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# Impact of Vaccination, Insecticide-Impregnated Collar, and Treatment on the Canine Leishmaniasis

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**ABSTRACT.** Leishmaniasis is a parasite disease transmitted by the bites of sandflies. There have been found more than 70 animal species that are natural reservoir hosts of Leishmania. Among the reservoirs, dogs are the most important ones due to their proximity to the human habitat. In this work, we formulate a model to assess the impact of vaccination, insecticide-impregnated collars, and treatment on the control of canine leishmaniasis. To this end, we calculated the Basic Reproduction Number of the disease and carried out a sensitivity analysis of this parameter concerning the epidemiological and demographic parameters. The numerical simulations show the correlation between the disease prevalence and the strategies effectiveness. Control of infection on dogs can be obtained by protecting around 35 percent of dogs with vaccination and insecticide-impregnated collar.

**Keywords:** basic reproduction number, endemic proportions, stability analysis.

## 1 INTRODUCTION

Leishmaniasis is a vector transmitted disease caused by more than 20 species of the protozoa Leishmania. These parasites are transmitted to animals and humans through the bite of infected females of at least 30 species of phlebotomine sandflies. Also, it has been documented sexual and transplacental transmission of leishmaniasis by some authors in mice, humans, and dogs [25]. In the Americas, more than 15 pathogenic types of Leishmania have been identified in humans, and nearly 54 non-vector species may potentially be involved in the disease transmission [19]. The disease has been associated with poverty, but social, environmental, and climatological factors also directly influence the epidemiology of the disease [19]. According to the Panamerican

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Health Organization (PAHO), leishmaniasis is among the top ten neglected tropical diseases with more than 12 million infected people, 0.9 to 1.6 million new cases each year, between 20,000 and 30,000 deaths, and 350 million people at risk of infection.

Depending on the Leishmania species and the host immune response, leishmaniasis can be subclinical, or present local skin lesions, or can produce a disseminated infection [2, 13]. There are three different clinical manifestations of the disease: visceral, mucocutaneous, and cutaneous. Visceral leishmaniasis (often called kala-azar) is the most serious form of the disease, and it is characterized by fever, weight loss, hepatosplenomegaly, and anemia. If not treated, the disease may cause death in more than 90% of the cases. Mucocutaneous leishmaniasis can lead to the partial or complete destruction of the mucous membranes in the nose and mouth and may cause severe disability. Cutaneous leishmaniasis is the most frequent form of this infection, causing mostly ulcerative lesions that leave long life scars [19, 21]. It is interesting to note that clinical manifestations of leishmaniasis vary by region. In the Mediterranean and South Asia regions, visceral leishmaniasis is the main form of the disease. In the Americas, the most common manifestations of the disease are cutaneous and mucocutaneous [5, 6]. The countries with the most cases of visceral leishmaniasis are India, South Sudan, Sudan, Brazil, Ethiopia, and Somalia [19].

Dogs are considered the main domestic reservoir of leishmaniasis, playing an important role in the occurrence of the disease in humans [4]. Canine leishmaniasis is produced by *Leishmania infantum* which can be transmitted by vectors of several species. In experimental conditions, infected asymptomatic dogs were able to successfully infected sandflies. This implies that they play an important role in disease transmission, and they should be taken into account since many dogs are asymptomatic [20, 24]. The leishmaniasis diagnosis in dogs is made considering the epidemiological origin and the set of clinical signs presented by the dog, but parasitological diagnosis is the more secure method, and it is based on observation of amastigotes [27, 28].

Parasitological elimination of canine leishmaniasis is very difficult to be achieved, and disease recurrence seems to be common after therapy. However, the actual medical protocols can promote clinical cure, increasing the dog's life expectancy as well as improving its life quality. To avoid reinfection, the dog must have medical treatment, use insecticide-impregnated collars, and has continuous veterinary monitoring [24]. In general, local application of insecticides, insecticide-impregnated collars, and culling of infected dogs have been used to control canine leishmaniasis since drog therapy is not a sufficient control measure. But, culling of all infected dogs is not acceptable and cost-effective since the replacement of them in the endemic areas is an observed common behavior among human populations.

According to [22], the induction of protective anti-leishmania immunity response in dogs is a feasible, important, and cost-effective goal. There are nowadays several types of vaccines for canine leishmaniasis in the market. These vaccines represent an important advance for the control of the disease, but, unfortunately, the complexity of the protective response that vaccines have to induce in the host difficult their efficiency. Therefore, comparisons among already registered vaccines should go beyond confirming negative serological and parasitological results, including

also cell-mediated immunity tests [18]. On the other hand, the use of insecticide-impregnated collars protects the dog against the vector biting in endemic areas [16].

Mathematical models have been important tools to understand different aspects of the leishmaniasis transmission and the effectiveness of its control measures. In particular, for canine leishmaniasis, [9] formulated an ordinary differential (ODE) model to evaluate the effectiveness of control campaigns on visceral leishmaniasis assuming that some dogs have an innate resistance to the disease. They conclude that infected dog removal or its treatment could be not the best strategy to decrease the canine infection prevalence. Instead, vector control or the reduction of the susceptible populations would be more effective controls. Considering explicitly the human population on disease dynamics, and adding a latent compartment on both human and dog populations, [23] demonstrates that insecticide-impregnated collars, and vector control is more effective than the elimination of seropositive dogs.

