$ and by dt, we get the equation for noninfected sandflies ($s_1(t)$).

Although this is a brief but detailed description of the noninfected categories equations (i.e., x_h, x_d, and s_1), we can note that each term of our system equation has a biological meaning. The meaning of each term depends on the respective parameters that set them (e.g., $\delta_d l_d(t) + \sigma_d$ means the amount of latent dogs that develop immunity per day).

3. The Number of Clinically Ill Humans and Reported Cases

In Brazil, ZVL is a notifiable disease [17, 34]. Thus, we can assume the following:

(i) An infected human should look for medical treatment when he/she will become clinically ill (y_h).

(ii) Only a fraction of those humans that are clinically ill will be reported to sanitary authorities. The remaining fraction (I) will not look for medical help, even if the clinical symptoms and signs appear or (II) will not be correctly reported in the hospitals.

Now, let us see again the equation for $y_h(t)$ in system (1):

$$\dot{y_h}(t) = \varphi_h l_h(t) - \left(\mu_h + \alpha_h + \sigma_h\right) y_h(t). \quad (4)$$

The term $\varphi_h l_h(t)$ in (4) means the rate of latent humans who become clinically ill per day. Thus, in order to calculate the total of humans that become clinically ill along an interval of time, we have

$$T_{y_h}\left(t_f\right) = \varphi_h \int_{t_0}^{t_f} l_h(t)\,dt, \quad (5)$$

where $T_{y_h}(t_f)$ is the total of humans that become clinically ill from an initial moment, t_0, to a final one, t_f.

Now, let us consider that, per day, the number $\varphi_h l_h(t)$ of humans is eligible to look for medical help. However, only a fraction $(1-\eta_h)$ of those clinically ill humans will be correctly notified to sanitary authorities, where $\eta_h = 0.705$ means the

Table 1: Parameters adopted in our model. The indexes h, d, and s stand for humans, dogs, and sandflies, respectively.

Parameter	Meaning	Value	Dimension	Source
μ_h	Natural mortality rate	3.67×10^{-5}	1/day	Brazilian Institute of Geography and Statistics, Brazil [19]
α_h	Kalazar specific lethality	6.31×10^{-3}	1/day	World Health Organization [20]
a_h	Average daily bitten humans rate	2.00×10^{-1}	Human/(sandfly × day)	Epidemiological Surveillance Direction, Santa Catarina State, Brazil [21]
$m_h(t)$	Vector density per host (time-dependent)	*Variable*	Sandfly/human	Fitted
w_{hc}	Human : house ratio	3	Human/house	Brazilian Institute of Geography and Statistics, Brazil [22]
b_h	Proportion of infective bites	1.00×10^{-2}	Dimensionless	Molineaux and Gramiccia [23]
r_h	Spontaneous recovery rate	5.48×10^{-4}	1/day	Badaro et al. [24]
γ_h	Loss of immunity rate	5.48×10^{-4}	1/day	Kault and Marsh [25]
δ_h	Latent recovery rate	1.10×10^{-2}	1/day	Badaro et al. [24]
φ_h	Inverse of incubation period	4.00×10^{-4}	1/day	Pearson and Souza [26]
σ_h	Recovery rate to immunes	2.50×10^{-3}	1/day	Ministry of Health, Brazil [17]
μ_d	Natural mortality rate	2.28×10^{-4}	1/day	Selman et al. [27]
α_d	Kalazar specific lethality	1.81×10^{-3}	1/day	Lanotte et al. [28]
a_d	Average daily bitten dogs rate	2.00×10^{-1}	Dog/(sandfly × day)	Epidemiological Surveillance Direction, Santa Catarina State, Brazil [21]
w_{dh}	Human : dog ratio for Araçatuba/SP city	10/1.8	Human/dog	Andrade et al. [29]
$m_d(t)$	Vector density per host	$w_{dh} \times m_h(t)$	Sandfly/dog	—
φ_d	Inverse of incubation period	3.78×10^{-4}	1/day	Greene [30]
b_d	Proportion of infective bites	1.00×10^{-2}	Dimensionless	Molineaux and Gramiccia [23]
r_d	Spontaneous recovery rate	2.74×10^{-4}	1/day	Lanotte et al. [28]
γ_d	Loss of immunity rate (recovery to susceptible)	2.74×10^{-3}	1/day	Kault and Marsh [25]
σ_d	Recovery rate from clinically ill to immunes	9.04×10^{-4}	1/day	Lanotte et al. [28]

proportion of unreported cases [35]. Therefore, the daily rate of reported human cases $\mathrm{Rep}(t)$ is defined by

$$\mathrm{Rep}\,(t) = \left(1 - \eta_h\right) \varphi_h I_h\,(t)\,. \tag{6}$$

The Centre of Epidemiological Surveillance of São Paulo State (CES-SP) [36] is the institution that administrates the data about ZVL in São Paulo State. In order to validate our model, we decided to use the data of human reported cases from the municipality of Araçatuba (São Paulo State, Brazil) as reference, because it is an endemic city for this disease. Those data are presented in Table 3 and are available on CES-SP website [36].

Note that we have the total of reported cases per year. Thus, since our time scale is *day*, we estimated an average of human reported cases per day for each year (dividing the total from each year by 365). Finally, we also have to consider that our model works with normalized population (all three populations are constant). Thus, as a last step, we have to divide each rate of human reported cases per day by the official population size of Araçatuba municipality. The population size of Araçatuba municipality is available on Brazilian Institute of Geography and Statistics website [22]

In order to fit and compare our results to real data, we also calculated a normalized average of reported cases per day from every 365 days of simulation. This simulation was run considering 60 years and the obtained curve was fitted by simple handling along the time-axis (e.g., we could assume the initial day $t_0 = 1$ as the first day of 1970 or 1980, depending on how best the simulated curve fits on the real data). Thus, we could obtain the yearly average of reported human cases per day and compare it to the real yearly average provided by CES-SP [36] (Table 3).

4. Fitting the Human : Sandflies Ratio ($m_h(t)$)

Among all used parameters for this work, the sandfly/human ratio is one of the most challenging to be estimated. Although we had found some field studies that tried to estimate sandfly population size and other demographic characteristics [37], we did not find any study regarding this ratio for Araçatuba city. Therefore, in our simulation, we decided to fit this ratio according to real data of human cases. Since we are studying visceral leishmaniasis dynamics, it is necessary that the disease is persistent in the population. Considering this condition, we assumed the condition $\mathscr{R}_0 > 1$ and estimated the minimum value for $m_h(t)$ (calculation is not shown, but we followed the method described by van den Driessche and Watmough [38]).

The real data provided in Table 3 suggests that the incidence was not constant along those years in which the data was collected (1999 to 2015). One reasonable hypothesis is the climate changes that have been occurring for the last years [39]. Thus, since the sandfly population dynamics depend on climate and geographical conditions, we can include this idea in our model by fitting $m_h(t)$ as time-function. It is not the scope of this paper to model the sandfly population dynamics according to climatic and geographic variations. Therefore, we will assume that a simple function for $m_h(t)$, which can fit the simulation data to the real data, should include those climatic and geographic variabilities.

Let us consider the following function for $m_h(t)$:

$$m_h(t) = m_{h0} + \left(\frac{te^{-(L+t/K_1)}}{K_1}\right)\left(A + B\sin\left(\frac{2\pi t}{T}\right)\right) \quad (7)$$

$$\lim_{t\to+\infty} m_h(t) = m_{h0}.$$

The parameter values for (7) are in Table 4. Biologically, we can suppose that sandfly population reaches stability and oscillations decrease over time. Thus, note that for $t \to +\infty$ we have $m_h(t)$ trending to m_{h0}.

5. Modeling the Dynamic of Control Strategies

System (1) models the disease dynamics over time, considering humans, dogs, and sandfly population. In order to evaluate the effect of preventive controls, we have to introduce new terms that indicate each of those methods. Since our focus is preventive control method, the target populations are dogs and sandflies.

In the following sections we present the inclusion of those new terms on system (1). We consider the parameters from Araçatuba municipality for simulation of those methods.

Each of the five control strategies considered in this work acts in a specific point of the ZVL dynamics. Because of this, it becomes clearer if we redescribe our model for each strategy separately. Therefore, we simulated 6 sceneries (one without control strategies and one for each strategy) and, for each evaluated strategy, we counted the number of individuals (dog or houses) that were controlled.

The estimation of control strategy rates is presented apart in the following sections.

5.1. Elimination of Positive Dogs

$$\begin{aligned}
\dot{x_d}(t) &= \left(\mu_d + \xi_d + \xi'_d\right)\left(l_d(t) + y_d(t) + z_d(t)\right) \\
&\quad + r_d l_d(t) + \alpha_d y_d(t) + \gamma_d z_d(t) \\
&\quad - b_d a_d m_d(t)\, s_3(t)\, x_d(t) \\
\dot{l_d}(t) &= \left(b_d a_d m_d(t)\, s_3(t)\right) x_d(t) \\
&\quad - \left(\mu_d + r_d + \delta_d + \varphi_d + \xi_d + \xi'_d\right) l_d(t) \\
\dot{y_d}(t) &= \varphi_d l_d(t) - \left(\mu_d + \alpha_d + \sigma_d + \xi_d + \xi'_d\right) y_d(t) \\
\dot{z_d}(t) &= \delta_d l_d(t) + \sigma_d y_d(t) \\
&\quad - \left(\mu_d + \gamma_d + \xi_d + \xi'_d\right) z_d(t).
\end{aligned} \quad (8)$$

The elimination of positive dogs has already been indicated as ξ_d in system (1), in the equations for dog population, and in Table 1. In this case, we suppose that this elimination rate is in accordance with the average produced by epidemiological surveillance system of Araçatuba [31]. In other words, ξ_d means the usual dog elimination rate (i.e., the dog elimination provided by health authorities in a common routine). In addition, since the official diagnosis method is serology, we assume any dog that is indicated as having antibody against *Leishmania* parasite as disease positive.

Note from Figure 1 that dog population is considered constant in our model. As a result, if the dog mortality is intensified due to elimination of positive ones (i.e., there is an extra/additional elimination rate by ξ'_d, e.g., if the health services receive better working conditions and if they are supplied by more materials), it induces an increase of dog population renewing. This renewing makes sense, since, ecologically, an eliminated dog allows a new one to replace it. In addition, as the official diagnostic techniques are based on serology, only susceptible dogs x_d are not eligible to be eliminated. We adopted this idea because we considered the latent (l_d), clinically ill (y_d), and recovering (z_d) dogs had contracted the *Leishmania* antigen in any moment of its life. Therefore, they are eligible to be positive for diagnostic test.

