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OPTIMAL CONTROL APPLIED TO A VISCERAL LEISHMANIASIS MODEL

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Abstract. In this article, we developed a deterministic model for the transmission dynamics of visceral leishmaniasis in humans, canine reservoirs and sandflies, which is the only vector that transmits the disease parasite. The theoretical and epidemiological findings of this study indicates that the disease-free equilibrium of the model is locally and globally asymptotically stable when the associated reproduction number is less than unity. We perform sensitivity analysis on the model parameter to determine the parameter with the most impact on the reproduction number. Following the results obtained from the sensitivity analysis, we apply optimal control theory using three time dependent control variables representing personal protection, insecticide spraying and culling of infected canine reservoirs. Simulation results are presented for various outbreak scenarios which indicates that leishmaniasis can be eliminated from a region by the application of three time dependent controls representing respectively, personal protection, insecticide spraying and culling infected canine reservoir.

1. Introduction

Leishmaniasis is a vector borne parasitic disease caused by a protozoan parasite called *Leishmania* which is transmitted by a bite of an infected female phlebotomine sandflies [7, 46]. These sandflies species feed on animal blood which is required for egg development [45]. When a sandfly bites an infected human or animal, it picks up the parasites and can transmit them into a new uninfected host while feeding on (or biting) the host [13]. During the feeding, the infected sandfly produces saliva and parasitic proteins that interact with the skin of the vertebrate host, crucial for establishing Leishmania in the skin of a vertebrate [7, 46]. The species of the Leishmania parasite determines the symptoms of the disease such as cutaneous, mucocutaneous and visceral [7, 46]. Like many other disease, leishmanasis is more prevalent in the poorest communities in the developing world. The actual number of annual new cases of leishmaniasis is not known with certainty [7], however, the World Health Organization (WHO) estimate is about 350 million people at risk of contracting leishmanasis and occurrence of about 2 million new cases every year [46].

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There are over 30 sandflies species which cause human and animal leishmaniasis. The clinical symptoms and disease progression depend on Leishmania species, host immune system and factors such as environmental conditions, seasons, socio-economic status [7, 46]. Three major forms of human leishmaniasis infection are reported: cutaneous, mucocutaneous and visceral. The cutaneous leishmaniasis (CL), which causes skin sores and lesions, is most common form of leishmaniasis and is considered least fatal [7, 8, 46]. Most skin lesions due to CL infection heal without medical intervention, however, some infection spread to several parts of the body such as eyebrows, earlobes, limbs and throats. These CL infections may not heal by their own and may require medical attention [7, 46]. In the past 5 years, about 1 million CL cases were reported worldwide, with the majority occurring in Americas, the Mediterranean basin, the Middle East and Central Asia [7, 46]. Mucocutaneous leishmaniasis (MCL), causes partial or total destruction of mucous membranes of the nose, mouth and throat and usually occurs in patients infected with visceral leishmaniasis or post kala-azar dermal leishmaniasis (PKDL) [7, 46]. The patients co-infected with leishmaniasis and other disease such as HIV may also have MCL infection [7, 46]. MCL does not heals all spontaneously but it can be cured with timely treatment [7, 46]. Almost 90% of MCL cases occurs in the Plurinational State of Bolivia, Brazil and Peru [46].

Visceral leishmaniasis (VL), also known as kala-azar, is the most severe form of all leishmaniasis infections. It is fatal in almost all cases if left untreated [7, 13, 46]. Caused by either of *L. donovani* or *L. infantum* [39, 46] parasites, it can infect people of any ages but children under 10 years are more susceptible [7, 46]. The incubation period of visceral leishmanasis ranges from 10 days to several months and the onset of the symptoms is usually gradual [7, 46]. VL makes up an estimated 0.2 million to 0.4 million cases annually with over 0.2 million deaths. Over 90% new cases of VL occur in Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan [7, 46] annually. Most VL infections are asymptomatic but some victims eventually develop clinical visceral leishmaniasis. Following recovery from visceral leishmania, some individuals develop post-kala-azar dermal leishmaniasis (PKDL) which appears as macular, papular or nodular rash on the face, upper arms, trunks and other parts of the body [39, 46]. PKDL usually appears 6 months to 1 or more years after successful treatments of visceral leishmaniasis.

In an endemic region, Leishmania species are sustained by the interactions between sandflies species and the reservoir host species. The reservoirs can be zoonotic or anthroponotic. The zoonotic reservoir hosts may be wild or domestic animals, and the anthroponotic reservoir hosts are humans [12, 36, 46]. Some zoonotic reservoirs may or may not show symptoms while others such as dogs may eventually die due to the disease. Such animals are perfect environment for Leishmania parasite spread since the parasites spread in their blood and on the dermis where they are bitten by sandflies [7, 46]. In an endemic area, an animal species is usually a principle reservoir host for a particular Leishmania species but other animal species in the same area may be an incidental reservoirs [7, 12, 36, 46]. In some VL endemic areas, seroprevalence test suggested that goats are reservoir host for VL [12, 36], however, many studies [12, 36, 46, 32] found that dogs are the principal reservoir host of *Leishmania infantum*, a major causative agent of visceral leishmaniasis, and more than 50% of all infected dogs are asymptotic carriers.

Because of technological advancement, many technologies for disease diagnosis, prevention and treatment for a wide range of diseases have been developed. However, population growth, movement, environmental changes and urbanization have created favorable epidemiological conditions for disease transmission and persistence of some diseases such as leishmaniasis [12]. In fact, because of the rarity of functioning control programs, the new cases of leishmaniasis is in the increasing trend [46]. Since the disease transmission is maintained in a complex biological system involving human and animal reservoir, and vectors, the control measures should target interaction between these components [13, 39, 40, 41, 46]. Current prevention strategies include indoor residual spray and using door and window screens or insect repellent. These measures are only effective in reducing indoor interactions between human and sand flies but have no effect for the species of sand flies who feed on animals outdoors [46]. Also, it has been reported that the use of insect repellent can decrease sand flies and human interactions in a particular house but their biting rate increased in the nearby unprotected human and animals [7, 46]. In some cases, culling of seropositive reservoir such as dogs has been implemented to reduce this interaction. Some vaccine have recently been introduced but its efficacy in human is yet to be determined [12, 23, 24]. Canine vaccine has shown promising decrease in infection in some countries such as Brazil, France and Iran but no vaccines are available for humans [12, 46].

Numerous mathematical studies have been carried out on leishamaniasis. Chaves et al. [8] developed a parasite-reservoir-incidental host model consisting a system of ordinary differential equation (ODE) to study the threshold conditions for the persistence of the infection for American cutaneous leishmaniasis (ACL). Ribas et al. [34] developed an ODE model that includes constant control strategies (treatment, vaccination, culling and insecticide collar) applied to dogs. Their study found that the strategy of culling infected dogs is not the most efficient way to control zoonotic visceral leishmaniasis (ZVL) from both efficiency and ethical point of views. Other methods such as vector control and use of insecticide impregnated dog collars are more efficient in reducing ZVL in humans. Their study also noted that treating infected dogs is not effective to reducing the infections in human. Palatnik-de-Sousa et al. [32] developed an ODE model to study the efficacy of the culling of seropositive dogs. Their findings suggest that removing about 25% of the seropositive dogs from the endemic region significantly decreases the possibility of an epidemic outbreak in the region [32]. Some other studies such as Elmojtaba et al. [13], Stauch et al. [39, 40], Subramanian et al. [41] also explored the combination of human drug treatment, vector and reservoir hosts control for the effectively curtailing the spread of VL in both human and reservoir populations. However, none of these studies incorporated the use of optimal control theory to investigate the impact of these intervention strategies and the cost of their application. In our model, we assume three different host populations: human host, sandflies (vector) and canine host; also, canine are assumed to be source of infection, i.e. sandflies may acquire the infection from dogs, as suggested by many studies; see for example [32]. Susceptible sandflies get infected after biting infected human or infected canine reservoir. Infected sandflies transmit the disease following their bites on susceptible human or canine hosts. We assume four compartments on human host populations, 2 compartments on vector population and 3 compartments on canine

reservoir populations. The detailed assumptions of our model are presented in Section 2.