In previous work, [11] studied the impact of asymptomatic carriers on the prevalence of leishmaniasis. They concluded that treating small percentages of asymptomatic dogs and humans has an important impact on disease reduction. Inspired by this work, here, a system of differential equations for the dynamics of canine leishmaniasis assuming medical treatment, protective measures (collars), as well as vaccination, is proposed. We obtained an expression for the Basic Reproductive Number that allows us to evaluate the effectiveness of the different treatments using epidemiological and demographic parameters coming from the literature. We complete our analysis with numerical simulations and sensitivity analysis to compare the different protection strategies and to evaluate the importance of the different parameters on the development of the disease.

This paper is organized as follows. In Section 2 we formulate the model. The mathematical analysis is given in Sections 3 and 4. Simulations and sensitivity analysis are carried out in Section 5, and finally, conclusions are presented in Section 6.

## 2 MATHEMATICAL MODEL

We assume that dogs that are vaccinated do not use insecticide-impregnate collars. The total dog population is divided into susceptible, vaccinated, dogs with collars, and infected at time $t$ which are denoted by $S_d(t)$, $V_d(t)$, $C_d(t)$, and $I_d(t)$, respectively. The total dog population is given by $N_d(t) = S_d(t) + V_d(t) + C_d(t) + I_d(t)$. We assume that the dog population has constant recruitment rate $\Lambda_d$, natural mortality rate given by $\mu$, and specific disease mortality rate due to leishmaniasis given by $\delta$, with $\delta < \mu$. We want to stress that the class of recovered dogs is not considered in our model since dogs do not recover from leishmaniasis and they do not acquire immunity [2, 13]. Furthermore, the vaccine only protects temporally, and after a period of time the dogs become susceptible again.

The vector population is recruited at a constant rate $\Lambda_v$, and has a mortality rate $\nu$. Since sandflies do not recover from infection, we only consider susceptible and infected individuals, with $S_v$, and $I_v$ denoting the total number on each class at time $t$, respectively. We assume that a particular dog

receives on average $b$ bites, where $b$ is the biting rate of sandflies, and a proportion $b\frac{I_v}{N_v}$ of these bites comes from infected sandflies, then dogs get infected at a rate of $b\beta S_d\frac{I_v}{N_v}$, where $\beta$ is the probability that an infected bite gives rise to a new case in the dog population. Reciprocally, sandflies get infected by dogs at a rate of $\alpha b\frac{S_v}{N_v}I_d$, where $\alpha$ is the transmission probability from dogs to sandflies.

The parameters $\sigma$ and $\eta$ are, respectively, the *per capita* vaccination of susceptible dogs and collar-use rates by susceptible dogs. In both cases, only $q\sigma S_d$ and $p\eta S_d$ of these dogs are effectively protected against the disease, where $q$ and $p$ are the vaccine and collar efficiency, respectively.

Dogs that are immunized mount an immunity response during a period of time equal to $1/\varepsilon$ after that they become susceptible again, and dogs that receive treatment become susceptible after $1/\tau$ elapsed time. Besides, collars offer protection for a $1/\kappa$ period of time. A summary of the model's parameters, their units, description, and main references are in Table 1.

Table 1: Summary of epidemiological and demographic parameters that appear in the model, with their corresponding descriptions and range of values [1, 3, 5, 7, 12, 19, 26]

| **parameter** | **meaning** | **range of values** |
|---|---|---|
| $b$ | sandfly biting rate | 0.14 - 0.79 day$^{-1}$ |
| $\beta$ | sandfly-dog probability of transmission | 0.15 - 0.25 |
| $\alpha$ | dog-sandfly probability of transmission | 0.05 - 0.385 |
| $\varepsilon$ | rate of losing immunity | 0.0033 - 0.0044 day$^{-1}$ |
| $\nu$ | average sandfly mortality rate | 0.09 - 0.42 day$^{-1}$ |
| $\mu$ | average dog's mortality rate | 0.0003 - 0.0009 day$^{-1}$ |
| $\delta$ | disease mortality rate | 0.0002 - 0.0007 days$^{-1}$ |
| $\kappa$ | rate of losing collar | 0.0028 - 0.0045 days$^{-1}$ |
| $\tau$ | rate of treatment | 0.0067 - 0.0083 days$^{-1}$ |
| $\sigma$ | vaccination rate | 0 - 1 |
| $\eta$ | rate of the collar use | 0 - 1 |
| $q$ | vaccine efficiency | 32.8 - 95.0% |
| $p$ | collar efficiency | 44.7 - 88.3% |

According to the assumptions above, the dynamics of the disease transmission is governed by the non-linear ordinary differential system:

$$\begin{aligned}
\frac{dS_d}{dt} &= \Lambda_d - q\sigma S_d - p\eta S_d - b\beta S_d \frac{I_v}{N_v} - \mu S_d + \varepsilon V_d + \kappa C_d + \tau I_d \\
\frac{dV_d}{dt} &= q\sigma S_d - \varepsilon V_d - \mu V_d \\
\frac{dC_d}{dt} &= p\eta S_d - \kappa C_d - \mu C_d \\
\frac{dI_d}{dt} &= b\beta S_d \frac{I_v}{N_v} - (\tau + \delta + \mu) I_d \\
\frac{dS_v}{dt} &= \Lambda_v - b\alpha S_v \frac{I_d}{N_d} - \nu S_v \\
\frac{dI_v}{dt} &= b\alpha S_v \frac{I_d}{N_d} - \nu I_v \\
\frac{dN_d}{dt} &= \Lambda_d - \mu N_d - \delta I_d.
\end{aligned} \tag{2.1}$$

Since $N_v(t) = S_v(t) + I_v(t) \to \dfrac{\Lambda_v}{\nu}$, we can assume that the vector population is already at equilibrium $\bar{N}_v = \dfrac{\Lambda_v}{\nu}$, that is, $S_v + I_v = \dfrac{\Lambda_v}{\nu} = \bar{N}_v$. Furthermore, it can be proved that the vector field of the system (2.1) points to the interior of the region

$$\Omega = \{S_d + V_d + C_d + I_d = N_d \leq \frac{\Lambda_d}{\mu},\ S_v + I_v = \bar{N}_v\},$$

which implies that the solution trajectories remain in $\Omega$ for all $t \geq 0$ .