5.2. Deltamethrin 4% Impregnated Dog Collar. Theoretically, the deltamethrin 4% impregnated dog collar could be applied in any dog. Therefore, we can assume that all of the four classes of dog in our model are eligible to use it and we adopted θ_d as the rate of dogs using collar per day. In this case, we indicated by C the categories of dogs that use collar (susceptible dogs using collar x_d^C, latent dogs using collar l_d^C, clinically ill dogs using collar y_d^C, and recovering dog using collar z_d^C) from those that do not use it. Basically, once a dog has this collar, it becomes protected from sandfly biting. If there is no contact between them, there will not be parasite transmission (either from infected dog to noninfected sandfly or from infective sandfly to susceptible dog).

Also, let us assume that those collars are available for inhabitants at local health centers. Thus, we suppose that owners would actively go to health center and acquire the collar for each dog they have. Since we consider that all preventive activities are supported by health policies, we can consider that the owner acquires the collar with no charge. If we imagine this simple hypothesis, we conclude that the only additional cost to the health policies is the purchasing of the collar.

Figure 2 refers to the flowchart considering the inclusion of deltamethrin 4% impregnated dog collar. Next, we have system (9), in which we included the collar-classes, and Table 5 where we describe the additional parameters for this control.

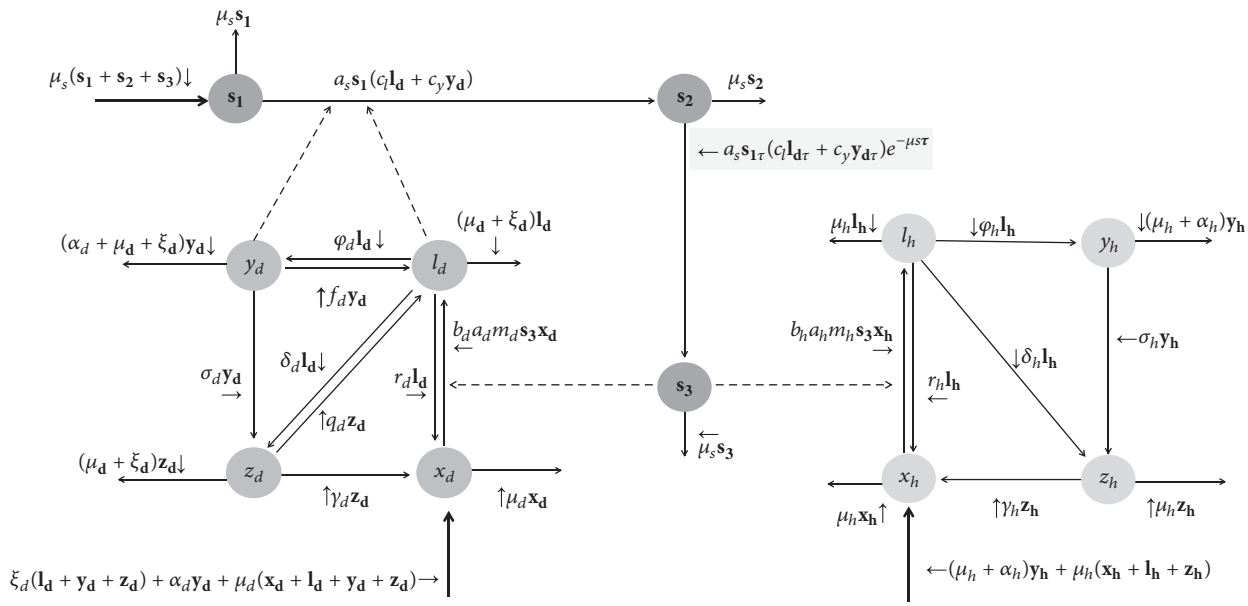

Figure 1: The compartment model and the flowchart. Note that only dogs are source of infection and sandflies transmit the *Leishmania* sp. to both dogs and humans.

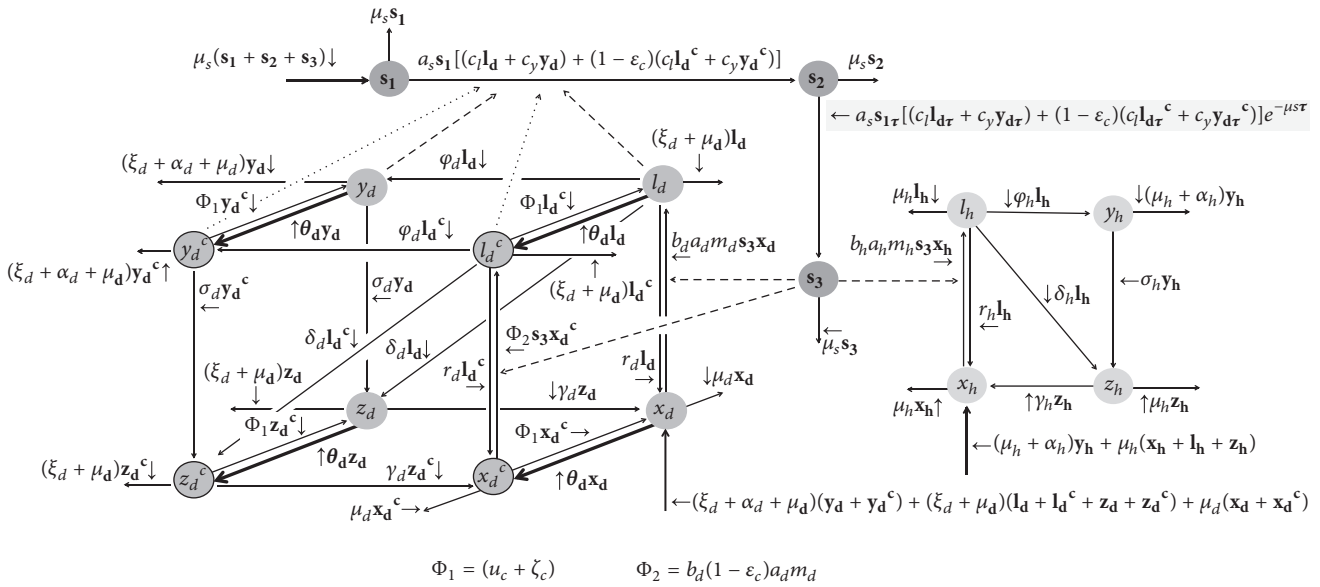

Figure 2: The compartment model and the flowchart, when the vaccination is introduced as preventive strategy control. Note that the dynamics for human population have not changed.

Note from Figure 2 that once the collar is fitted, there is a loss rate ζ_c and a decrease of insecticide effect rate u_c. Also, according to Halbig et al. [42], the efficacy of the collar is around 80%. Therefore, we considered that a proportion ε_c of those dogs using collar is protected.

$$\begin{aligned}\dot{x_d}(t) &= \mathbf{B}(t) + (u_c + \zeta_c)\, x_d^C(t) + r_d l_d(t) + \gamma_d z_d(t) \\ &\quad - (\theta_d + b_d a_d m_d s_3(t))\, x_d(t)\end{aligned}$$

$$\begin{aligned}\dot{l_d}(t) &= (u_c + \zeta_c)\, l_d^C(t) + b_d a_d m_d s_3(t)\, x_d(t) \\ &\quad - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d + \theta_d)\, l_d(t)\end{aligned}$$

$$\begin{aligned}\dot{y_d}(t) &= (u_c + \zeta_c)\, y_d^C(t) + \varphi_d l_d(t) \\ &\quad - (\mu_d + \alpha_d + \sigma_d + \xi_d + \theta_d)\, y_d(t)\end{aligned}$$

$$
\begin{aligned}
&\dot{z_d}(t)\\
&\quad = (u_c + \zeta_c) z_d^C(t) + \delta_d l_d(t) + \sigma_d y_d(t)\\
&\qquad - (\mu_d + \gamma_d + \xi_d + \theta_d) z_d(t)\\
&\mathbf{B}(t)\\
&\quad = \mu_d (1 - x_d(t)) + \xi_d \left(1 - x_d(t) - x_d^C(t)\right)\\
&\qquad + \alpha_d \left(y_d(t) + y_d^C(t)\right)\\
&\dot{x_d^C}(t)\\
&\quad = \theta_d x_d(t)\\
&\qquad - (\mu_d + u_c + \zeta_c + (1 - \varepsilon_c) b_d a_d m_d s_3(t)) x_d^C(t)\\
&\qquad + r_d l_d^C(t) + \gamma_d z_d^C(t)\\
&\dot{l_d^C}(t)\\
&\quad = \theta_d l_d(t) + (1 - \varepsilon_c) b_d a_d m_d s_3(t) x_d^C(t)\\
&\qquad - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d + u_c + \zeta_c) l_d^C(t)\\
&\dot{y_d^C}(t)\\
&\quad = \theta_d y_d(t) + \varphi_d l_d^C(t)\\
&\qquad - (\mu_d + \alpha_d + \sigma_d + \zeta_c + u_c + \xi_d) y_d^C(t)\\
&\dot{z_d^C}(t)\\
&\quad = \theta_d z_d(t) + \delta_d l_d^C(t) + \sigma_d y_d^C(t)\\
&\qquad - (\mu_d + \gamma_d + \zeta_c + u_c + \xi_d) z_d^C(t)\\
&\dot{s_1}(t) = \mu_s (s_2(t) + s_3(t)) - a_s \left(\mathbf{I}_d(t) + \mathbf{I}_d^C(t)\right) s_1(t)\\
&\dot{s_2}(t)\\
&\quad = a_s \left(\mathbf{I}_d(t) + \mathbf{I}_d^C(t)\right) s_1(t) - \mu_s s_2(t)\\
&\qquad - a_s \left(\mathbf{I}_d(t - \tau) + \mathbf{I}_d^C(t - \tau)\right) s_1(t - \tau) e^{-\mu_s \tau}\\
&\dot{s_3}(t)\\
&\quad = a_s \left(\mathbf{I}_d(t - \tau) + \mathbf{I}_d^C(t - \tau)\right) s_1(t - \tau) e^{-\mu_s \tau}\\
&\qquad - \mu_s s_3(t)\\
&\mathbf{I}_d(t) = c_l l_d(t) + c_y y_d(t)\\
&\mathbf{I}_d^C(t) = (1 - \varepsilon_c) \left(c_l l_d^C(t) + c_y y_d^C(t)\right).
\end{aligned}
\tag{9}
$$

5.3. Dog Vaccination. Biologically, the vaccination would be effective only in susceptible dogs x_d, avoiding them to become infected by infective sandfly bites. Thus, if the vaccine distribution was only for susceptible dogs, it would be necessary to submit several dogs to diagnostic procedure. However, in practical terms, this is not feasible. Therefore, we suppose that all dogs are eligible to be vaccinated and this category of vaccinated dogs is indicated by v_d (lowercase "v").