In this study, we aim to investigate the effect of optimal intervention strategies for visceral leishmanasis and the cost of applying these controls. In Section 2, we develop and analyze the dynamics of the mathematical model involving human-vector-reservoir populations and studied the stability of disease free equilibrium. In Section 3, we carry out the sensitivity analysis to identify parameters with the most impact in the disease transmission. We formulate the optimal control problem is Section 4, characterize the optimal controls, and present the numerical results in Section 5. Section 6 presents conclusions and discussions of our study.

2. Model formulation

To formulate our model we consider three different populations: human host population, $N_H(t)$, canine host population, $N_R(t)$, and vector population, $N_S(t)$. The human host population is divided into four sub-populations: susceptible individuals $S_H(t)$, visceral leishmaniasis infected individuals $I_H(t)$, those who develop PKDL after the treatment of visceral leishmaniasis, $P_H(t)$, and those who are recovered and have permanent immunity, $R_H(t)$. This implies that

$$N_H(t) = S_H(t) + I_H(t) + P_H(t) + R_H(t).$$

Similarly, the canine host population is divided into three sub-populations: susceptible, $S_R(t)$, vaccinated, $V_R(t)$ and infected, $I_R(t)$, such that

$$N_R(t) = S_R(t) + V_R(t) + I_R(t),$$

and finally, the sandfly population have two sub-populations: susceptible, $S_S(t)$, and infected sandflies, $I_S(t)$, such that

$$N_S(t) = S_S(t) + I_S(t).$$

It is assumed that susceptible individuals are recruited into the population at a constant rate Λ_H, where recruitment is mainly by births. Also, assume that the susceptible animals acquire infection with leishmaniasis following contacts with infected sandflies at a per capita rate $\beta_H b_S \frac{I_S}{N_H}$, where β_H is the transmission probability per bite per human (as the case for malaria, [28, 35]) and b_S is the per capita biting rate of sandflies on humans. Infected humans die due to leishmaniasis at an average rate δ_H, or get treatment at an average rate γ_H, and a fraction α of them recover and acquire permanent immunity, and the complement fraction $(1-\alpha)$ develop PKDL. Humans with PKDL get treated at an average rate τ_H, or recover naturally at an average rate σ_H, and acquire permanent immunity in both cases. There is a per capita natural mortality rate μ_H in all human sub-population.

Susceptible sandflies are recruited at a constant rate Λ_S, and acquire leishmaniasis infection following contacts with a leishmaniasis infected human or with a human having PKDL or leishmaniasis infected canine at an average rate equal to $\beta_S b_S \frac{I_H}{N_H} + \beta_S b_S \frac{P_H}{N_H} + \beta_S b_{SR} \frac{I_R}{N_R}$, where b_S is the per capita biting rate on human and b_{SR} is the per capita biting rate on canine, and β_S is the transmission probability for sandfly infection after biting a human or a canine. Sandflies suffer natural mortality at a per capita rate μ_S regardless of their infection status.

Susceptible canine reservoirs are recruited into the population at a constant rate Λ_R, acquire infection with leishmaniasis following contacts with infected sandflies at a rate $\beta_R b_{SR} \frac{I_S}{N_R}$ where β_R and b_{SR} as described above; or vaccinated at an

average constant rate ν_R. Vaccinated canine reservoir acquire infection with leishmaniasis following contacts with infected sandflies at a rate $\beta_R b_{SR}(1-\epsilon)\frac{I_S}{N_R}$ where ϵ is a modification parameter measures the efficacy of the vaccination, and it is assumed that the vaccine does not wane. Infected canine reservoirs die because of leishmaniasis at an average rate δ_R.

Using the above description, the following mathematical model is proposed

$$\begin{aligned}
S_H' &= \Lambda_H - \frac{\beta_H b_S I_S S_H}{N_H} - \mu_H S_H \\
I_H' &= \frac{\beta_H b_S I_S S_H}{N_H} - (\gamma_H + \mu_H + \delta_H) I_H \\
P_H' &= (1-\alpha)\gamma_H I_H - (\tau_H + \sigma_H + \mu_H) P_H \\
R_H' &= \alpha\gamma_H I_H + (\tau_H + \sigma_H) P_H - \mu_H R_H \\
S_S' &= \Lambda_S - \frac{\beta_S b_S (I_H + P_H) S_S}{N_H} - \frac{\beta_S b_{SR} I_R S_S}{N_R} - \mu_S S_S \\
I_S' &= \frac{\beta_S b_S (I_H + P_H) S_S}{N_H} + \frac{\beta_S b_{SR} I_R S_S}{N_R} - \mu_S I_S \\
S_R' &= \Lambda_R - \frac{\beta_R b_{SR} I_S S_R}{N_R} - (\nu_R + \mu_R) S_R \\
V_R' &= \nu_R S_R - \frac{\beta_R b_{SR}(1-\varepsilon) I_S V_R}{N_R} - \mu_R V_R \\
I_R' &= \frac{\beta_R b_{SR} I_S S_R}{N_R} + \frac{\beta_R b_{SR}(1-\varepsilon) I_S V_R}{N_R} - (\mu_R + \delta_R) I_R
\end{aligned} \tag{2.1}$$

with initial conditions

$$\begin{gathered}
S_H(0) = S_H^0, \quad I_H(0) = I_H^0, \quad P_H(0) = P_H^0, \quad R_H(0) = R_H^0, \\
S_V(0) = S_V^0, \quad I_V(0) = I_V^0, \quad S_R(0) = S_R^0, \quad I_R(0) = I_V^0.
\end{gathered}$$

and

$$N_H' = \Lambda_H - \mu_H N_H - \delta_H I_H, \quad N_S' = \Lambda_S - \mu_S N_S, \quad N_R' = \Lambda_R - \mu_R N_R - \delta_R I_R.$$

Invariant region. All parameters of the model are assumed to be constant and nonnegative and all state variables are non-negative at time $t = 0$. Also, note that in the absence of disease induced death (i.e. $\delta_H = \delta_R = 0$), the total human population, $N_H \to \Lambda_H/\mu_H$ as $t \to \infty$. Similarly, $N_R \to \Lambda_R/\mu_R$ and $N_S \to \Lambda_S/\mu_S$ as as $t \to \infty$. This shows that the biologically-feasible region:

$$\begin{aligned}
\Omega = \big\{ &(S_H, I_H, P_H, R_H, S_S, I_S, S_R, V_R, I_R) \in \mathbb{R}_+^9 : \\
&S_H, I_H, P_H, R_H, S_S, I_S, S_R, V_R, I_R \geq 0,\ N_H \leq \frac{\Lambda_H}{\mu_H}, N_S \leq \frac{\Lambda_S}{\mu_S}, N_R \leq \frac{\Lambda_R}{\mu_r} \big\}
\end{aligned}$$

is positively-invariant domain, and thus, the model is epidemiologically and mathematically well posed, and it is sufficient to consider the dynamics of the flow generated by the system (2.1) in this positively-invariant domain Ω.

The flow diagram of the system (2.1) is depicted in Figure 1 and the associated variables and parameters are described in Table 1.