To simplify, (2.1) we normalize the dog and vector populations

$$s_d = \frac{S_d}{\Lambda_d/\mu}, \quad v_d = \frac{V_d}{\Lambda_d/\mu}, c_d = \frac{C_d}{\Lambda_d/\mu}, \quad i_d = \frac{I_d}{\Lambda_d/\mu}, \quad n_d = \frac{N_d}{\Lambda_d/\mu},$$

and

$$s_v = \frac{S_v}{\bar{N}_v}, \quad i_v = \frac{I_v}{\bar{N}_v}.$$

Since $s_v = 1 - i_v$, the ODE system for the proportions $s_d, v_d, c_d, i_d, i_v, n_d$ are given by

$$\begin{aligned}
\frac{ds_d}{dt} &= \mu - (q\sigma + p\eta) s_d - b\beta s_d i_v + \varepsilon v_d + \kappa c_d + \tau i_d - \mu s_d \\
\frac{dv_d}{dt} &= q\sigma s_d - \varepsilon v_d - \mu v_d \\
\frac{dc_d}{dt} &= p\eta s_d - \kappa c_d - \mu c_d \\
\frac{di_d}{dt} &= b\beta s_d i_v - (\tau + \delta + \mu) i_d \\
\frac{di_v}{dt} &= b\alpha (1 - i_v) i_d - \nu i_v \\
\frac{dn_d}{dt} &= \mu - \mu n_d - \delta i_d.
\end{aligned} \tag{2.2}$$

## 3 DISEASE-FREE EQUILIBRIUM AND BASIC REPRODUCTIVE NUMBER

We find the equilibrium states of the system (2.2) by setting the derivatives on the left-hand side to zero and solving the resulting algebraic equations. The *disease-free equilibrium* corresponds to the state where dogs and sandfly populations are free of leishmaniasis, that is, ($i_d = i_v = 0$), and it is given by

$$E_0 = (\bar{s}_d, \bar{v}_d, \bar{c}_d, 0, 0, 1)$$

where

$$\begin{aligned} \bar{s}_d &= \frac{1}{1+\frac{p\eta}{\kappa+\mu}+\frac{q\sigma}{\varepsilon+\mu}} \\ \bar{v}_d &= \frac{q\sigma\bar{s}_d}{\varepsilon+\mu} \\ \bar{c}_d &= \frac{p\eta\bar{s}_d}{\kappa+\mu}. \end{aligned} \tag{3.1}$$

The *Basic Reproductive Number* represents the number of secondary cases that one primary infected individual can generate over the course of its infectious period in a wholly susceptible population. It is a threshold condition that says when the infection can persist or die out. To calculate the basic reproductive number associated with the model (2.2), we assume a scenario without vaccination or collars use. Therefore, in this case, the disease-free equilibrium is given by $(1,0,0,0,0,1)$. In [8], the authors define mathematically the basic reproductive number of a disease as the spectral ratio of the *next-generation operator* $\Phi$ associated to the disease-free equilibrium.

The next-generation operator $\Phi$ corresponding to model (2.2) is given by the product of two matrices: the non-negative matrix of the infection terms, $K$, and the inverse of the matrix of the transmission terms, $T$, which for the model given by (2.2) are

$$K = \begin{pmatrix} 0 & b\beta \\ b\alpha & 0 \end{pmatrix}$$

and

$$T = \begin{pmatrix} \tau+\delta+\mu & 0 \\ 0 & \nu \end{pmatrix}.$$

Therefore, $\Phi = KT^{-1}$ is written as

$$\Phi = \begin{pmatrix} 0 & \frac{b\beta}{\nu} \\ \frac{b\alpha}{\tau+\delta+\mu} & 0, \end{pmatrix}$$

and

$$\bar{R}_0 = \sqrt{\frac{b\beta}{\nu}\frac{b\alpha}{\tau+\delta+\mu}}. \tag{3.2}$$

Observe that $b\beta/\nu$ and $b\alpha/(\tau+\delta+\mu)$ are the partial reproduction numbers corresponding to the infections produced by an infected sandfly over a susceptible dog population, and an infected dog over a sandfly population, respectively; and $\bar{R}_0$ is the geometric mean of those quantities.

Following [30], in this paper we will define the basic reproductive number as $R_0 = \bar{R}_0^2$.