In our model, we considered that leishmaniasis vaccination would be offered together with rabies vaccine. In other words, we suppose that the rabies vaccination campaign would distribute not only rabies vaccines but also leishmaniasis vaccine. Since the rabies vaccination campaign has been already included in the annual municipality budget, the minimum additional cost to operation of vaccination as control strategy would be only the leishmaniasis vaccine purchasing. This is an idea similar to the one adopted to dog collar. However, in this model we are considering only the leishmaniasis vaccination rate υ_d (lowercase "ipsilon") and its respective impact as control activity.

Figure 3 refers to the flowchart considering the inclusion of leishmaniasis vaccination. Next, we have system (10), in which we included the vaccinated dog compartment, and Table 6 where we describe the additional parameters for this control.

Note from Figure 3 that once the dog is vaccinated, there is a loss of immunity rate p_c [43]. Also, according to Fernandes et al. [44], the efficacy of leishmaniasis vaccination is around 96.4%. Therefore, we considered that a proportion ε_v of these vaccinated dogs against leishmaniasis is immunized.

$$
\begin{aligned}
\dot{x_d}(t) &= \mathbf{B}(t) + r_d l_d(t) + \gamma_d z_d(t) + p_d v_d(t)\\
&\qquad - (b_d a_d m_d(t) s_3(t) + \varepsilon_v \upsilon_d) x_d(t)\\
\dot{l_d}(t) &= b_d a_d m_d(t) s_3(t) x_d(t)\\
&\qquad - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d) l_d(t)\\
\dot{y_d}(t) &= \varphi_d l_d(t) - (\mu_d + \alpha_d + \sigma_d + \xi_d) y_d(t)\\
\dot{z_d}(t) &= \delta_d l_d(t) + \sigma_d y_d(t) - (\mu_d + \gamma_d + \xi_d) z_d(t)\\
\dot{v_d}(t) &= \varepsilon_v \upsilon_d x_d(t) - (p_d + \mu_d + \xi_d) v_d(t)\\
\mathbf{B}(t) &= (\mu_d + \xi_d)(1 - x_d(t)) + \alpha_d y_d(t).
\end{aligned}
\tag{10}
$$

5.4. Dog Treatment. In this control strategy, the objective is reducing the number of infected dogs, which works as source of infection. However, the probability of treating a latent dog is quite null, since this category of dog is visually healthy. Thus, we assume that only dogs that present clinical signs and/or symptoms are eligible to be treated and the dog treatment rate is indicated as ω_d.

We will consider the treatment protocol described by Miró et al. [45], which was composed by meglumine antimoniate plus allopurinol. In this work, the authors found a proportion of dogs that healed but still continued to be infected. In other words, once a dog is treated, there is a probability of a dog eliminating the parasitemia or not.

Furthermore, we also consider that the dog treatment would be offered by public health policies. Therefore, if the public health services have already included veterinarians

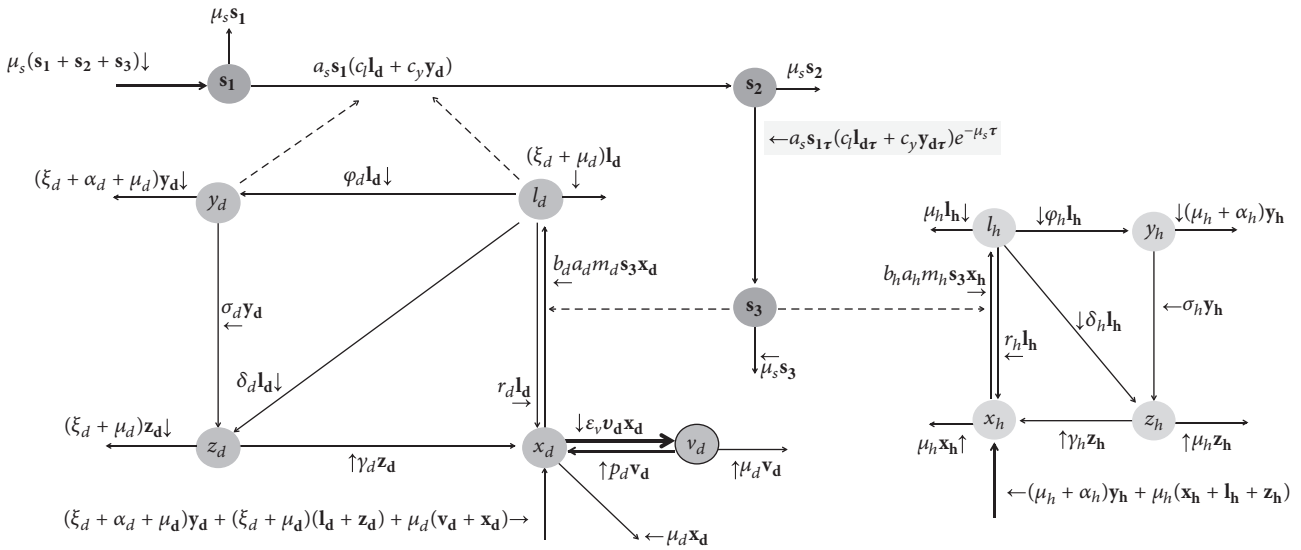

Figure 3: The compartment model and the flowchart, when the vaccination is introduced as preventive strategy control. Note that the dynamics for human and sandfly populations have not changed.

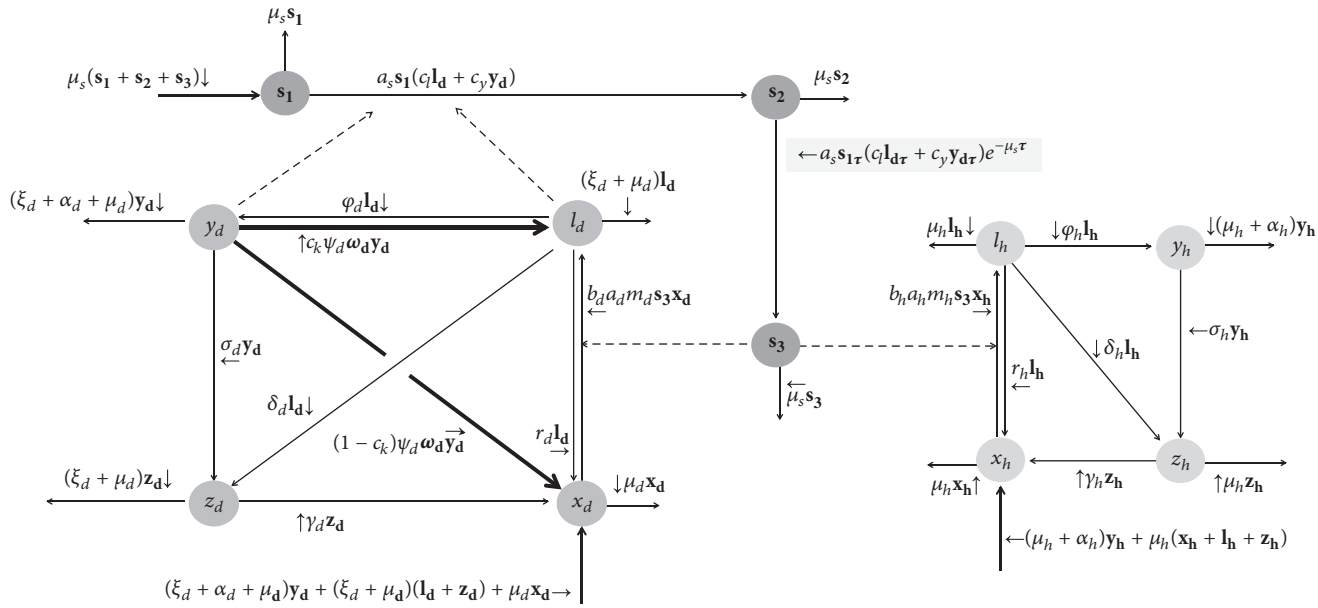

Figure 4: The compartment model and the flowchart, when the dog treatment is introduced as preventive strategy control. Note that the dynamics for human and sandfly populations have not changed.

in the staff, the minimum additional cost would be the acquisition of the medicine (meglumine antimoniate and allopurinol) and hospital material (e.g., syringes and needles).

Figure 4 refers to the flowchart considering the inclusion of dog treatment. Then, we have system (11), in which we included the treated dogs flux (from clinically ill to susceptible or to latent), and Table 7 where we describe the additional parameters for this control.

Note from Figure 4 that once the dog is treated, there is a probability to be recovered, but without parasitemia elimination. We adopt c_k as a proportion of dogs that obtain only clinical recovery but are still infected [45]. Also, once the treatment started, we assumed that any dog gives up on the treatment process over time (i.e., the proportion of dogs that receive the complete treatment is $\psi_d = 1$).

$$\begin{aligned}
\dot{x_d}(t) &= \mathbf{B}(t) + (1-c_k)\psi_d\omega_d y_d(t) + r_d l_d(t) \\
&\quad + \gamma_d z_d(t) - b_d a_d m_d(t) s_3(t) x_d(t) \\
\dot{l_d}(t) &= c_k\psi_d\omega_d y_d(t) + b_d a_d m_d(t) s_3(t) x_d(t) \\
&\quad - (\mu_d + r_d + \delta_d + \varphi_d + \xi_d) l_d(t) \\
\dot{y_d}(t) &= \varphi_d l_d(t) - (\mu_d + \alpha_d + \sigma_d + \xi_d + \psi_d\omega_d) y_d(t)
\end{aligned}$$