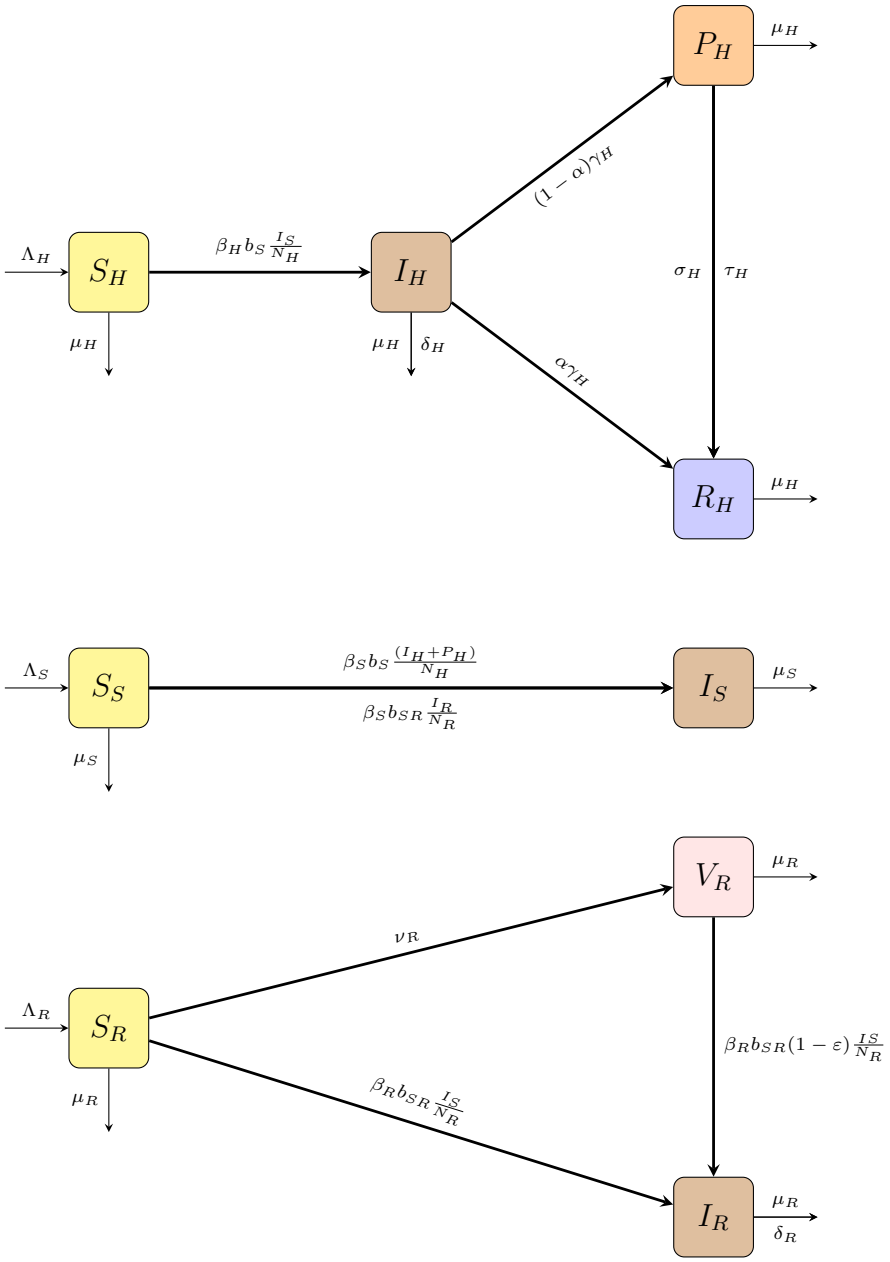

FIGURE 1. Systematic flow diagram of model (2.1).

TABLE 1. Description of the variables and parameters for model (2.1)

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Variable	Description
S_H	Population of susceptible humans
I_H	Population of symptomatic humans
P_H	Population of symptomatic humans
R_H	Population of recovered humans
S_S	Population of susceptible sandflies
I_S	Population of infected sandflies
S_R	Population of susceptible reservoir (canine)
V_R	Population of vaccinated reservoir (canine)
I_R	Population of infected reservoir (canine)
Param.	**Description**
Λ_H	Recruitment rate of humans
Λ_S	Recruitment rate of sandflies
Λ_R	Recruitment rate of reservoir (canine)
β_H	Transmission probability per contact for susceptible humans
β_S	Transmission probability per contact for susceptible sandflies
β_R	Transmission probability per contact for susceptible reservoir (canine)
b_S	Sandflies biting rate in humans
b_{SR}	Sandflies biting rate in reservoir (canine)
μ_H	Natural death rate of humans
μ_S	Natural death rate of sandflies
μ_R	Natural death rate of reservoir (canine)
δ_H	Disease induced death rate of humans
δ_R	Disease induced death rate of symptomatic reservoir (canine)
γ_H	Recovery rate of infected humans with VL dues to treatment
α	Fraction successfully treated for VL
τ_H	Recovery rate of humans with PKDL due to treatment
σ_H	Instantaneous recovery rate of humans with PKDL
ν_R	Vaccination rate in reservoir (canine)
ε	Vaccination efficacy in reservoir (canine)

2.1. **Analysis of the Model.** The disease-free equilibrium (DFE) of the system (2.1) is given by

$$\begin{aligned}\mathcal{E}_0 &= \Big(S_H^*, I_H^*, P_H^*, R_H^*, S_S^*, I_S^*, S_R^*, V_R^*, I_R^*\Big)\\ &= \Big(\frac{\Lambda_H}{\mu_H}, 0, 0, 0, \frac{\Lambda_S}{\mu_S}, 0, \frac{\Lambda_R}{\mu_R+\nu_R}, \frac{\nu_R\Lambda_R}{\mu_R(\mu_R+\nu_R)}, 0\Big).\end{aligned}$$

To study the stability of the disease-free equilibrium, first we have to find the reproduction number which is defined as the number of secondary infections that occur when an infected individual is introduced into a completely susceptible population [11, 16]. To calculate the effective reproduction number, we will use the next generation approach [11, 42]. First, we take the variables I_H, P_H, I_S, I_R as the infected compartments and then use the notation in [42], the Jacobian F and V matrices for new infectious terms and the remaining transfer terms, respectively,

are defined as:

$$\mathbf{F} = \begin{pmatrix} 0 & 0 & \beta_H b_S & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\beta_S b_S \Lambda_S \mu_H}{\mu_S \Lambda_H} & \frac{\beta_S b_S \Lambda_S \mu_H}{\mu_S \Lambda_H} & 0 & \frac{\beta_S b_{SR} \Lambda_S \mu_R}{\mu_S \Lambda_R} \\ 0 & 0 & \frac{\beta_R b_{SR}[\mu_R + (1-\varepsilon)\nu_R]}{\mu_R + \nu_R} & 0 \end{pmatrix}$$

$$\mathbf{V} = \begin{pmatrix} k_1 & 0 & 0 & 0 \\ -(1-\alpha)\gamma_H & k_2 & 0 & 0 \\ 0 & 0 & \mu_S & 0 \\ 0 & 0 & 0 & k_3 \end{pmatrix}$$

where $k_1 = \gamma_H + \delta_H + \mu_H$, $k_2 = \tau_H + \sigma_H + \mu_H$, $k_3 = \mu_R + \delta_R$. Then the reproduction number is

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{(\mathcal{R}_H + \mathcal{R}_R)\mathcal{R}_S}$$

where, ρ is the spectral radius and

$$\mathcal{R}_H = \frac{b_S^2 \mu_H \beta_H [(1-\alpha)\gamma_H + k_2)]}{k_1 k_2 \Lambda_H},$$
$$\mathcal{R}_R = \frac{b_{SR}^2 \beta_R \mu_R [\mu_R + (1-\varepsilon)\nu_R]}{k_3 \Lambda_R (\mu_R + \nu_R)},$$
$$\mathcal{R}_S = \frac{\beta_S \Lambda_S}{\mu_S^2}.$$

Furthermore, the quantity $\mathcal{R}_H$ is the number of secondary infections in humans host by one infectious sandfly, $\mathcal{R}_R$ is the number of secondary infections in the canine reservoir host by one introduced infectious sandfly, and lastly $\mathcal{R}_S$ is the number of secondary infections in sandflies resulting from a newly introduced infectious human and canine reservoirs respectively. Using van den Driessche and Watmough [42, Theorem 2], the following result is established:

Lemma 2.1. *The disease-free equilibrium ($\mathcal{E}_0$) is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

To study the global behavior of system (2.1), we use a theorem by Castillo-Chavez et al. [6], stated here for convenience.