Assuming that a fraction $q\sigma$ of the population is protected by vaccination per unit of time, and a fraction $p\eta$ is protected by collars use, the fraction of susceptible in the absence of the disease becomes $\bar{s}_d$, and the number of secondary cases derived from a primary case is reduced to

$$\tilde{R}_0 = R_0\bar{s}_d, \tag{3.3}$$

which implies that the disease can be eradicated if

$$\bar{s}_d \leq \frac{1}{R_0}.$$

Substituting $\bar{s}_d$ obtained in (3.1), assuming $R_0 > 1$, and a fixed proportion $\eta$ of dogs with collars, the fraction $\sigma$ of dogs that should be vaccinated to eradicate the disease should satisfy

$$\frac{((R_0-1)(\kappa+\mu)-p\eta)(\varepsilon+\mu)}{q(\kappa+\mu)} < \sigma. \tag{3.4}$$

Similarly, assuming $R_0 > 1$ and a fixed proportion $\sigma$ of vaccinated dogs, the fraction $\eta$ of dogs that have to use collars to eradicate the disease should satisfy

$$\frac{((R_0-1)(\varepsilon+\mu)-q\sigma)(\kappa+\mu)}{p(\varepsilon+\mu)} < \eta. \tag{3.5}$$

### 3.1 Stability of disease-free equilibrium

The characteristic equation corresponding to the linearization of the system (2.2) around the trivial steady state $P_0$ has an eigenvalue equal to $-\mu$, and the others are given by the roots of the two polynomials

$$p_1(\lambda) = \lambda^2 + (\tau+\delta+\mu+\nu)\lambda + \nu(\tau+\delta+\mu)(1-R_0\bar{s}_d)$$

and

$$p_2(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$$

where

$$\begin{aligned} a_1 &= q\sigma + (p\eta+\mu) + (\varepsilon+\mu) + (\kappa+\mu), \\ a_2 &= (p\eta+\mu)(\varepsilon+\mu) + (q\sigma+\mu+p\eta)(\kappa+\mu) + (\varepsilon+\mu)(\kappa+\mu+q\sigma), \\ a_3 &= (q\sigma+p\eta+\mu)(\varepsilon+\mu)(\kappa+\mu). \end{aligned}$$

The two coefficients of the polynomial $p_1(\lambda)$ are positive if $R_0\bar{s}_d = \tilde{R}_0 < 1$, therefore, its roots have negative real parts. On the other hand, the three coefficients of $p_2(\lambda)$ are positive, and it is clear that $a_1a_2 > a_3$. By the Routh-Hurwitz criteria [14] for a polynomial of degree 3, the roots of $p_2$ have negative real parts. Therefore, we have proven the following result.

**Theorem 1.** *The disease-free equilibrium is locally asymptotically stable if and only if* $\tilde{R}_0 = R_0\bar{s}_d < 1$. *In particular, this holds for* $R_0 < 1$, *and any* $\bar{s}_d \in [0,1]$.

Global stability of the disease free-equilibrium for $\bar{R}_0 < 1$, which gives $R_0 < 1$, can be proved using the next generation operator and a comparison theorem. Therefore, it follows that, if $\bar{R}_0 < 1$, the disease can not be maintained independently of the initial conditions.

**Theorem 2.** *The disease free-equilibrium is globally asymptotically stable for* $\bar{R}_0 < 1$. **Proof.** Since $s_d$ and $(1-i_v)$ are less or equal than one, then system (2.2) satisfies the following inequality for $t \geq 0$:

$$\frac{d}{dt}\begin{pmatrix} i_d(t) \\ i_v(t) \end{pmatrix} \leq (K-T)\begin{pmatrix} i_d(t) \\ i_v(t) \end{pmatrix}.$$

If $\bar{R}_0 < 1$, the spectral radius of $KT^{-1}$ is less than one, equivalently $K-T$ has all of its eigenvalues on the left half plane. It follows that the linear system $\bar{Z}' = (K-T)\bar{Z}(t)$, $\bar{Z} = (Z_1(t), Z_2(t))$, is asymptotically stable for $\bar{R}_0 < 1$, and consequently the solutions of this system tend to zero as $t$ goes to infinity. By comparison results given in [15], it follows that the solutions of system (2.2) approach zero when $t \to \infty$. Therefore, the disease-free equilibrium is globally asymptotically stable for $\bar{R}_0 < 1$. □

## 4 ENDEMIC EQUILIBRIUM

Denote by $E_1 = (s_d^*, v_d^*, c_d^*, i_d^*, i_v^*, n_d^*)$ the endemic equilibrium of system (2.2). In terms of $s_d^*$ and $i_v^*$, the variables $v_d^*, c_d^*$, $i_d^*$ and $n_d^*$ can be written as

$$v_d^* = \frac{q\sigma}{\varepsilon+\mu}s_d^*, \quad c_d^* = \frac{\eta p}{\kappa+\mu}s_d^*, \qquad i_d^* = \frac{b\beta s_d^* i_v^*}{\tau+\delta+\mu}, \quad \text{and} \quad n_d^* = \frac{\mu_d - \delta i_d^*}{\mu_d} > 0.$$

Substituting $i_d^*$ in the equation (5) of system (2.2) we obtain

$$(R_0(1-i_v^*)s_d^* - 1)i_v^* = 0.$$

By hypothesis $i_v^* \neq 0$, which implies

$$s_d^* = \frac{1}{R_0(1-i_v^*)}. \tag{4.1}$$

We notice that for $0 < s_d^* < 1$ and $0 < i_v^* < 1$, it is necessary that $R_0 > 1$.