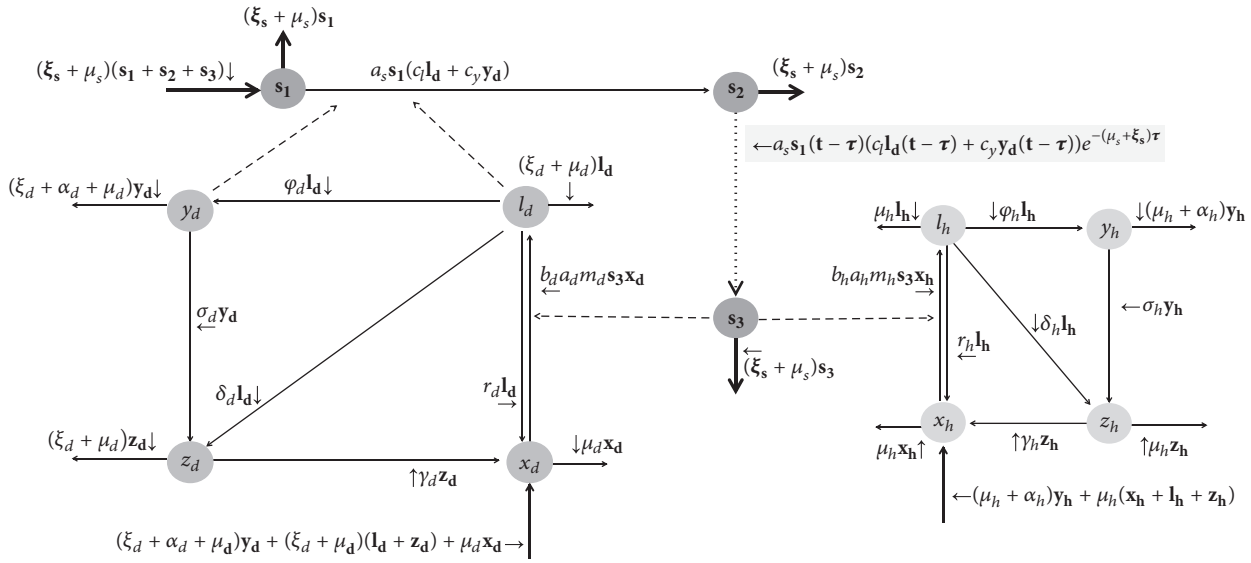

FIGURE 5: The compartment model and the flowchart, when the sandfly population control is introduced as preventive strategy control. Note that the dynamics for human and dog populations have not changed.

$$\begin{aligned} \dot{z_d}(t) &= \delta_d l_d(t) + \sigma_d y_d(t) - (\mu_d + \gamma_d + \xi_d) z_d(t) \\ \mathbf{B}(t) &= (\mu_d + \xi_d)(1 - x_d(t)) + \alpha_d y_d(t). \end{aligned} \tag{11}$$

5.5. Sandfly Population Control. The activities of sandfly population control focus on two approaches, both of them on the environment. First, according to Brazilian Ministry of Health [17], the sandfly population control includes a chemical control (spraying of insecticide on the houses) and a land clearing (that reduces the sandfly carry capacity). In order to simplify our study, we just considered that those both approaches included in the sandfly population control result in an increase of sandfly mortality rate, ξ_s. On the other hand, it is unfeasible to organize a sandfly control considering the sandfly mortality rate, as "eliminated sandfly/day" (i.e., working in function of the amount $\xi_s \times S$). Because of this, we considered as sandfly control rate the dimension of "treated houses/(sandfly × day)": ξ_c. Therefore, once the number of treated houses to be treated per day and per sandfly is determined, we can easily find the additional sandfly mortality rate:

$$\xi_s = \xi_c \times w_{hc} \times m_{h0}, \tag{12}$$

where w_{hc} means the average human/house and m_{h0} is the ratio sandfly/human.

It would be very complex to estimate the sandfly population control budget, but for this model we considered the economical evaluation presented by Camargo-Neves [31] (Table 8).

Figure 5 refers to the flowchart considering the inclusion of sandfly population control. Then, we have system (13), in which we presented the additional sandfly mortality rate $\xi_s = \xi_c w_{hc} m_{h0}$.

In a proportional approach, note from Figure 5 that sandfly population is considered constant in our model (we remember that our three populations in our model are normalized). As a result, the proportional increase of its mortality rate induces an increase of population renewing at the same proportion. This acceleration of population renewing refers to the conception of carry capacity. Here, carry capacity means the maximum population size of biological species in an environment. Thus, whenever the sandfly population is under the carry capacity, it will tend to increase until it becomes fitted to it. Also, the opposite occurs if it is over the carry capacity (the population will decrease until its size fits the carry capacity). Finally, as our model considers the sandfly population proportionally constant, it means that when sandflies die, the population will decrease and it will be under the maximum size allowed by carry capacity. As a consequence, the population will increase by recruitment of new individuals (mathematically, this is the entrance term $\mu_s(S_2(t) + S_3(t))$). Therefore, in short, we conclude that if the sandfly mortality rate increases, the sandfly population renewing rate will also increase.

According to Burattini et al. [10], the acceleration of the sandfly population renewing (or, in other words, the decrease of life expectancy of sandfly population) affects directly the LVZ dynamics, since the infected sandfly s_2 is also eliminated in a shorter time. As a consequence, the parasite *Leishmania* s_2 will not have time enough to complete its development inside the sandfly and the proportion of infective s_3 will also naturally decrease.

$$\begin{aligned} \dot{s_1}(t) &= (\mu_s + \xi_c w_{hc} m_{h0})(s_2(t) + s_3(t)) \\ &\quad - a_s \mathbf{I}_d(t) s_1(t) \\ \dot{s_2}(t) &= a_s \mathbf{I}_d(t) s_1(t) - (\mu_s + \xi_c w_{hc} m_{h0}) s_2(t) \\ &\quad - a_s \mathbf{I}_d(t - \tau) s_1(t - \tau) e^{-(\mu_s + \xi_c w_{hc} m_{h0})\tau} \end{aligned}$$

Table 2: Parameters adopted in our model. The indexes h, d, and s stand for humans, dogs, and sandflies, respectively (continuation of Table 1).

Parameter	Meaning	Value	Dimension	Source
δ_d	Latent recovery rate	8.22×10^{-3}	1/day	Lanotte et al. [28]
ξ_d	Dog elimination rate	3.36×10^{-4}	1/day	Camargo-Neves [31]
μ_s	Natural mortality rate	5.00×10^{-2}	1/day	Ministry of Health, Brazil [17]
τ	Extrinsic incubation period	7	Day	Neva and Sacks [32]
a_S	Average daily biting rate (on dogs)	2.00×10^{-1}	1/day	Estimated as Epidemiological Surveillance Direction, Santa Catarina State, Brazil [21]
c_l	Probability of latent dog to infect the sandfly	0.385	Dimensionless	Laurenti et al. [33]
c_y	Probability of clinically ill dog to infect the sandfly	0.247	Dimensionless	Laurenti et al. [33]

$$\begin{aligned} \dot{s_3}(t) &= a_s \mathbf{I}_d(t-\tau)\, s_1(t-\tau)\, e^{-(\mu_s+\xi_c w_{hc} m_{h0})\tau} \\ &\quad - (\mu_s + \xi_c w_{hc} m_{h0})\, s_3(t) \\ \mathbf{I}_d(t) &= c_l l_d(t) + c_y y_d(t). \end{aligned} \tag{13}$$

6. The Estimated Costs and Calculation of Control Strategy Rates

It is very important to consider not only the result of the control strategy at the light of epidemiological approach but also the economical one too. Therefore, since the number of controlled elements is in dimension of elements/day, the estimation of the cost/elements would provide us with the estimated cost per day (i.e., cost/individual × individual/day = cost/day). Here we suppressed the cost calculation of each method, but we indicated the references from where we preceded our estimations. Table 8 summarizes those costs.

Usually, the operating of preventive control strategies is limited by logistic and financial resources. Therefore, in order to estimate the preventive control rates, firstly it is necessary to estimate those restrictions.

First, considering the data from Table 3. From "Human reported cases per year" column we estimated the year average, which is 20.18 human cases/year. Then, from Table 8, the estimated cost for human treatment is around 397.25 USD/human [46]. Therefore, per year, the average expanses with human treatment are around 20.18 × 397.25 = 8015 USD/year. If we consider the costs per day, we have around 22 USD/day. For simplicity, we will consider that this value includes not only financial aspects but also logistic one.

Now, let us suppose that instead of this 22 USD/day that is invested on patient treatments, it would be invested on preventive control strategies. However, we should consider that this 22 USD/day is invested on the prevention of the whole dog population or houses. If we consider the human : dog ratio for Araçatuba/SP city of 10/1.8 human/dog [29] and the human : house ratio of 3 humans/house [22], the estimation of dog population and the number of houses for 2016 is around 34889 dogs and 64609 houses. Then, the invested cost per dog is estimated as 22/34889 = 6.29×10^{-4} USD/(dog × day) and, considering houses, 22/64609 = 3.40×10^{-4} USD/(house × day). Since we obtained the estimated costs for each control strategy (Table 8), it is possible to estimate the maximum rate of each control. As example, if the cost for elimination of one positive dogs is 170.71 USD/dog, the maximum rate of elimination dog per day would be $6.29 \times 10^{-4}/170.71 = 3.69 \times 10^{-6}$/day. In the same way, we just repeated the calculation process and estimated the maximum rate of each control strategy, but in the case of vector control we used the estimated number of houses instead of estimated dog population. All estimated control rates are in Table 8.

It is important to present a special consideration about ξ_c dimension. According to (12), ξ_c dimension is "houses/(sandfly × day)." Since the dimension of estimated investment cost per house is "USD/(house × day)," we concluded that the cost estimated of sandfly population control presents the dimension "USD × sandfly/(house)^2." This dimension can be splitted as "(USD/house) × (sandfly/house)." Thus, we can observe that the cost of sandfly population control depends on density sandfly/house. The higher this density sandfly/house is, the more expensive the cost becomes. Therefore, we considered the sandfly population control average cost as 23.24 USD × sandfly/(house)^2.

7. The Impact of Control Strategies on Total of Saved Humans

According to Table 2, we accessed official data of Araçatuba municipality from 1999 to 2015. Later, from those data, we were able to fit the model from system (1) by observing the resulting curve from reported human cases in (4) from fitting $m_h(t)$ in (7).

Once we have the model from system (1) defined and calibrated, we are able to evaluate the dynamics of each control strategy and compare them with the no-control strategy scenery.

First, we considered the numerical simulation of system (1) from 1999 to 2025. Since we are interested in understanding the dynamics of the disease over time in an as real as possible behavior, we present Figure 6 with bars

Table 3: Human and dog demographic data from Araçatuba municipality and estimated human reported cases.