Theorem 2.2 ([6])**.** *For the system*

$$\frac{dX}{dt} = F(X, Z)$$
$$\frac{dZ}{dt} = G(X, Z)$$
$$G(X, 0) = 0\,,$$

where the components of the column-vector $X \in R^m$ denote the number of uninfected individuals and the components of vector $Z \in R^n$ denote the number of infected individuals. $U_0 = (X^*, 0)$ denotes the disease-free equilibrium of this system. The fixed point $U_0 = (X^*, 0)$ is a globally asymptotically stable equilibrium for this system provided that $\mathcal{R}_0 < 1$ (locally asymptotically stable) and the following two conditions satisfied:

(H1) *For $\frac{dX}{dt} = F(X, 0)$, X^* is globally asymptotically stable,*

(H2) $G(X,Z) = AZ - \hat{G}(X,Z)$, $\hat{G}(X,Z) \geq 0$ *for* $(X,Z) \in \Omega$, *where* $A = D_Z G(X^*, 0)$ *is an M-matrix (off-diagonal elements of A are non-negative) and* Ω *is the region where the model has biological meaning.*

We can rewrite our system (2.1) using above notation, where

$$X = (S_H, R_H, S_S, S_R, V_R), \quad Z = (I_H, P_H, I_S, I_V) \tag{2.2}$$

$$F(X,0) = \begin{pmatrix} \Lambda_H - \mu_H S_H & 0 & \Lambda_S - \mu_S S_S & \Lambda_R - (\nu_R + \mu_R) S_R & \nu_R S_R - \mu_R V_R \end{pmatrix}^T$$

$$\mathbf{A} = \begin{pmatrix} -k_1 & 0 & \beta_H b_s & 0 \\ (1-\alpha)\gamma_H & -k_2 & 0 & 0 \\ \beta_S b_S \frac{S_S}{N_H} & \beta_S b_S \frac{S_S}{N_H} & -\mu_S & \beta_S b_{SR} \frac{S_S}{N_R} \\ 0 & 0 & \beta_S b_{SR} \frac{S_R + (1-\epsilon) V_R}{N_R} & -k_3 \end{pmatrix}$$

$$\hat{G}(X,Z) = \begin{pmatrix} \beta_H b_S I_S \big(1 - \frac{S_H}{N_H}\big) \\ 0 \\ \beta_S b_S S_S \big(1 - \frac{I_H + P_H}{N_H}\big) + \beta_S b_{SR} S_H \big(1 - \frac{I_R}{N_R}\big) \\ \beta_R b_{SR} \big(1 - \frac{S_R + (1-\epsilon) V_R}{N_R}\big) \end{pmatrix}$$

it is clear that A is an M matrix and $\hat{G}(X,Z) > 0$, and hence we have the following lemma.

Lemma 2.3. *The disease-free equilibrium is globally asymptotically stable when* $\mathcal{R}_0 < 1$.

3. Sensitivity analysis

The impact of leishmaniasis model (2.1) significant parameters are determined via sensitivity analysis [3, 29, 31] on the model outcome using Latin hyper-cubic sampling (LHS) technique and partial rank correlation coefficient (PRCC). LHS is a stratified sampling without replacement method which allows for an efficient analysis of parameter variations across simultaneous uncertainty ranges in each parameter [3, 29, 30, 37]. PRCC measures the strength of the relationship between the model outcome and the parameters, stating the degree of the effect that each parameter has on the outcome [3, 29, 30, 37]. A total of 1,000 simulations of the model (2.1) *per* LHS run were carried out, using the ranges and baseline values tabulated in Table 2 (with the reproduction number, $\mathcal{R}_0$, as the response function). The values of the parameters are taken from published literature as mentioned in Table 2 and for each parameter value, an interval within 20% range of the parameter value is formed to test the sensitivity.

Figure 2 depicts the PRCC values for each parameter of the models using the reproduction number, $\mathcal{R}_0$, as the response function. Parameters with the highest PRCC values have the largest impact on $\mathcal{R}_0$. Bars extending to the left (for negative PRCC values) or to the right (for positive PRCC values). The parameters γ_H, α, σ_H, ν_R, all have every low PRCC values with p-values > 0.01 (i.e., p-values 0.4390, 0.6311, 0.0215, 0.6777 respectively) indicating they have the least influence on the reproduction number, $\mathcal{R}_0$. Therefore, the key parameters influencing $\mathcal{R}_0$ are separated into those that decrease $\mathcal{R}_0$ when increased (those with significantly negative PRCC values) and those that causes $\mathcal{R}_0$ to increase when increased (those with significantly positive PRCC values).

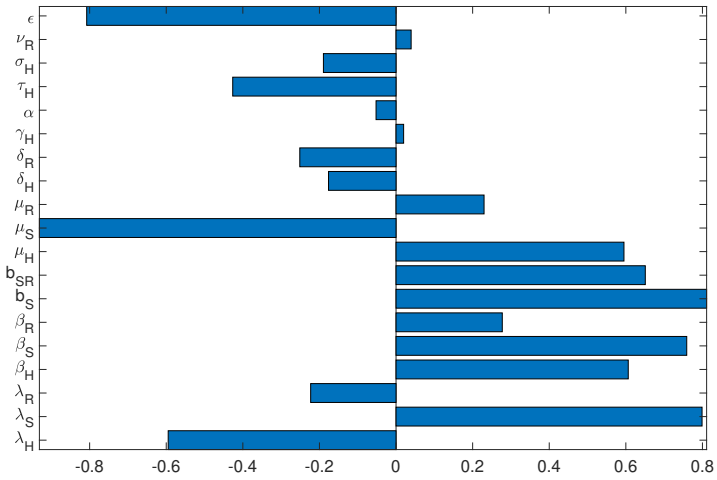

FIGURE 2. PRCC values for the leishmaniasis model (2.1), using the reproduction number ($\mathcal{R}_0$) as the response function. Parameter values (baseline) and ranges used are as given in Table 2.

The identification of these key parameters with significant impact on the reproduction number $\mathcal{R}_0$ is vital to the formulation of effective control strategies necessary to combat the spread of the disease. The results from the sensitivity analysis therefore suggest that, to effectively curtail the spread of leishmaniasis transmission in a region, the control strategy to be implemented should decrease the transmission probability *per* contact for susceptible canine population (reduce β_R), this should be followed by decreasing the transmission probability for susceptible sandflies (reduce β_S), the recruitment rate of sandflies (reduce Λ_S), the sandflies biting rate on humans (reduce b_S), the sandflies biting rate on the canine population (reduce b_{SR}), and the transmission probability for susceptible humans (reduce β_H).

The result from the sensitivity analysis further suggests control strategy that increases the natural death rate of sand flies (increase μ_S), the vaccination efficacy in canine reservoir (increase ε), and the disease-induced death rate of infected canine population (reduce δ_R) will help to reduce the reproduction number and thereby reduce the spread of leishmaniasis transmission among humans and the canine population.

Thus, in summary, the sensitivity analysis of the leishmaniasis transmission model (2.1) shows that the significant parameters are the natural death rate of sandflies (μ_S), sandflies biting rate on the canine population (b_{SR}), transmission probability for susceptible sandflies (β_S), recruitment rate of sandflies (Λ_S), sandflies biting rate in humans (b_S), transmission probability for susceptible canine population (β_R), transmission probability for susceptible humans (β_H), vaccination efficacy in canine population (ε), recruitment rate of canine population (Λ_R), and the disease-induced death rate of infected canine population (δ_R).

TABLE 2. Parameters values of the leishmaniasis model (2.1).