Now, substituting $s_d^*$, $v_d^*$, $i_d^*$ in the equation (1) of system (2.2), and multiplying the result by $R_0(1-i_v^*)$, we obtain

$$\mu R_0(1-i_v^*) - \left(\frac{q\sigma\mu}{\varepsilon+\mu} + \frac{p\eta\mu}{\kappa+\mu} + b\beta\, i_v^* + \mu\right) + \frac{\tau\beta b}{\tau+\delta+\mu}i_v^* = 0.$$

After some simplifications, we can rewrite the last expression as

$$\mu R_0 - \frac{q\sigma\mu}{\varepsilon+\mu} - \frac{p\eta\mu}{\kappa+\mu} - \mu = \left( b\beta \frac{\delta+\mu}{\tau+\delta+\mu} + \mu R_0 \right) i_v^*.$$

The right-hand side of this equation is bigger than zero. The left-hand side can be written as

$$\mu \left( R_0 - \frac{p\eta(\varepsilon+\mu)+q\sigma(\kappa+\mu)}{(\varepsilon+\mu)(\kappa+\mu)} - 1 \right) = \mu \left( R_0 - \frac{1}{\bar{s}_d} \right) = \mu \frac{1}{\bar{s}_d} \left( R_0 \bar{s}_d - 1 \right).$$

The expression above is bigger than zero if and only if $\tilde{R}_0 = R_0 \bar{s}_d > 1$, where $\bar{s}_d$ is given in (3.1), and it follows that,

$$\bar{i}_v^* = \frac{\mu(R_0\bar{s}_d - 1)}{\bar{s}_d(b\beta \frac{\delta+\mu}{\tau+\delta+\mu} + \mu R_0)}. \tag{4.2}$$

Therefore, we have the following result.

**Theorem 1.** *If $\tilde{R}_0 = R_0\bar{s}_d > 1$, system (2.2) has a unique endemic equilibrium $E_1$. For this, it is necessary that $R_0 > 1/\bar{s}_d$.*

### 4.1 Global stability of the endemic equilibrium

In this section we prove the global stability of the endemic equilibrium $E_1$ under the conditions $\varepsilon = \kappa = \tau = \delta = 0$. For this end we construct the following Lyapunov function as in [10]

$$\begin{aligned} V(X) &= c_1 \left( s_d - s_d^* - s_d^* \ln \frac{s_d}{s_d^*} \right) + c_2 \left( i_d - i_d^* - i_d^* \ln \frac{i_d}{i_d^*} \right) \\ &+ c_3 \left( s_v - s_v^* - s_v^* \ln \frac{s_v}{s_v^*} \right) + c_4 \left( i_v - i_v^* - i_v^* \ln \frac{i_v}{i_v^*} \right) \end{aligned} \tag{4.3}$$

where $X = (s_d, i_d, s_v, i_v)$. The orbital derivative of $V$ is given by

$$\begin{aligned} \dot{V}(X) &= c_1 \left( 1 - \frac{s_d^*}{s_d} \right) (\mu - b\beta_m s_d i_v - (q\sigma + p\eta + \mu) s_h) \\ &+ c_2 \left( 1 - \frac{i_d^*}{i_d} \right) (b\beta_m s_d i_v - \mu i_d) \\ &+ c_3 \left( 1 - \frac{s_v^*}{s_v} \right) (\nu - b\alpha s_v i_d - \nu s_v) \\ &+ c_4 \left( 1 - \frac{i_v^*}{i_v} \right) (b\alpha s_v i_d - \nu i_v). \end{aligned} \tag{4.4}$$

From system (2.2) at equilibrium we obtain the following identities:

$$\begin{aligned}
\mu &= b\beta s_d^* i_v^* + (q\sigma + p\eta + \mu) s_d^* \\
\mu &= \frac{b\beta_m s_d^* i_v^*}{i_d^*} \\
\nu &= b\alpha s_v^* i_d^* + \nu s_v^* \\
\nu &= \frac{b\alpha s_v^* i_v^*}{\nu i_v^*}.
\end{aligned} \tag{4.5}$$

Substituting the above identities in (4.4), and after several calculations and simplifications, we obtain

$$\begin{aligned}
\dot{V}(X) &= -c_1(q\sigma + p\eta + \mu)\frac{(s_d - s_d^*)^2}{s_d} - c_3\nu\frac{(s_v - s_v^*)^2}{s_v} \\
&+ c_1 b\beta s_d^* i_v^* \left[1 - \frac{s_d^*}{s_d} - \frac{s_d i_v}{s_d^* i_v^*} + \frac{i_v}{i_v^*}\right] + c_2 b\beta s_d^* i_v^* \left[1 + \frac{s_d i_v}{s_d^* i_v^*} - \frac{i_d}{i_d^*} - \frac{s_d i_v i_d^*}{s_d^* i_v^* i_d}\right] \\
&+ c_3 b\alpha s_v^* i_d^* \left[1 - \frac{s_v^*}{s_v} - \frac{s_v i_d}{s_v^* i_d^*} + \frac{i_d}{i_d^*}\right] + c_4 b\alpha s_v^* i_d^* \left[1 + \frac{s_v i_d}{s_v^* i_d^*} - \frac{i_v}{i_v^*} - \frac{s_v i_d i_v^*}{s_v^* i_v i_d^*}\right].
\end{aligned} \tag{4.6}$$

Taking $c_1 = c_2$, $c_3 = c_4$, and $c_1, c_3$ such that $c_1 b\beta s_d^* i_v^* = c_3 b\alpha s_v^* i_d^* = A$, after some simplifications $\dot{V}(X)$ becomes

$$\begin{aligned}
\dot{V} &= -c_1(q\sigma + p\eta + \mu)\frac{(s_d - s_d^*)^2}{s_d} - c_3\nu\frac{(s_v - s_v^*)^2}{s_v} \\
&\quad -4A\left[\frac{1}{4}\left(\frac{s_d^*}{s_d} + \frac{s_v^*}{s_v} + \frac{s_d i_v i_d^*}{s_d^* i_v^* i_d} + \frac{s_v i_d i_v^*}{s_v^* i_v i_d^*}\right) - 1\right] \\
&\leq -c_1(q\sigma + p\eta + \mu)\frac{(s_d - s_d^*)^2}{s_d} - c_3\nu\frac{(s_v - s_v^*)^2}{s_v} \leq 0
\end{aligned} \tag{4.7}$$

due to the fact that the geometric mean is less or equal than the arithmetic mean. Therefore $(s_d(t), i_d(t), s_v(t), i_v(t)) \to (s_d^*, i_d^*, s_v^*, i_v^*)$.