Year	Human reported cases per year (CES-SP) [36]	Araçatuba's human population size (BIGS) [22]	Average of normalized human reported cases per day	Estimated dog population according to Andrade et al. [29]	Estimated number of houses (BIGS) [22]
1999	15	169303	2.43×10^{-7}	30475	56434
2000	12	170296	1.93×10^{-7}	30653	56765
2001	29	171289	4.64×10^{-7}	30832	57096
2002	52	172768	8.25×10^{-7}	31098	57589
2003	40	174399	6.28×10^{-7}	31392	58133
2004	41	177823	6.32×10^{-7}	32008	59274
2005	16	179717	2.44×10^{-7}	32349	59906
2006	20	181598	3.02×10^{-7}	32688	60533
2007	42	181371	6.34×10^{-7}	32647	60457
2008	27	181143	4.08×10^{-7}	32606	60381
2009	15	182204	2.26×10^{-7}	32797	60735
2010	4	182365	6.01×10^{-8}	32826	60788
2011	5	182526	7.51×10^{-8}	32855	60842
2012	6	183441	8.96×10^{-8}	33019	61147
2013	3	190536	4.31×10^{-8}	34296	63512
2014	12	191662	1.72×10^{-7}	34499	63887
2015	4	192757	5.69×10^{-8}	34696	64252

Table 4: Parameter values for (7) and their biological meaning.

Parameter	Meaning	Value	Dimension	Source
m_{h0}	Vector density per host (baseline value)	0.75	Sandfly/human	Fitted
A	Vector density per host	3.4	Sandfly/human	Fitted
B	Vector density per host	8.3	Sandfly/human	Fitted
L	Linear constant	3.0	Dimensionless	Fitted
K_1	Proportionality constant	3.5×365	Day	Fitted
T	Sandfly population dynamics period	5.5×365	Day	Fitted

Table 5: Additional parameters adopted for evaluation of deltamethrin 4% impregnated dog collar.

Parameter	Meaning	Value	Dimension	Source
θ_d	Rate of dogs using collar	Variable	1/day	—
u_c	Inverse of activity period of collar	6.70×10^{-3}	1/day	Scalibor ® [40]
ζ_c	Loss of insecticide impregnated collar	6.00×10^{-3}	1/day	Reithinger et al. [41]
ε_c	Decrease of biting rate due to insecticide impregnated collar	8.00×10^{-1}	Dimensionless	Halbig et al. [42]

Table 6: Additional parameters adopted for evaluation of dog vaccination.

Parameter	Meaning	Value	Dimension	Source
v_d	Leishmaniasis vaccination rate	Variable	1/day	—
p_d	Loss of immunity rate (Leishmune® vaccination)	2.74×10^{-3}	1/day	Moreira [43]
ε_v	Efficacy of ZVL vaccination	0.964	Dimensionless	Fernandes et al. [44]

Table 7: Additional parameters adopted for evaluation of dog treatment.

Parameter	Meaning	Value	Dimension	Source
ω_d	Dog treatment rate	Variable	1/day	—
c_k	Proportion of clinically recovered dogs but that are still infected	0.154	Dimensionless	Miró et al. [45]
ψ_d	Proportion of dogs that receive the complete treatment	1	Dimensionless	Assumed

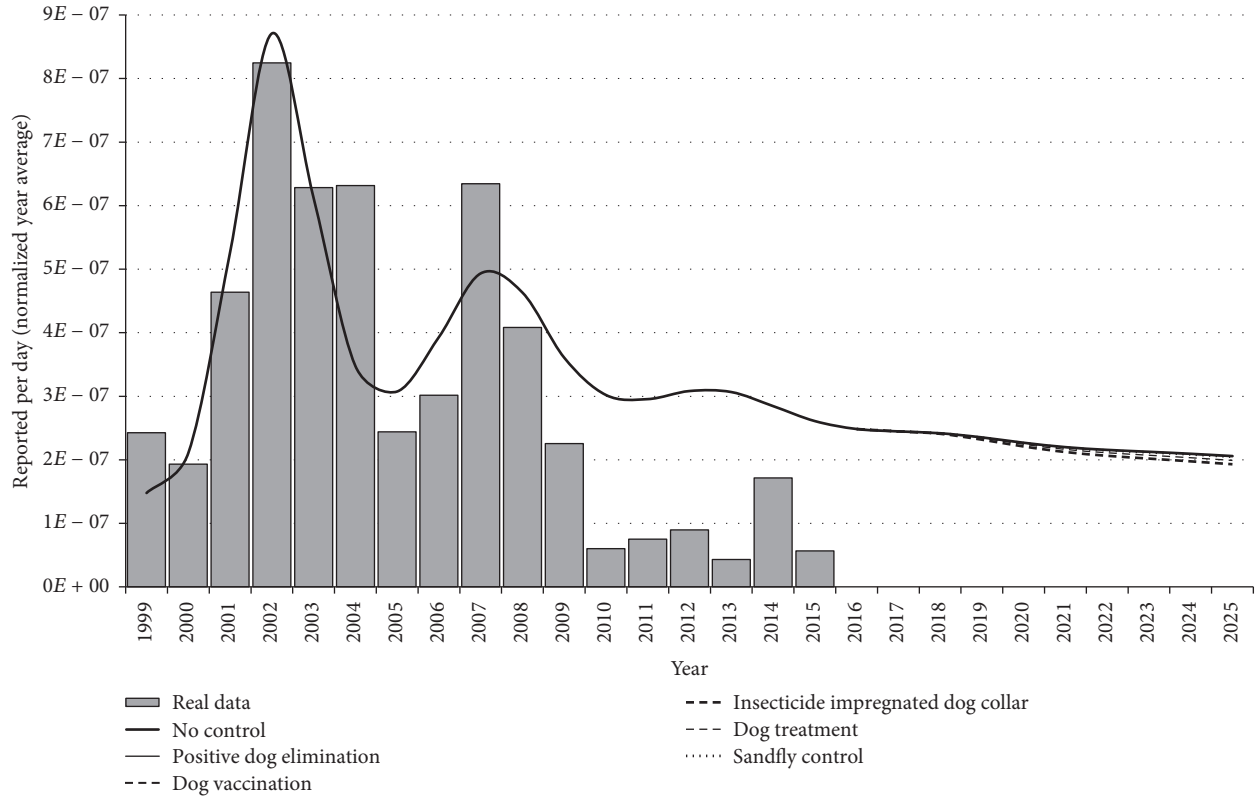

Figure 6: Total disease dynamics and plotting of official data over time. The control strategies were supposed to be introduced from 2018. Observe that the prediction of reported human cases from 2018 for each control strategy is quite close and, therefore, in this scale the curves are overlapped (see Figure 7 for a larger scale).

that indicate the official data. However, considering the prediction evaluation of the control strategies, we assumed in our simulation that those control strategies would start to be operated in 2018. Therefore, we observe in Figure 6 the numerical simulation and the prediction result if we consider the introduction of those strategies starting from 2018 (for a better view, see Figure 7).

Once we observed the control strategy dynamics in terms of reported human cases, it is very useful to estimate the quantity of people that avoided the infection. Just for simplification, in this text we refer to those people as "saved" human.

Since we developed a computational simulation, we had the control of sceneries. Therefore, in order to evaluate the impact of each control strategy, we compared the simulation results between introduced control strategy and no-control simulations. It is important to remember that in all simulations we computed the real total of clinically ill humans, according to (14). However, if we calculate the difference between the no-control simulation and introduced control simulation, we have the quantity of humans that were prevented to become clinically ill (the saved one).

$$\begin{aligned}\mathcal{T}^{i}_{\text{saved}} &= T^{\text{no-control}}_{y_h}\left(t_f\right) - T^{i}_{y_h}\left(t_f\right)\\ &= \varphi_h \int_{t_0}^{t_f} \left(I^{\text{no-control}}_{h}(t) - I^{i}_{h}(t)\right) dt,\end{aligned} \tag{14}$$

where $\mathcal{T}^{i}_{\text{saved}}$ is the total of saved humans until time t_f and i is the correspondent control strategy. Figure 8 represents the result of those totals of saved humans for each control strategy.

According to Figure 8, the dog treatment was the strategy that presented the lower number of saved people. It makes some sense, since the dog treatment does not eliminate the parasitemia status. Therefore even if an infected dog is treated, it may still continue being source of infection. On the other hand, the insecticide impregnated dog collar and dog vaccination were the strategies that most saved

Table 8: Summary of average costs for strategy controls and for human patient treatment.

	Meaning	Cost	Cost dimension	Source	Normalized cost (in terms of patient cost)	Normalized cost dimension	Control rate	Control rate dimension
ξ'_d	Elimination of positive dog	170.71	USD/dog	Estimated as Camargo-Neves [31]	0.43	Patient/dog	3.69×10^{-6}	1/day
θ_d	Deltamethrin 4% impregnated dog collar	12.00	USD/dog	Estimated as Camargo-Neves et al. [47]	0.03	Patient/dog	5.25×10^{-5}	1/day
ω_d	Dog treatment with allopurinol and meglumine antimoniate	265.76	USD/dog	Estimated as Miró et al. [45]	0.67	Patient/dog	2.37×10^{-6}	1/day
υ_d	Vaccine	33.00	USD/dog	F. F. Gonzales (Personel communication, 2016)	0.08	Patient/dog	1.91×10^{-5}	1/day
ξ_c	Sandfly population control	23.24	USD × sandfly/(house)^2	Estimated as Camargo-Neves [31]	0.06	Patient × sandfly/(house)^2	1.46×10^{-5}	House/(sandfly × day)
—	Human patient treatment	397.25	USD/patient	Estimated as Akhavan [46]	1.00	Patient/patient	—	—

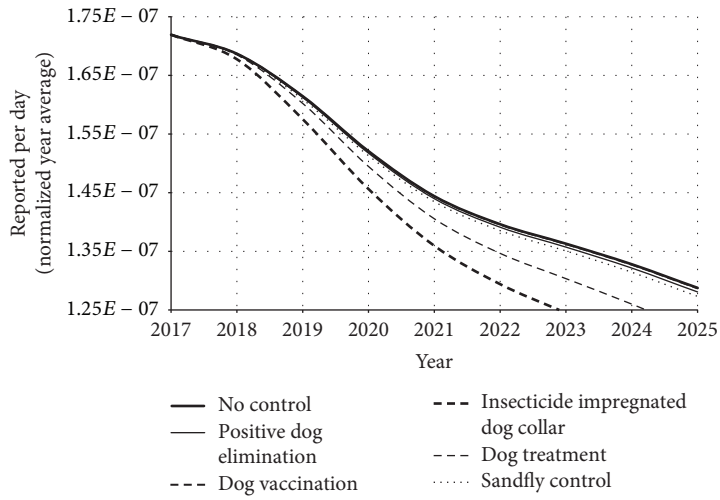

Figure 7: Disease dynamics considering the introduction of control strategies. Here we present a larger scale of the vertical and horizontal axis in order to provide a better observation of the curves. Note that the insecticide impregnated dog collar is the strategy that generates lower reducing of reported human cases. On the other hand, the dog treatment curve is overlapped with the no-control curve. Therefore, it is the strategy that presented the worst result in terms of reported human cases reduction.