Param.	Values	Range	References
Λ_H	4.16×10^{-5}	$(1-0.2)4.16 \times 10^{-5}$ - $(1+0.2)4.16 \times 10^{-5}$	[44]
Λ_S	0.155	0.124 - 0.186	[20]
Λ_R	0.0027	0.00216 - 0.00324	assumed
β_H	0.5	0.4 - 0.6	[40]
β_S	0.22	0.176 - 0.264	[13]
β_R	0.0714	0.05712 - 0.08568	[13]
b_S	0.2856	0.22848 - 0.34272	[13]
b_{SR}	0.56	0.448 - 0.672	assumed
μ_H	1.64×10^{-5}	1.312×10^{-5} - 2.952×10^{-5}	[44]
μ_S	0.056	0.0448 - 0.0672	[20]
μ_R	2.11×10^{-4}	1.688×10^{-4} - 2.532×10^{-4}	assumed
δ_H	0.0014	0.00112 - 0.00168	[38]
δ_R	0.0014	0.00112 - 0.00168	[2]
γ_H	0.5	0.4 - 0.6	assumed
α	0.40	0.32 - 0.48	[15]
τ_H	0.033	0.02643 - 0.0396	[13]
σ_H	0.00556	0.00448 - 0.006672	[13]
ν_R	0.5	0.4 - 0.6	assumed
ε	0.8	0.64 - 0.96	[12]

4. Optimal control problem

Following the results obtained from the sensitivity analysis, we introduce three time dependent controls into the system (2.1). Let $u_1(t)$ be the time dependent rate of use of personal protection such as insect repellant, door and window screens against sand flies in the bid to reduce human contact with the flies. Let $u_2(t)$ be the time dependent indoor insecticide spraying rate (insecticide such as pyrethroids are effective against sandflies both indoors and outdoors [1]). Lastly, let $u_3(t)$ be the time dependent culling rate of the infected canine population [36]. Then the above system of ODEs (2.1) becomes

$$
\begin{aligned}
S_H' &= \Lambda_H - \frac{\beta_H b_S[1-u_1(t)]I_S S_H}{N_H} - \mu_H S_H \\
I_H' &= \frac{\beta_H b_S[1-u_1(t)]I_S S_H}{N_H} - (\gamma_H + \delta_H + \mu_H) I_H \\
P_H' &= (1-\alpha)\gamma_H I_H - (\tau_H + \sigma_H + \mu_H) P_H \\
R_H' &= \alpha\gamma_H I_H + (\tau_H + \sigma_H) P_H - \mu_H R_H \\
S_S' &= \Lambda_S - \frac{\beta_S b_S[1-u_1(t)](I_H + P_H) S_S}{N_H} - \frac{\beta_S b_{SR} I_R S_S}{N_R} - [\mu_S + u_2(t)] S_S \\
I_S' &= \frac{\beta_S b_S[1-u_1(t)](I_H + P_H) S_S}{N_H} + \frac{\beta_S b_{SR} I_R S_S}{N_R} - [\mu_S + u_2(t)] I_S \\
S_R' &= \Lambda_R - \frac{\beta_R b_{SR} I_S S_R}{N_R} - [\mu_R + \nu_R] S_R
\end{aligned}
$$

$$V_R' = \nu_R S_R - \frac{\beta_R b_{SR}(1-\varepsilon) I_S V_R}{N_R} - \mu_R V_R$$
$$I_R' = \frac{\beta_R b_{SR} I_S S_R}{N_R} + \frac{\beta_R b_{SR}(1-\varepsilon) I_S V_R}{N_R} - [\mu_R + \delta_R + u_3(t)] I_R. \tag{4.1}$$

We want to find the controls that minimizes the total infected humans (with VL and PKDL), infected canine population and the cost of controls. In other words, we want to find the optimal values of (u_1^*, u_2^*, u_3^*) that minimizes the objective functional $J(u_1, u_2, u_3)$ where

$$J(u_1, u_2, u_3) = \int_0^T [A_1 I_H + A_2 P_H + A_3 I_R + B_1 u_2 S_S + B_2 u_2 I_S + B_3 u_3 I_R + C_1 u_1^2 + C_2 u_2^2 + C_3 u_3^2] dt. \tag{4.2}$$

subject to the differential equations (4.1), where T is the final time. This performance specification involves the total infected humans (with VL and PKDL), infected reservoir (canine), along with the cost of applying the controls $u_1(t), u_2(t)$ and $u_3(t)$). In this paper, a quadratic objective functional is implemented for measuring the control cost, such a cost has been frequently used [17, 18, 21, 22, 25, 47]. The positive coefficients, $A_i, B_i, C_i; i = 1, \cdots, 3$ are balancing weight parameters. The controls, $u_1(t), u_2(t)$ and $u_3(t)$, are bounded, Lebesgue integrable functions [18, 48]. And we seek to find optimal controls, u_1^*, u_2^* and u_3^*, such that

$$J(u_1^*, u_2^*, u_3^*) = \min_{(u_1, u_2, u_3) \in \mathcal{U}} \{J(u_1, u_2, u_3)\} \tag{4.3}$$

where the admissible set is

$$\mathcal{U} = \{(u_1, u_2, u_3) \in (L^\infty(0,T))^3 : 0 \le u_i \le M_i; M_i \in \mathbb{R}^+, i = 1, 2, 3\}.$$

The following theorem proves the existence of the solution of the system (4.1) as well as the non negativity and boundedness of the state variables.

Theorem 4.1. *Given controls $u = (u_1, u_2, u_3) \in \mathcal{U}$, there exist non-negative bounded solutions $(S_H, I_H, P_H, R_H, S_S, I_S, S_R, I_R)$ to the state system (4.1) in the finite interval $[0, T]$ with given initial conditions.*

The existence and uniqueness of solutions for the state system (4.1) with a given control pair can be proven by using a result from Lukes [26]. The structure of system (4.1) gives the non-negativity and uniform boundedness of the state solutions. The next theorem proves the existence of the optimal controls.

Theorem 4.2. *There exists an optimal control tuple $u^* = (u_1^*, u_2^*, u_3^*) \in \mathcal{U}$ with corresponding states $(S_H^*, I_H^*, P_H^*, R_H^*, S_S^*, I_S^*, S_R^*, V_R^*, I_R^*)$ that minimizes the objective functional $J(u_1, u_2, u_3)$.*

Proof. Since the controls and the state variables are uniformly bounded and non-negative on the finite interval $[0, T]$, there exists a minimizing sequence (u_1^n, u_2^n, u_3^n) such that

$$\lim_{n \to \infty} J(u_1^n, u_2^n, u_3^n) = \inf_{(u_1, u_2, u_3) \in \mathcal{U}} J(u_1, u_2, u_3).$$

Let us denote

$$(S_H^n, I_H^n, P_H^n, R_H^n, S_S^n, I_S^n, S_R^n, V_R^n, I_R^n) = (S_H, I_H, P_H, R_H, S_S, I_S, S_R, V_R, I_R)(u_i^n, u_2^n, u_3^n).$$

Since all of the state variables are bounded (Theorem 4.1), then their first derivatives are also bounded. Also, the control functions are assumed to be bounded. This implies that all state variables are Lipschitz continuous with the same Lipschitz constant. Thus the sequence $(S_H^n, I_H^n, P_H^n, R_H^n, S_S^n, I_S^n, S_R^n, V_R^n, I_R^n)$ is uniformly equicontinuous in $[0,T]$. Then by the Arzela-Ascoli Theorem [26], the state sequence has a subsequence that converges uniformly to $(S_H^*, I_H^*, P_H^*, R_H^*, S_S^*, I_S^*, S_R^*, V_R^*, I_R^*)$ in $[0,T]$.

The control sequence (u_1^n, u_2^n, u_3^n) has a subsequence that converges weakly in $L^2(0,T)$. Let $(u_1^*, u_2^*, u_3^*) \in U$ be such that $u_i^n \rightharpoonup u_i^*$ weakly in $L^2(0,T)$ for $i = 1,2,3$. This result together with the uniform convergence of the state system implies the convergence of the terms like $B_1 u_2^n S_S^n$. Using lower semi-continuity of norms in weak L^2, we obtain

$$\|u_i^*\|_{L^2}^2 \le \liminf_{n\to\infty} \|u_i^n\|_{L^2}^2 \quad \text{for } i = 1,2,3.$$

Hence,

$$\begin{aligned} J(u_1^*, u_2^*, u_3^*) &\le \liminf_{n\to\infty} \int_0^T \big[A_1 I_H^n + A_2 P_H^n + A_3 I_R^n + B_1 u_2^n S_S^n + B_2 u_2^n I_S^n \\ &\quad + B_3 u_3^n I_R^n + C_1 (u_1^n)^2 + C_2 (u_2^n)^2 + C_3 (u_3^n)^2\big] dt \\ &= \liminf_{n\to\infty} J(u_1^n, u_2^n, u_3^n) \end{aligned}$$

Thus, there exists a vector $\vec{u} = (u_1^*, u_2^*, u_3^*)$ of controls that minimizes the objective functional $J(u_1, u_2, u_3)$. □

Next, we characterize the optimal control triple $(u_1(t), u_2(t), u_3(t))$. Pontryagin's Maximum Principle [33] introduces adjoint functions that allow the state system (4.1) to be attached to the objective functional (4.2).