Since $s_d(t) \to s_d^*$, and $i_d \to i_d^*$, $v_d(t)$, $c_d(t)$ and $n_d(t)$ in (2.2) satisfy

$$v_d(t) \to \frac{q\sigma s_d^*}{\varepsilon + \mu} = v_d^*,$$

$$c_d(t) \to \frac{p\eta s_d^*}{\kappa + \mu} = c_d^*,$$

and

$$n_d \to \frac{\mu_d}{\mu_d} = 1.$$

Therefore, we have the following result.

**Theorem 4.** Under the conditions $\varepsilon = \kappa = \tau = \delta = 0$, the endemic equilibrium $E_1$ is globally asymptotically stable.

## 5 NUMERICAL RESULTS AND SENSITIVITY ANALYSIS

Sensitivity Analysis is a method that measures how the variations of one or more input parameters impact the model response. This analysis is useful because it indicates the most important parameters and the less important ones. In this work, we use the partial rank correlation coefficient (PRCC) method to measure the sensitivity of $\tilde{R_0}$ to parameter variations [17, 29]. The results are illustrated in Figure 1. The contribution of each parameter for the $\tilde{R_0}$ value is ranked by the height of each bar. Positive values indicate that the increase of the parameter promotes the increase of $\tilde{R_0}$, while negative ones indicate that the increase of the parameter promotes the decrease of $\tilde{R_0}$.

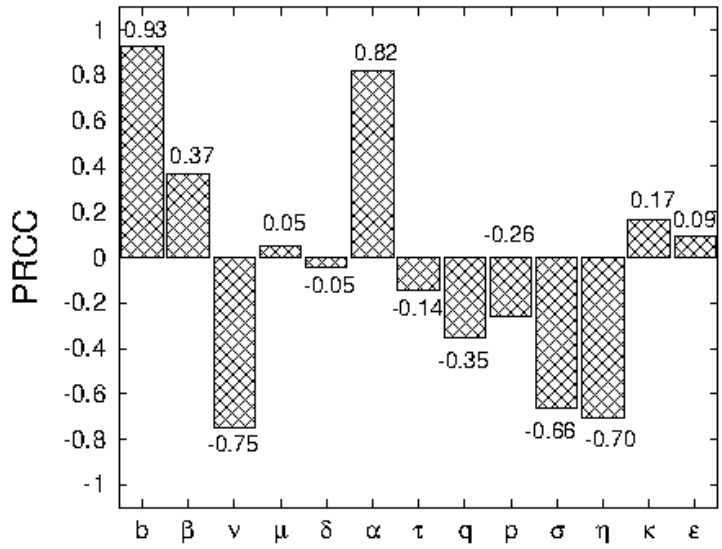


Figure 1: Sensitivity analysis. The output is $\tilde{R_0}$. The inputs are $b$, $\beta$, $\nu$, $\mu$, $\delta$, $\alpha$, $\tau$, $q$, $p$, $\sigma$, $\eta$, $\kappa$, and $\varepsilon$, respectively, sandfly biting rate, probability of transmission from vector-to-dog, sandfly mortality rate, dog natural mortality rate, disease-induced mortality rate, probability of transmission dog-to-vector, rate of treatment, vaccine efficacy, collar efficacy, the proportion of vaccinated dogs, proportion of dogs using the collar, rate of losing collar, and rate of losing immunity.

It is worth mentioning that PRCC is a global sensitivity analysis that permits us to rank the importance of the parameters for the output of the model, but it does not provide a measure for quantitative rank. The main hypothesis behind this method is that the relationship between each input parameter and the output, $\tilde{R}_0$, is monotone increasing or monotone decreasing. To carry out the sensitivity analysis, we use the Latin hypercube sampling (LHS) method. $N = 80,000$ sets were formed with parameters values taken uniformly from their range given in Table 1. This ensures that the parameter space is explored properly.

As we can see in Figure 1, the sensitivity analysis shows that the parameters that have more influence in $\tilde{R}_0$, in decreasing order, are $b$, $\alpha$, $\nu$, $\eta$, $\sigma$, $\beta$, $q$, $p$, $\kappa$, $\tau$, $\varepsilon$ and finally, with PRCC of the same magnitude, $\delta$ and $\mu$. These parameters denote respectively, sandfly biting rate, probability of transmission from dog to sandfly, sandfly mortality rate, proportion of dogs using the collar, the proportion of vaccinated dogs, probability of transmission from sandfly to the dog, vaccine efficiency, collar efficiency, rate of losing collar, rate of treatment, rate of losing immunity, disease-induced mortality rate, and dog mortality rate.