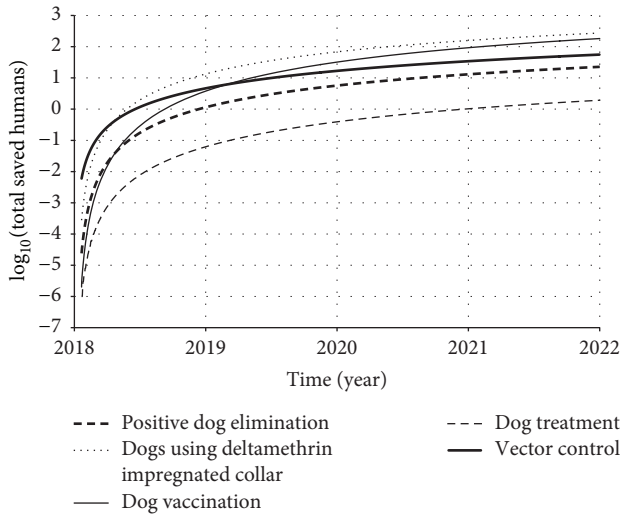

Figure 8: Total of saved humans over time, according to each strategy. Observe that using of deltamethrin impregnated collar and vaccination were the strategies which saved more humans. On the other hand, the dog treatment saved around hundred times fewer individuals, if compared to those two best strategies. Since those curves exponentially grow up, we used a log-scale in vertical axis.

humans. Those two strategies reduce the amount of exposed susceptible individuals to infective sandfly biting. As a consequence, the proportion of infected humans decreases. However, although this interpretation is correct, we did not consider the restriction of resources, as financial, material, or human support. In the next section, we will include our observations about this.

8. Number of Controlled Elements and the Estimation of Total Cost

According to Table 8, each control strategy has a cost per controlled element (dog or house). Therefore, it is essential to understand how to find the equilibrium between the disease control and the available resources (material and/or financial).

In general idea, to count the controlled elements it is necessary to sum the amount of controlled elements per day over an interval of time: total of controlled elements = controlled elements/day × interval of time (days).

From total of controlled elements it is simple to estimate the invested total. Here, we are interested to compare the cost of the control strategies with the cost of human treatment. Therefore, if the cost of each strategy per element has already been normalized in terms of the human treatment cost, we are able to estimate the total cost as total cost = total of

Table 9: Summary of the expressions for total of controlled elements and for total cost. The initial values of the time interval and the ending are represented by t_0 and t_f, respectively. $N_d = 34889$ is the estimated dog population and $H = 64609$ is the estimated total of houses, both for Araçatuba municipality in 2016.

	Meaning	Total of controlled elements $(T_i)^\dagger$	Normalized cost* $(\mathscr{C}_i)^\dagger$	Normalized cost dimension	Total cost* $(C_i^T)^\dagger$
ξ'_d	Elimination of positive dog	$N_d\xi'_d \int_{t_0}^{t_f} (I_d(t) + y_d(t) + z_d(t))\,dt$	0.43	Patient/dog	$T_{\xi'_d} \times \mathscr{C}_{\xi'_d}$
θ_d	Deltamethrin 4% impregnated dog collar	$N_d\theta_d \int_{t_0}^{t_f} (x_d(t) + I_d(t) + y_d(t) + z_d(t))\,dt$	0.03	Patient/dog	$T_{\theta_d} \times \mathscr{C}_{\theta_d}$
ω_d	Dog treatment with allopurinol and meglumine antimoniate	$N_d\omega_d \int_{t_0}^{t_f} y_d(t)\,dt$	0.67	Patient/dog	$T_{\omega_d} \times \mathscr{C}_{\omega_d}$
υ_d	Vaccine	$N_d\upsilon_d \int_{t_0}^{t_f} (x_d(t) + I_d(t) + y_d(t) + z_d(t))\,dt$	0.08	Patient/dog	$T_{\upsilon_d} \times \mathscr{C}_{\upsilon_d}$
ξ_c	Vector control	$H\xi_c \int_{t_0}^{t_f} dt$	0.06	Patient/house	$T_{\xi_c} \times \mathscr{C}_{\xi_c}$

*In terms of patient cost.
†The index i stands for the respective control strategy.

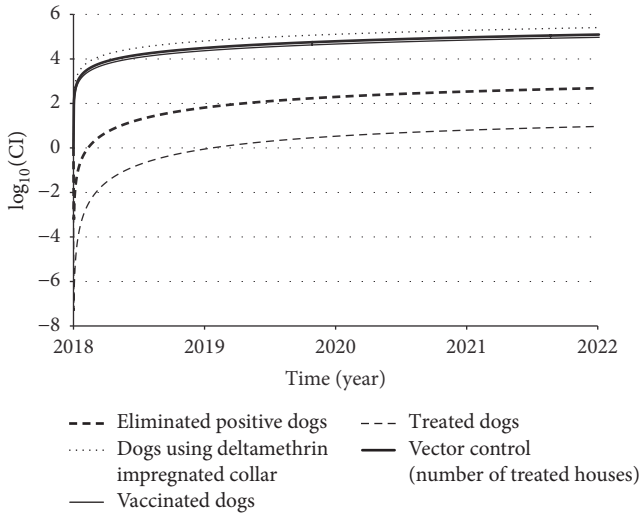

Figure 9: Total of controlled individuals (dogs or houses) over time, according to each strategy. Note that the dynamics of total number of treated houses for vector control and the number of vaccinated dogs are very similar. Since those curves exponentially grow up, we used a log-scale in vertical axis.

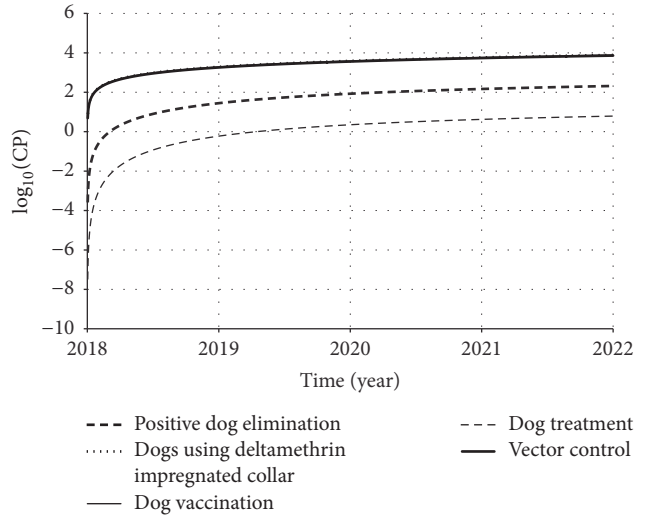

Figure 10: Total cost of each strategy over time, normalized by cost of human treatment. Note that three curves are overlapped: vector control, dog vaccination, and dog using deltamethrin impregnated collar. Since those curves exponentially grow up, we used a log-scale in vertical axis.

controlled elements × cost (normalized by human patient cost)/element.

Table 9 presents the expressions that calculate the total of controlled elements and the total cost of each strategy. Figures 9 and 10 present, respectively, the dynamics of total of controlled dogs or houses and the total cost normalized by human patient cost.

From Figures 9 and 10, it is possible to observe a similarity and correspondence between the curve responses. In terms of costs, vector control, dog vaccination, and dog collar are very close to each other. But, the difference is related to the number of controlled elements, in which we found that there were more dogs with collar than vaccinated dogs or treated houses. Also, although dog treatment and dog elimination presented reduced costs, they also controlled fewer elements too.

9. Calculation of $\mathscr{R}_0$ as Function of Each Preventive Control and Evaluation of $\mathscr{R}$ Dynamics

For each evaluation, we calculated the respective $\mathscr{R}_0$ (Basic Reproduction Number) in function of the preventive control method. The Basic Reproduction Number indicates the quantity of infected individuals generated from one infective individual, when introduced in a population in disease-free equilibrium state [48]. We assumed that $\mathscr{R}_0$ is calculated

Table 10: Summary of the expressions for total of controlled elements and for total cost. The initial values of the time interval and the ending are represented by t_0 and t_f, respectively. $N_d = 34889$ is the estimated dog population and $N_{\text{houses}} = 64609$ is the estimated total of houses, both for Araçatuba municipality in 2016.

	Meaning	$\mathscr{R}_0$ expression
ξ'_d	Elimination of positive dog	$\mathscr{R}_0^{\xi'_d} = \frac{w_{dh} m_{h0} b_d a_d a_s e^{-\mu_s \tau} \left(c_l \left(\sigma_d + \alpha_d + \mu_d + \xi_d + \xi'_d\right) + c_y \varphi_d\right)}{\left(r_d + \delta_d + \varphi_d + \mu_d + \xi_d + \xi'_d\right)\left(\sigma_d + \alpha_d + \mu_d + \xi_d + \xi'_d\right)\mu_s}$
θ_d	Deltamethrin 4% impregnated dog collar	$\mathscr{R}_0^{\theta_d} = \frac{w_{dh} m_{h0} a_d a_s b_d e^{-\mu_s \tau}}{a_1 a_3 \left(a_1 + a_2 + \theta_d\right)\left(a_3 + a_2 + \theta_d\right)\mu_s} \times \left(P_1 + P_2\right),$ where $P_1 = c_l a_3 \left(a_1 + a_2 + \left(1 - \varepsilon_c\right)\theta_d\right)\left(a_2 + a_3 + \theta_d\right)$ $P_2 = c_l \varphi_d \left(a_1 a_3 + \left(a_2 + \left(1 - \varepsilon_c\right)\theta_d\right)\right)\left(a_1 + a_2 + a_3 + \theta_d\right)$ $a_1 = \mu_d + r_d + \delta_d + \varphi_d + \xi_d$ $a_2 = \zeta_c + u_c$ $a_3 = \mu_d + \alpha_d + \sigma_d + \xi_d$
ω_d	Dog treatment with allopurinol and meglumine antimoniate	$\mathscr{R}_0^{\omega_d} = \frac{w_{dh} m_{h0} a_d a_s b_d e^{-\mu_s \tau} \left(c_l \left(\sigma_d + \alpha_d + \mu_d + \xi_d + \psi_d \omega_d\right) + c_y \varphi_d\right)}{\left(r_d + \delta_d + \varphi_d + \mu_d + \xi_d\right)\left(\sigma_d + \alpha_d + \mu_d + \xi_d + \psi_d \omega_d\right)\mu_s}$
υ_d*	Vaccine	$\mathscr{R}_0^{\upsilon_d} = \frac{w_{dh} m_{h0} a_d a_s b_d e^{-\mu_s \tau} \left(c_l \left(\sigma_d + \alpha_d + \mu_d + \xi_d\right) + c_y \varphi_d\right)}{\left(r_d + \delta_d + \varphi_d + \mu_d + \xi_d\right)\left(\sigma_d + \alpha_d + \mu_d + \xi_d\right)\mu_s}$
ξ_c	Vector control	$\mathscr{R}_0^{\xi_c} = \frac{w_{dh} m_{h0} a_d a_s b_d e^{-\left(\mu_s + \xi_c w_{hc} m_{h0}\right)\tau} \left(c_l \left(\sigma_d + \alpha_d + \mu_d + \xi_d\right) + c_y \varphi_d\right)}{\left(r_d + \delta_d + \varphi_d + \mu_d + \xi_d\right)\left(\sigma_d + \alpha_d + \mu_d + \xi_d\right)\left(\mu_s + \xi_c w_{hc} m_{h0}\right)}$