Characterization of optimal controls. The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle [33]. This principle converts (4.1) and (4.2) into a problem of minimizing pointwise a Hamiltonian H, with respect to the controls $u_1, u_2, u_3 \in \mathcal{U}$. First we formulate the Hamiltonian [25] from the cost functional (4.2) and the governing dynamics (4.1) to obtain the optimality conditions.

$$\begin{aligned} H &= A_1 I_H + A_2 P_H + A_3 I_R + B_1 u_2 S_S + B_2 u_2 I_S + B_3 u_3 I_R + C_1 u_1^2 + C_2 u_2^2 + C_3 u_3^2 \\ &\quad + \lambda_{S_H}\Big[\Lambda_H - \frac{\beta_H b_S [1-u_1(t)] I_S S_H}{N_H} - \mu_H S_H\Big] \\ &\quad + \lambda_{I_H}\Big[\frac{\beta_H b_S [1-u_1(t)] I_S S_H}{N_H} - (\gamma_H + \delta_H + \mu_H) I_H\Big] \\ &\quad + \lambda_{P_H}\Big[(1-\alpha)\gamma_H I_H - (\tau_H + \sigma_H + \mu_H) P_H\Big] \\ &\quad + \lambda_{R_H}\Big[\alpha\gamma_H I_H + (\tau_H + \sigma_H) P_H - \mu_H R_H\Big] \\ &\quad + \lambda_{S_S}\Big[\Lambda_S - \frac{\beta_S b_S [1-u_1(t)](I_H + P_H) S_S}{N_H} - \frac{\beta_S b_{SR} I_R S_S}{N_R} - [\mu_S + u_2(t)] S_S\Big] \\ &\quad + \lambda_{I_S}\Big[\frac{\beta_S b_S [1-u_1(t)](I_H + P_H) S_S}{N_H} + \frac{\beta_S b_{SR} I_R S_S}{N_R} - [\mu_S + u_2(t)] I_S\Big] \\ &\quad + \lambda_{S_R}\Big[\Lambda_R - \frac{\beta_R b_{SR} I_S S_R}{N_R} - [\mu_R + \nu_R] S_R\Big] \end{aligned}$$

$$+\lambda_{V_R}\Big[\nu_R S_R-\frac{\beta_R b_{SR}(1-\varepsilon)I_S V_R}{N_R}-\mu_R V_R\Big]$$
$$+\lambda_{I_R}\Big[\frac{\beta_R b_{SR} I_S S_R}{N_R}+\frac{\beta_R b_{SR}(1-\varepsilon)I_S V_R}{N_R}-[\mu_R+\delta_R+u_3(t)]I_R\Big].$$

Using the system of adjoint variables,

$$\begin{aligned}\lambda'_{S_H}&=-\frac{\partial H}{\partial S_H}\\&=(\lambda_{S_H}-\lambda_{I_H})\beta_H b_S[1-u_1(t)]I_S\frac{(I_H+P_H+R_H)}{N_H^2}+\mu_H\lambda_{S_H}\\&\quad+(\lambda_{I_S}-\lambda_{S_S})\beta_S b_S[1-u_1(t)]S_S\frac{(I_H+P_H)}{N_H^2},\end{aligned}\tag{4.4}$$

$$\begin{aligned}\lambda'_{I_H}&=-\frac{\partial H}{\partial I_H}\\&=-A_1+(\lambda_{I_H}-\lambda_{S_H})\frac{\beta_H b_S[1-u_1(t)]I_S S_H}{N_H^2}-\lambda_{P_H}(1-\alpha)\gamma_H-\lambda_{R_H}\alpha\gamma_H\\&\quad+\lambda_{I_H}(\gamma_H+\delta_H+\mu_H)+(\lambda_{S_S}-\lambda_{I_S})\beta_S b_S[1-u_1(t)]S_S\frac{[S_H+R_H]}{N_H^2},\end{aligned}$$

$$\begin{aligned}\lambda'_{P_H}&=-\frac{\partial H}{\partial P_H}\\&=-A_2+(\lambda_{I_H}-\lambda_{S_H})\frac{\beta_H b_S[1-u_1(t)]I_S S_H}{N_H^2}+\lambda_{P_H}(\tau_H+\sigma_H+\mu_H)\\&\quad-\lambda_{R_H}(\tau_H+\sigma_H)+(\lambda_{S_S}-\lambda_{I_S})\beta_S b_S[1-u_1(t)]S_S\frac{[S_H+R_H]}{N_H^2},\end{aligned}$$

$$\begin{aligned}\lambda'_{R_H}&=-\frac{\partial H}{\partial R_H}\\&=(\lambda_{I_H}-\lambda_{S_H})\beta_H b_S[1-u_1(t)]I_S\frac{S_H}{N_H^2}+\lambda_{R_H}\mu_H\\&\quad+(\lambda_{I_S}-\lambda_{S_S})\beta_H b_S[1-u_1(t)]S_S\frac{(I_H+P_H)}{N_H^2},\end{aligned}$$

$$\begin{aligned}\lambda'_{S_S}&=-\frac{\partial H}{\partial S_S}\\&=(\lambda_{S_S}-\lambda_{I_S})\Big[\beta_S b_S[1-u_1(t)]\frac{(I_H+P_H)}{N_H}+\frac{\beta_S b_R I_R}{N_R}\Big]\\&\quad-B_1u_2(t)+\lambda_{S_S}[\mu_S+u_2(t)],\end{aligned}$$

$$\begin{aligned}\lambda'_{I_S}&=-\frac{\partial H}{\partial I_S}\\&=-B_2u_2(t)+(\lambda_{S_H}-\lambda_{I_H})\frac{\beta_H b_S[1-u_1(t)]S_H}{N_H}+\lambda_{I_S}[\mu_S+u_2(t)]\\&\quad+(\lambda_{S_R}-\lambda_{I_R})\frac{\beta_R b_{SR}S_R}{N_R}+(\lambda_{V_R}-\lambda_{I_R})\frac{\beta_R b_{SR}(1-\varepsilon)V_R}{N_R},\end{aligned}$$

$$\begin{aligned}
\lambda'_{S_R} &= -\frac{\partial H}{\partial S_R} \\
&= (\lambda_{I_S} - \lambda_{S_S})\frac{\beta_S b_{SR} I_R S_S}{N_R^2} \\
&\quad + (\lambda_{S_R} - \lambda_{I_R})\frac{\beta_R b_{SR} I_S (I_R + V_R)}{N_R^2} + \lambda_{I_R}(\mu_R + \nu_R) \\
&\quad - \lambda_{V_R}\nu_R + (\lambda_{I_R} - \lambda_{V_R})\frac{\beta_R b_{SR}(1-\varepsilon) I_S V_R}{N_R^2},
\end{aligned}$$

$$\begin{aligned}
\lambda'_{V_R} &= -\frac{\partial H}{\partial V_R} \\
&= (\lambda_{I_S} - \lambda_{S_S})\frac{\beta_S b_{SR} I_R S_S}{N_R^2} + (\lambda_{I_R} - \lambda_{S_R})\frac{\beta_R b_{SR} I_S S_R}{N_R^2} \\
&\quad + (\lambda_{V_R} - \lambda_{I_R})\beta_R b_{SR}(1-\varepsilon) I_S \frac{(S_R + I_R)}{N_R^2} + \lambda_{V_R}\mu_R,
\end{aligned}$$

$$\begin{aligned}
\lambda'_{I_R} &= -\frac{\partial H}{\partial I_R} \\
&= -A_3 - B_3 u_3(t) + (\lambda_{S_S} - \lambda_{I_S})\frac{\beta_S b_{SR} S_S (S_R + V_R)}{N_R^2} \\
&\quad + (\lambda_{I_R} - \lambda_{S_R})\frac{\beta_R b_{SR} I_S S_R}{N_R^2} + (\lambda_{I_R} - \lambda_{V_R})\frac{\beta_R b_{SR}(1-\varepsilon) I_S V_R}{N_R^2} \\
&\quad + \lambda_{I_R}(\mu_R + \delta_R + u_3),
\end{aligned}$$

with the transversality condition

$$\lambda_i(t_f) = 0 \quad \text{for } i = S_H, I_H, P_H, R_H, S_S, I_S, S_R, V_R, I_R. \tag{4.5}$$