Let us define

$$Q_1 = \frac{p\eta}{\kappa+\mu} \quad \text{and} \quad Q_2 = \frac{q\sigma}{\varepsilon+\mu},$$

which represent the average number of dogs that are protected with collars and vaccination, respectively. Applying the PRCC method, we measure the sensibility of $\tilde{R}_0$ under variations of the transmission rates, $b\beta$, $b\alpha$, vector mortality $\nu$, and $Q_1$, $Q_2$. For this, we fixed the parameter values $\mu = 0.0006$, $\tau = 0.0075$, $\varepsilon = 0.00385$, $\kappa = 0.00365$, $\delta = 0.00045$ corresponding to their mean values which, according to Figure 1, are the less relevant to $\tilde{R}_0$ variations. In Figure 2 we observe that the transmission rate from dog to sandfly $b\alpha$, sandfly mortality rate $\nu$, average protected dogs $Q_1$ and $Q_2$ have a similar impact on the increase or reduction of $\tilde{R}_0$. On the other hand, the same figure shows that the effect on $\tilde{R}_0$ of the transmission rate from dog to sandfly, $b\alpha$, is greater than the transmission from sandfly to dog, $b\beta$, which indicates the importance of dogs on the disease prevalence.

From the first equation of (3.1) and equation (3.3) we derived a linear relation between $Q_1$ and $Q_2$ which is illustrated in Figure 3 for different values of $R_0$. Given a value of $R_0$, the relation $R_0\bar{s}_d < 1$ is satisfied above the corresponding line $Q_1Q_2$. Furthermore, the values of $Q_1$ and $Q_2$ increase when vaccine efficiency, or the fraction of vaccinated dogs, or dogs population with collar increase, and they decrease when the rate of loss of immunity increases.

Figure 4 shows the prevalence of the infection $i_d^*$ in dog's population as a function of the vaccination and collar-use rates. The parameters are $b = 0.7$, $\beta = 0.25$, $\alpha = 0.385$, $\nu = 0.2$, $\mu = 0.0003$, $\tau = 0.0067$, $\delta = 0.0005$, $R_0 = 5.6$, $\varepsilon = 0.0033$, $\kappa = 0.0045$, $q = 0.7$, and $p = 0.6$. As vaccination and collar-use increase, disease prevalence rapidly decreases.

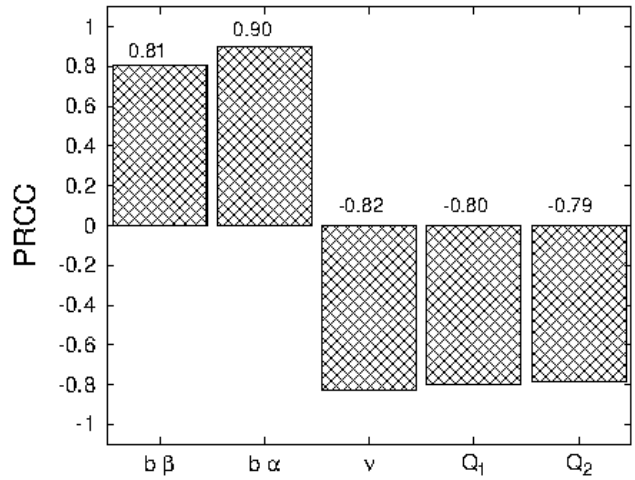


Figure 2: Sensitivity analysis. The output is $\tilde{R}_0$. The inputs are $b\beta$, $b\alpha$, $\nu$, $Q_1$ and $Q_2$, respectively, rate of transmission from vector-to-dog, rate of transmission dog-to-vector, sandfly mortality rate, the average number of dogs that are protected from getting leishmaniose because of collar-use and that vaccination. The length of the bars indicates the importance of the corresponding parameter on $\tilde{R}_0$. The positive bars indicate increasing and the negative ones decreasing of $\tilde{R}_0$.

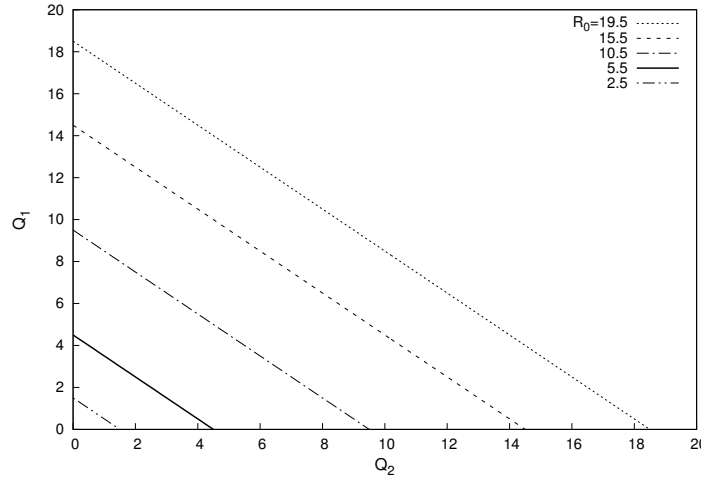


Figure 3: Parameter space of $Q_1 \times Q_2 \times R_0$. Each straight line corresponds to a given value of $R_0$. Above each line the disease can be controlled, below it the disease persists on the population.