*Note that $\mathscr{R}_0^{\upsilon_d}$ does not depend on υ_d.

when the time t is high enough, where $\lim_{t \to +\infty} m_h(t) = m_{h0}$. As stated before, the full calculations are not described in this work, but we adopted the review published by van den Driessche and Watmough [38]. Once $\mathscr{R}_0$ is calculated, we calculated the respective $\mathscr{R}(t)$ (effective reproduction number) and investigated which one of the 5 control strategies (elimination of positive dogs ξ'_d, use of deltamethrin 4% impregnated dog collar θ_d, dog treatment with allopurinol and meglumine antimoniate ω_d, dog vaccination υ_d, and sandfly population control ξ_c) makes $\mathscr{R}(t)$ converge fastest to a value lower than 1.

Table 10 summarizes the $\mathscr{R}_0$ expressions for each control strategy.

The conception of $\mathscr{R}_0$ is restricted on population's disease-free equilibrium state, since the mathematical approach that defines it considers the system in equilibrium states. Usually, a dynamic system has two classes of equilibrium states: a trivial and nontrivial state. If our dynamics system is a disease dynamics one, the trivial equilibrium is this disease-free equilibrium state and it is considering this equilibrium in which $\mathscr{R}_0$ is calculated.

However, it is natural that there is generation of infected individuals immediately after the transmission has started. In this case, it is important to consider the susceptible individual dynamics. Therefore, the number of infected individuals generated from an infective one depends on the remaining susceptible individuals in the population:

$$\mathscr{R}(t) = \mathscr{R}_0 \times x(t), \tag{15}$$

where $x(t)$ is the proportion of susceptible individuals in population. Theoretically, we have two host populations for your model: humans and dogs. From those two populations, we have three classes of susceptibles: $x_h(t)$, $x_d(t)$, and $(1 - \varepsilon_c)x_d^C(t)$ (since the collar has a proportion of efficacy). Therefore, we estimated $\mathscr{R}(t)$ as

$$\begin{aligned} \mathscr{R}_d^i(t) &= \mathscr{R}_0^i \times \left(x_d(t) + \left(1 - \varepsilon_c\right) x_d^C(t)\right) \\ \mathscr{R}_h^i(t) &= \mathscr{R}_0^i \times x_h(t), \end{aligned} \tag{16}$$

where d stands for dogs, h stands for humans, and the index i stands for each of the control strategies. Figures 11 and 12 present the dynamic of $\mathscr{R}_d^i(t)$ and $\mathscr{R}_h^i(t)$, respectively, over time.

Observing both Figures 11 and 12 we see that $\mathscr{R}(t)$ dynamics for dog and human population have similar behavior, but some strategies worked better on dog population than human population (and vice versa). In the case of dog population, the insecticide impregnated dog collar and dog vaccination presented higher reduction of $\mathscr{R}(t)$ than the other strategies. On the other hand, in the case of human population, insecticide impregnated dog collar was the strategy that most reduced $\mathscr{R}(t)$, followed by vector control and positive dog elimination. Those results reflect the fact that humans and dogs play different roles in ZVL chain. Thus, since each strategy acts in a specific point of this chain, they also present different impacts on each population.

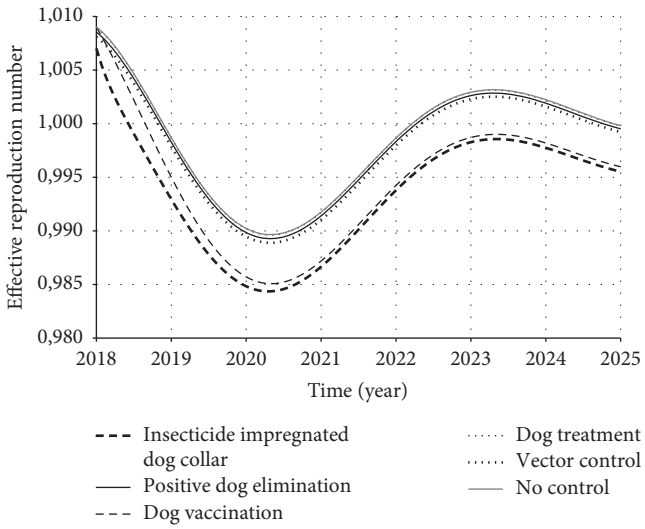

Figure 11: $\mathscr{R}(t)$ dynamics for dog population over time. The control strategies were supposed to be introduced from 2018. Observe that insecticide impregnated dog collar and dog vaccination were the strategies that most reduced $\mathscr{R}(t)$. Note also that dog treatment presented the lowest impact and, therefore, its curve is overlapped with no-control curve.

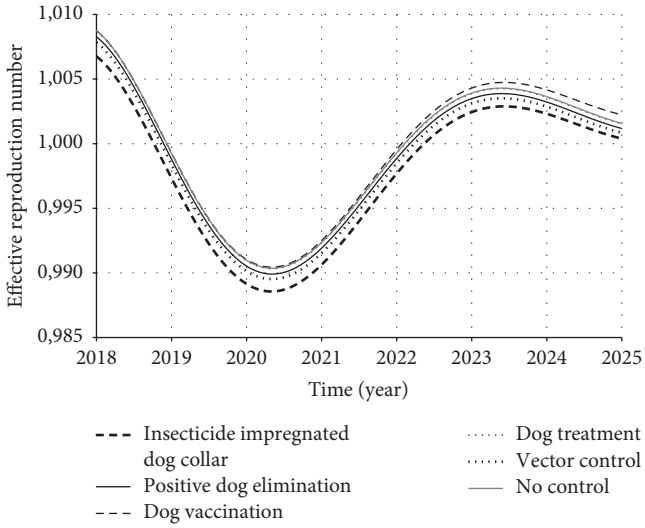

Figure 12: $\mathscr{R}(t)$ dynamics for human population over time. The control strategies were supposed to be introduced from 2018. Observe that insecticide impregnated dog collar was the strategy that most reduced $\mathscr{R}(t)$, followed by vector control and positive dog elimination. Note also that dog treatment curve is overlapped with no-control curve.

10. Control Strategies Analysis: The Best Efficacy and Investment Result

At this point of this study, for each control strategy, we estimated the total of saved humans, controlled individuals (dogs or houses), and cost of investment, normalized by human treatment.

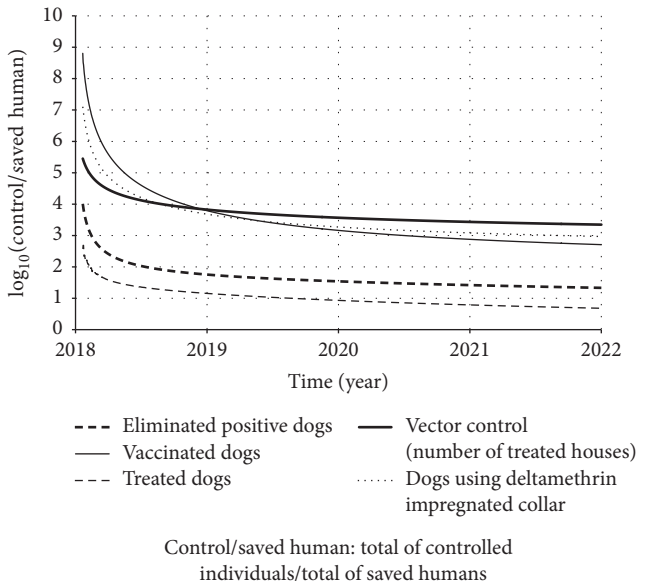

Figure 13: Result of the simulations of expression (17) over time, according to each strategy.

In order to make a decision about which control strategy is the most efficient and cost-effective, a simple criterion was adopted. This criterion analyzed the amount of controlled individuals necessary to avoid one human to become clinically ill. In the same way, it is also possible to analyze how much the investment for each strategy to have one saved human is.

For each strategy we calculated the ratio total of controlled individuals/total of saved humans (17) and total cost/total of saved humans (18).

$$\mathfrak{T}_i\left(t_f\right) = \frac{T_i\left(t_f\right)}{\mathscr{T}^i_{\text{saved}}\left(t_f\right)}, \tag{17}$$

where $\mathfrak{T}_i$ means the ratio of total controlled individuals/total saved humans, T_i is the total of controlled elements, $\mathscr{T}^i_{\text{saved}}$ means the total of saved humans, i stands for the respective control strategy, and t_f is the final time.

$$\mathfrak{C}_i\left(t_f\right) = \mathfrak{T}_i\left(t_f\right) \times \mathscr{C}_i, \tag{18}$$

where $\mathscr{C}_i$ is the cost of the strategy per individual.

Figures 13 and 14 present the result of those ratios over time.

From Figure 13, we observed that insecticide impregnated dog collar, dog vaccination, and sandfly population control were the strategies that require more elements to be controlled (in the case of collar or vaccination, we refer to dogs; in the case of sandfly population control, we refer to houses). In other words, those three strategies need to be applied in more individuals (or houses) in order to avoid one human being infected by LVZ. Our argument is based on the number needed to be treated (NNT) conception, which means how many individuals need to be controlled in order to avoid one infected individual.