The optimality conditions are given as

$$\frac{\partial H}{\partial u_j} = 0, \quad j = 1, 2, 3.$$

in the interior of the control set $\mathcal{U}$. Thus, we have

$$\begin{aligned}
&2C_1 u_1 + \lambda^*_{S_H}\frac{\beta_H b_S I^*_S S^*_H}{N^*_H} - \lambda^*_{I_H}\frac{\beta_H b_S I^*_S S^*_H}{N^*_H} \\
&+ \lambda^*_{S_S}\frac{\beta_S b_S (I^*_H + P^*_H) S^*_S}{N^*_H} - \lambda^*_{I_S}\frac{\beta_s b_S (I^*_H + P^*_H) S^*_S}{N^*_H} = 0, \\
&B_1 S^*_S + B_2 I^*_S + 2C_2 u_2 - \lambda^*_{S_S} S^*_S - \lambda^*_{I_S} I^*_S = 0, \\
&B_3 I^*_R + 2C_3 u_3 - \lambda^*_{I_R} I^*_R = 0.
\end{aligned}$$

Hence, the control characterization is

$$\begin{aligned}
u^*_1 &= \min\Big[1, \max\Big(\frac{1}{2C_1 N^*_H}[\beta_H b_S I^*_S S^*_H(\lambda^*_{I_H} - \lambda^*_{S_H}) \\
&\qquad + \beta_S b_S S^*_S (I^*_H + P^*_H)(\lambda^*_{I_S} - \lambda^*_{S_S})], 0\Big)\Big], \\
u^*_2 &= \min\Big[1, \max\Big(\frac{1}{2C_2}[-B_1 S^*_S - B_2 I^*_S + \lambda^*_{S_S} S_S + \lambda^*_{I_S} I^*_S], 0\Big)\Big],
\end{aligned}$$

$$u_3^* = \min\Big[1, \max\Big(\frac{1}{2C_3}[-B_3 I_R^* + \lambda_{I_R}^* I_R^*], 0\Big)\Big].$$

Setting bounds on the control. We set the bounds on the time dependent control, $u_1(t)$, for the personal protection rate between 0 and 1 (i.e, $0 \le u_1(t) \le 1$). The value of $u_1(t) = 1$ means highly effective control with no contact between human and sand flies while the value of $u_1(t)$ close to 0 means high contact between human and sand-flies. For the the control $u_2(t)$, which is the rate of insecticide spray, the lower bound is assumed to be 0 which means no spraying. For the upper bound, we assume that in an ideal condition, at most 75% of whiteflies can be killed within 10 days. With this assumption, the upper bound of the spray rate $u_2(t)$ is 0.13 i.e, $0 \le u_2(t) \le 0.13$. Since the insecticide spray kills the sandflies that come in contact with the spray, we think killing coverage of 75% of the sandflies in 10 days is reasonable. Finally, for the infected dog culling rate $u_3(t)$, the lower bound for $u_3(t)$ is zero for no culling. For the upper bound, we assume that in an ideal condition, at most 50% of the infected dogs can be killed within a week. With this assumption, the upper bound of $u_3(t)$ is 0.1 i.e, $0 \le u_3(t) \le 0.1$.

Next, we discuss the numerical solutions of the optimality system, the corresponding optimal control and the interpretations from various cases.

5. Numerical results

The following algorithm was used to compute the optimal controls and state values using a Runge Kutta method of the fourth order in the interval [0,180] days i.e.(6 months). First, an initial estimate for the controls are made. Then the state variables are solved forward in time using the dynamics (4.1). The results obtained for the state variables are substituted into the adjoint equations (4.4). These adjoint equations with given final conditions (4.5) are then solved backwards in time, employing the backward fourth order Runge Kutta method. Both the state and adjoint values are then used to update the controls, and the process is repeated until the current state, adjoint, and controls values converge sufficiently [25].

To illustrate the optimal control strategies, the following initial conditions were used: $S_H(0) = 1000$, $I_H(0) = 25$, $P_H(0) = 25$, $R_H(0) = 14$, $S_S(0) = 500$, $I_S(0) = 152$, $S_R(0) = 224$, $V_R(0) = 125$, $I_R(0) = 114$. Furthermore, the values $A_1 = A_2 = A_3 = 1.00$, $B_1 = B_2 = B_3 = 0.01$, $C_1 = C_2 = C_3 = 0.01$ were chosen as the baseline weight parameters. It should be noted that the weights in the simulations here are only of theoretical sense to illustrate the control strategies proposed in this paper. Using parameter values in Table 2, the reproduction number is obtained as $\mathcal{R}_0 = 2.33 > 1$, thus indicating that the disease is endemic in the population.

The results of the optimal control simulations of the leishmaniasis model (4.1) are depicted in Figures 3, where the total number of infectious humans, sandflies and canine reservoir in the absence of controls are denoted by blue curves and the corresponding numbers with optimal controls are denoted by pink curve. From the figure 3(a), we observed that the total number of infected humans (I_H and P_H) are reduced considerably with the applications of the optimal controls compared to those in the absence of controls. The total number of infected canine reservoirs and sandflies are shown in Figures 3(b) and 3(c). There are more infected in the absence of controls compared to the total number of infected with the applications of the optimal controls. The corresponding controls (u_1, u_2, u_3) are depicted in Figures 4(a)-4(c). The time dependent control $u_1(t)$ is observed to be at its upper

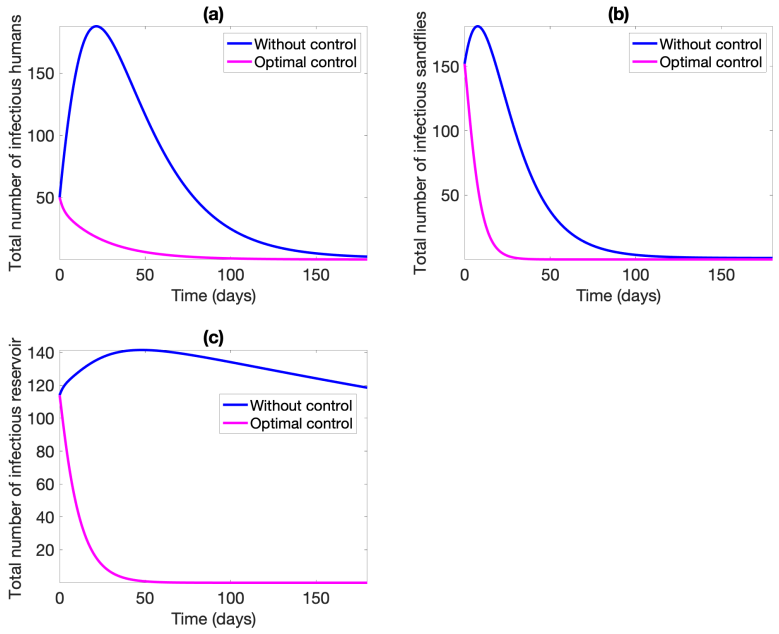

FIGURE 3. Simulation of the leishmaniasis model (4.1) as a function of time without control (blue curves) and with optimal control (pink curves) for: (a) Total number of infected humans; (b) Total number of infected reserviors; (c) Total number of infected sandflies

bound for about 2 months and then can be reduced to get the optimal results. Similarly, the control $u_2(t)$ is observed to be at its upper bound for about 3 and half months and is tapered down before gradually reducing and then turns off at 124 days. Finally, the control $u_3(t)$ is at the upper bound for about four and half months and can be reduced gradually.