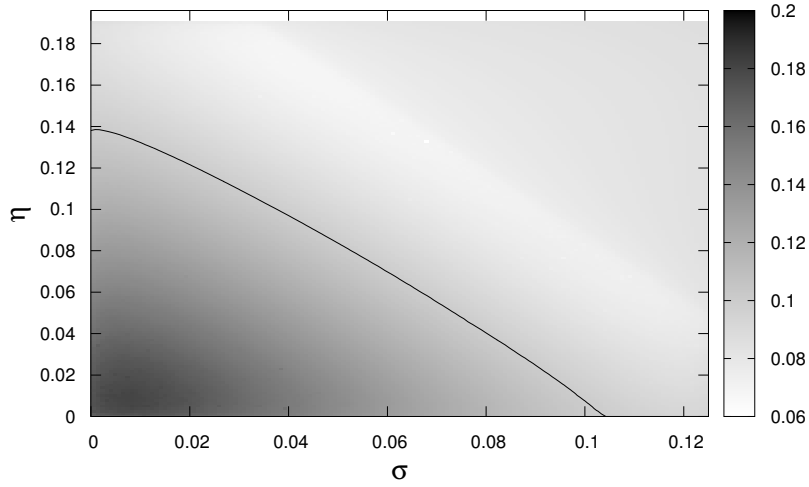


Figure 4: Plot of $\eta \times \sigma \times i_d^*$. Disease prevalence, $i_d^*$ as a function of vaccination rate and collar-use rate, $\sigma$ and $\eta$, respectively. The level curve corresponds to $i_d^* = 0.1$.

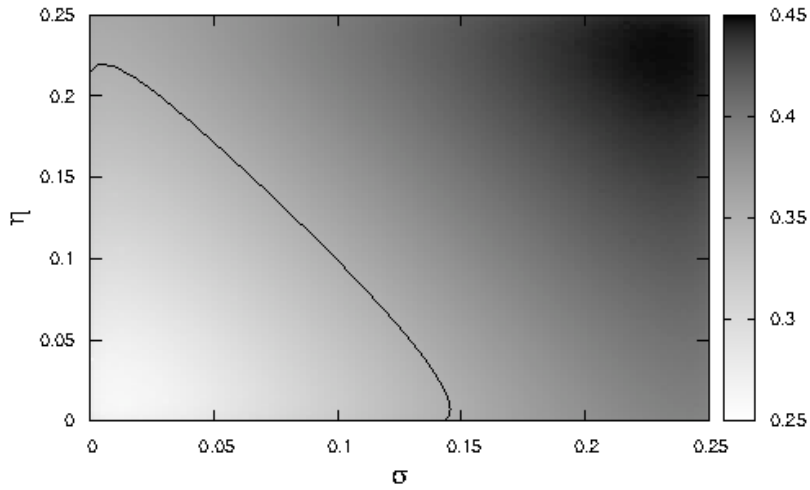


Figure 5: Plot of $\eta \times \sigma \times P$. Proportion of susceptible dogs that are protected from Leishmaniasis $P$ as a function of vaccination rate and collar-use rate, respectively, $\sigma$ and $\eta$. The level curve corresponds to the contour $P = 0.35$.

Figure 5 shows the relation between the proportion of vaccinated individuals (or using collar), and vaccination rate (or collar-use rate). The parameter set is the same as in Figure 4. The proportion $P$ is measured as

$$P = \frac{s_d^*(u) - s_d^*(p)}{s_d^*(u)}, \tag{5.1}$$

where the denominator represents the number of susceptible individuals before the introduction of the protection strategy, and the numerator corresponds to the number of unprotected individuals moved from the susceptible compartment to the protected one after the application of the protection strategy. We use $\bar{s}_d$ given in (3.1) with and without protection, $s_d^* = (R_0(1 - i_v^*))^{-1}$, with $i_v^*$ given by equation (4.2) to obtain $s_d^*(u)$ and $s_d^*(p)$.

Comparing Figures 4 and 5 we can see that low prevalence of canine leishmaniasis can be achieved when the chosen control strategy achieves around 35% of the population. Furthermore, the same disease prevalence can be attained by combining both controls and taking into account the efficiency and cost of each one.

## 6 DISCUSSION

Canine leishmaniasis is a vector-borne disease that is widely distributed in the world. As with many other parasite diseases, a lot of factors challenge its control, among them, we can cite its multi-host characteristics, development of drug resistance, high percentage of asymptomatic hosts, environmental and socioeconomic factors. In the human population, 90% of affected individuals are located in five countries: India, Bangladesh, Nepal, Brazil, and Sudan. In the Americas, the case fatality rate can achieve 8% and physical effects associated with the disease can range from mild scars to disfigurement [19]. The development of efficient vaccines and leishmaniasis treatment is still a challenge. Vector control relies on the use of nets and insecticides, not always correctly used.

Dogs are considered an important target to disease control due to their closeness to humans, and for this reason vaccination, collars impregnated with insecticide, treatment, and culling of infected dogs have been used as alternatives to diminishing the spread of the disease. In this work, we proposed a model to evaluate the efficiency of collars, vaccination, and treatment as a strategy against canine leishmaniasis. To this end, we obtained the basic reproduction number, $R_0$, as a measure of the disease prevalence, and control strategies efficiency. Using field and laboratory parameter values given in Table 1, we obtained that the vaccination and insecticide-impregnated collar use have practically the same efficiency (see Figure 2). The difficulty associated with collar use relies on its expiration date, renew of the collar, and its cost. On the other hand, the low efficiency of the actual vaccines jeopardizes the disease control by this method. According to the values of the parameters in Table 1, equation (5.1) indicates that the control of infection on dogs can be obtained by protecting around 35 percent of dogs with vaccination and collars (see Figure 5).

Culling of infected dogs is recommended in many countries where human leishmaniasis is endemic. But, as mention in the Introduction, there is a general agreement that controls efforts must

focus on the use of vaccines, collars, and control of the transmitter vector. This argument is supported by the observation that in endemic regions, culling dogs are replaced by new ones that can be rapidly spread the disease.

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