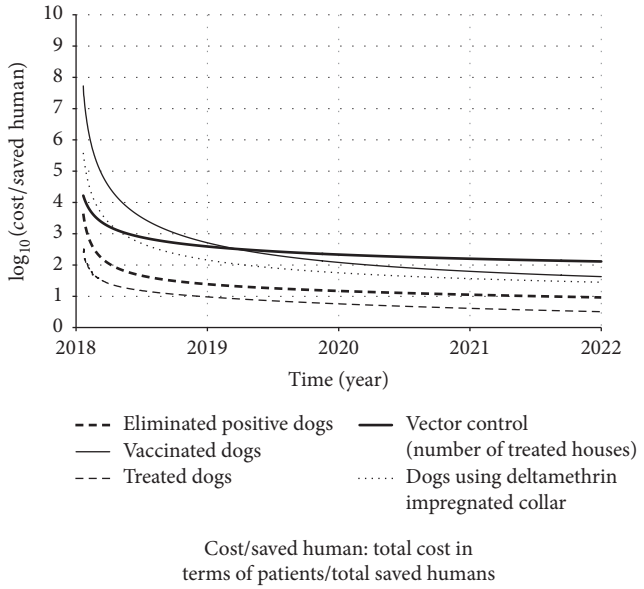

Figure 14: Result of the simulations of expression (18) over time, according to each strategy.

On the other hand, as more elements are controlled, the total cost becomes higher. Thus, the cost of those three strategies was also the one which required more investment among the control strategies studied (Figure 14). However, among those three strategies, we noted that the insecticide impregnated dog collar prevails as the strategy that most saved humans (Figure 8). And, observing Figure 14, we see that the insecticide impregnated dog collar also prevails as the less expensive strategy (per saved human) among those three (followed by dog vaccine and sandfly population control). Therefore, according to our model, the insecticide impregnated dog collar should be the first-choice control strategy, if used isolated.

11. Discussion

In this work, we analyzed the impact and cost-effectiveness of five control strategies considering basic mathematical model, published by Burattini et al. [10] and Ribas et al. [11]. Here, we not only updated most of parameters but also developed a study of those strategies regarding reported human cases prediction, $\mathscr{R}(t)$ dynamics, and investment to control one individual (dog or house) in terms of human patient cost.

According to our modeling of each strategy, it became clearer to understand how each one works in the prevention of infection in humans. First of all, remember that dogs are the main source of infection and sandfly bite is the main transmission way. Therefore, positive dog elimination strategy reduces the source of infection available by instantaneous remotion and avoids more noninfected sandflies acquiring the parasites. Dog treatment strategy also works reducing the source of infection, but without elimination. However, treating the dog does not necessarily eliminate the parasite from dog's organism. Dog vaccination does not eliminate the source of infection, but it protects the remaining susceptible dogs to become infected. Thus, there is the reduction of infected dog by natural elimination. The use of insecticide impregnated dog collar (if used by all dogs) works by protecting the susceptible ones (similar to the vaccine activity) and isolating the source of infection (similar to positive dog elimination). Finally, the sandfly population control aims at reducing the chance of disease transmission by intensifying the cycle of life of the mosquito. As a consequence, if the replacing of mosquito is accelerated, there is no time enough to mature the parasite inside the sandfly. In other words, the cycle of life of mosquito is not long enough to support the incubation period.

The comprehension of how each strategy works on the epidemiologic chain allows us to better understand the results of this study. For instance, since the dog treatment has shown a probability of parasitemia elimination around 84.6% [45], some clinically ill dogs would remain as source of infection; besides they become visually healthy. Since it is more probable for noninfected sandfly to acquire the parasite from a latent rather than a clinically ill dog [33], the dog treatment allows some dogs to remain as source of infection. From a public health point of view, this is epidemiologically undesirable, because there is the probability of increasing the proportion of latent dogs. This explains why the curve regarding dog treatment was considered the less efficient one and, in some cases, was overlapped with no-control curve.

On the other hand, we observed some differences among the impacts of control strategies on human and dog populations. All control strategies are applied on dog or sandfly population and, therefore, the impact on those populations reflects on human population. However, the consequences on human population are not immediate. This helps us to understand the fact that the impact on dog population is more intense and faster than on human population.

Although the consequences on each population are different, in both the use of insecticide impregnated dog collar presented the most positive impact in terms of disease control. This strategy not only reduces the frequency of contact between dogs and sandflies but also reduces the infective sandfly population. As a consequence, the probability of a susceptible human acquiring the infection is also decreased.

Following the insecticide impregnated dog collar, we found different strategies depending on the population. If we observe the dog population, dog vaccination presented a good result. Classically, the vaccination is well known as a preventive strategy, as it removes the susceptible individuals to a vaccinated category, in which it is immune to infection. But, if we analyze the human population, we found that sandfly population control and positive dog elimination were the strategies that presented good results. First, we have to remember that humans are not source of infection and, therefore, the objective for this population is to decrease the force of infection. The force of infection is mathematically defined as $\lambda_i = b_i \times a_i \times m_i \times s_3(t)$ [48], where $i = h, d$. According to our results, to reduce the intensity of source of infection, it is necessary to control $s_3(t)$. Basically, focusing on human population, the reduction of $s_3(t)$ is most efficient if we consider the sandfly population control

(as the sandfly life cycle becomes shorter) and positive dog elimination (we obtain the immediate elimination of source of infection). In the case of human population, dog vaccination presented a low impact, since the vaccination of dog does not immediately remove the infected dog. In this case, those dogs would be naturally eliminated and they would be able to continue playing as source of infection.

Our model provided us with those important results, but it is also necessary to consider real-world restrictions. Here we may simplify those restrictions explaining that they include economical, material, and human resources. Regarding visceral leishmaniasis, there are few works that economically evaluated the preventive control strategies [9]. There are studies that presented an economical analysis approaching treatment and diagnosis of human cases [9, 49, 50] and one of the conclusions pointed out was that investing on preventive activities is beneficially economical [49, 51, 52]. In our study, we not only elaborated a cost-effectiveness evaluation but also observed it dynamically. However, even though our study was based on simple analysis (e.g., we did not include disability adjusted life years or potentially productive years of life lost), our results are very important to fulfill a gap between epidemiological and economical analysis.

In our study, we estimated the total of saved humans and of controlled individuals (dogs or houses) over time and we found that insecticide impregnated dog collar, dog vaccination, and sandfly population control were the ones that saved more humans. On the other hand, they required more individuals to be controlled and, as a consequence, they required more investments too (Figures 9 and 10). Observing Figure 10, dog treatment was the less expensive strategy. If we strongly impose the financial resource as restriction (or if our priority is to save financial resources), we should choose treating dog as control strategy. However, we have already known that this strategy presented low effect to control this disease. Therefore, we need to find equilibrium between the control efficacy and cost-effectiveness.

Figure 10 pointed out that the sandfly population control, insecticide impregnated dog collar, and dog vaccination are the most expensive strategies, if we consider the total cost. This is in agreement with the results described by Camargo-Neves [31] in her field study at Araçatuba municipality. This result can be biologically explained as follows. First, a dog lives for a time longer than a sandfly and the sandfly/dog ratio is higher than the sandfly/house ratio. Thus, if only sandfly population control operates as control strategy, we would have to keep sandfly elimination rate ξ_c until the density of latent and clinically ill dogs reduction reflects on the reduction of reported human cases rate. In other words, while sandflies would be eliminated, it would also be necessary to wait for dog's natural death. This fact would result in continued remotion of sandflies, in which it would generate a fixed cost rate. Still, if the latent and clinically ill dogs are reduced by elimination, the impact on prevalence would be more intense, since the positive dog elimination is an immediate way to reduce source of infection. In the course of time, if the positive dog elimination is kept constant, the number of eliminated dogs tends to decrease. However, we should remember that sandfly population control may be an interesting option in terms of cost-effectiveness, depending on social and economical aspects of the area [52].

Although we have not found any economical study regarding dog vaccination, Lee et al. [53] presented an economical analysis for human vaccine. Although the authors considered some disease dynamics hypothesis different from the one from Brazil, it was demonstrated by computational simulations that vaccination can be cost-effective. However, more studies are necessary to understand the real impact of visceral leishmaniasis vaccination as control strategy [6, 44, 53].

In order to make a correct decision, we need to find a relationship between the total of investment on control strategy and the total of saved humans. From this relation, we can understand how expensive it was to prevent human from becoming clinically ill (see expression (18)). Observing Figure 13, we note that, in most of the simulated period, sandfly control population was the strategy that required more elements (houses) to be controlled per saved human. On the other hand, this is the opposite of dog treatment, in which we had fewer elements (dogs) to be treated per saved human. However, despite the fact that dog treatment required fewer elements per saved human, it also resulted in lowest impact among all considered strategies.

But if the controlled elements/saved human ratio is changed to control strategy cost/saved human ratio, we obtain a new approach. According to Figure 14, among those three most efficient strategies (insecticide impregnated dog collar, dog vaccination, and sandfly population control), the insecticide impregnated dog collar was the strategy that showed the best relation of epidemiological control with cost-effectiveness. This is in agreement with a field study developed by Camargo-Neves et al. [47] at Andradina municipality (São Paulo State, Brazil), in which the impacts of insecticide impregnated dog collar against sandfly population control were compared and it was found that the use of dog collar was economically more convenient. In this case, the dog collar is able to repel the sandfly, reducing the contact between dog and sandfly. Also, it avoids both the dog to become infected and the noninfected sandfly to acquire the parasite.

12. Conclusion

In this work, we presented an evaluation of ZVL control strategies, considering epidemiological control impact and cost-effectiveness as analysis criteria. Our results pointed out that focusing the control activities on source of infection and on sandfly population is the way to reach the optimal control and that is why insecticide impregnated dog collar was considered the most efficient and cost-effective among the control strategies. However, since human and dog populations play different roles in this epidemiological chain, choosing criteria on the best control strategy is different. Furthermore, as each control strategy works in different points of disease maintenance and transmission, there is the possibility of improving the disease control results by operating more than one strategy simultaneously. The combination of two or more control strategies is in our upcoming works.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Helio Junji Shimozako and Eduardo Massad were responsible for study design and planning. Helio Junji Shimozako and Jianhong Wu conducted the mathematical analysis. Helio Junji Shimozako conducted model simulations. Helio Junji Shimozako, Jianhong Wu, and Eduardo Massad contributed to results interpretation and discussion. Helio Junji Shimozako contributed to writing the manuscript. All authors read and approved the final version of the manuscript.

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