The total number of infectious humans $(I_H + P_H)$ are at highest level (about 188) in the absence of time dependent control and decrease gradually but in the presence of control, the number of infectious humans start to decrease from the beginning and becomes less than one at the end of 95 days. The total number of infectious sandflies peaked at 9th day with value 181 and decreases with no control but the value decreases from the beginning in the presence of control and becomes zero in about a month. The number of infectious canine reservoir peaks at 48th day with value 142 and slightly decreases thereafter if no controls are applied. At the end of 6 months with no controls, the number of infected dogs is about 120. This implies that a huge number in the reservoir is present at the end of six months if no controls measures are applied. With optimal control the number of infectious reservoir decreases from the beginning and becomes zero on 50th day. The value of objective functional J without optimal control is 3.5128×10^5 and with optimal control J is about 70% less which is 1.0701×10^5.

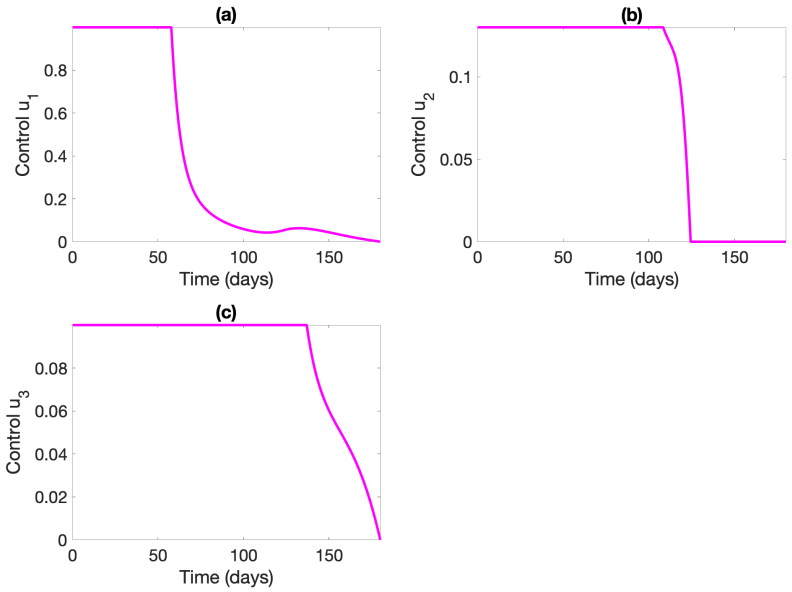

FIGURE 4. Optimal controls of the leishmaniasis model (4.1) for: (a) Personal protection control; (b) Sandflies insecticide control; (c) Reservoir culling control.

Control within varying values of parameters Λ_R, Λ_S, b_{SR} and τ_H. To carry out the sensitivity analysis test in Section 3, we set the values of the parameters to be within $\pm 20\%$ range of their baseline values and found the parameters τ_H, Λ_R, Λ_S and b_{SR} among others to have a high impact on the reproduction number $\mathcal{R}_0$. However, the time dependent controls $u_1(t)$, $u_2(t)$ and $u_3(t)$ incorporated into system (4.1) did not directly act on these parameters. Hence, we vary these four parameters using a range of $\pm$ 50% from their baseline values and determine their impact on the system as well as the control variables. We have used the $\pm$ 50% range for emphasis purpose, the result is expected to be similar in the $\pm$ 20% range. All other parameters in the model 4.1 and the balancing parameters in the objective functional are taken to be in the baseline values from Table 2.

The results of the optimal control simulations of the leishmaniasis model (4.1) in the uncertainty interval for these parameters Λ_R, Λ_S and b_{SR} are depicted in Figures 5(a)- refs1(c) where the total number of infectious humans, sandflies and canine reservoir in the absence of controls are denoted by blue curves and the corresponding numbers with optimal controls are denoted by pink curve. These parameters are related to the canine reservoirs and sandflies.

From Figure 5, we observed that the upper bounds of these three parameters lead to slightly bigger number of infectious humans, canine reservoirs and sandflies. However, these numbers are not very different and follows the same patterns as with the baseline values of these parameters. Also, as observed in 6(a)-6(c), the control profiles within the uncertainty interval considered are almost the same. Hence, regardless of the parameter values chosen within the uncertainty interval of

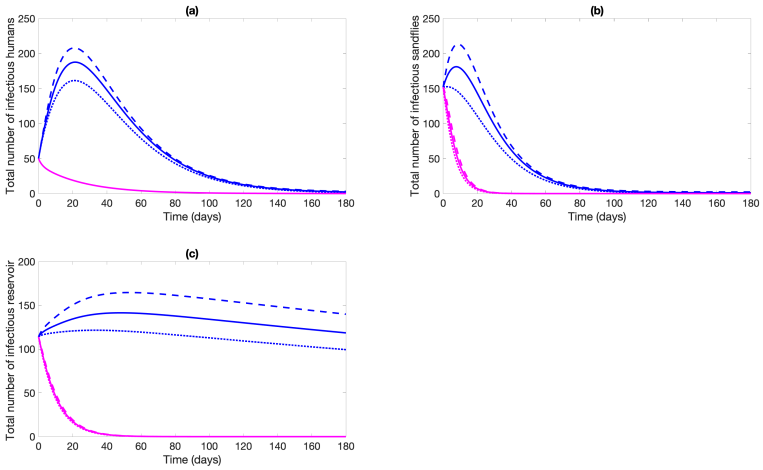

FIGURE 5. Simulation of the Leishmaniasis model (4.1) as a function of time without control and with optimal control for: (a) Total number of infected humans; (b) Total number of infected reserviors; (c) Total number of infected sandflies. The parameters Λ_R, Λ_S and b_{SR} are set within $\pm 50\%$ interval of their baseline values given in Table 2 and all other parameters are taken in their baseline values. In all plots, the solid curves represent the plot for baseline values of all parameters, the dotted curves represent the plot for lower bound of the three parameters and the dashed curves represent the plot for upper bound of these three parameters. The blue curves are without controls and the pink curves are with the optimal controls.

these parameters (Λ_R, Λ_S and b_{SR}), the control profile remained the same although the actions of the controls are higher for the upper bound and lower for the lower bound. Note, that we have used very low weights, the profile is the same even for higher weights and tighter intervals as the $\pm 20\%$ uncertainty interval used for the sensitivity analysis.

Next, we investigate the optimal control of system (4.1) within the uncertainty interval of parameter τ_H; this parameter is the human recovery rate and we use the $\pm 50\%$ range from the baseline value. The results are depicted in Figures 7, where the blue curves represent total number of infectious humans, sandflies and canine reservoir in the absence of controls and the corresponding numbers with optimal controls are denoted by pink curves. We observed in Figure 7(a) that more infected humans at the lower bound and fewer at the upper bound of τ_H. Similarly for the optimal controls $u_1(t)$, $u_2(t)$ and $u_3(t)$ in Figures 7(b)-7(d). More control efforts are required when humans recover slowly, particularly in the use of insecticide spray rate ($u_1(t)$) and dog culling rate ($u_3(t)$).

In summary, numerical simulations of the leishmaniasis control model (4.1) show that leishmaniasis can be reduced in the community by the application of the time dependent control triple ($u_1(t), u_2(t)$ and $u_3(t)$) which represent respectively the of personal protection($u_1(t)$) such as insect repellant, door and window screens against sand flies, insecticide spraying ($u_2(t)$) and culling of infected canine reservoir ($u_3(t)$).

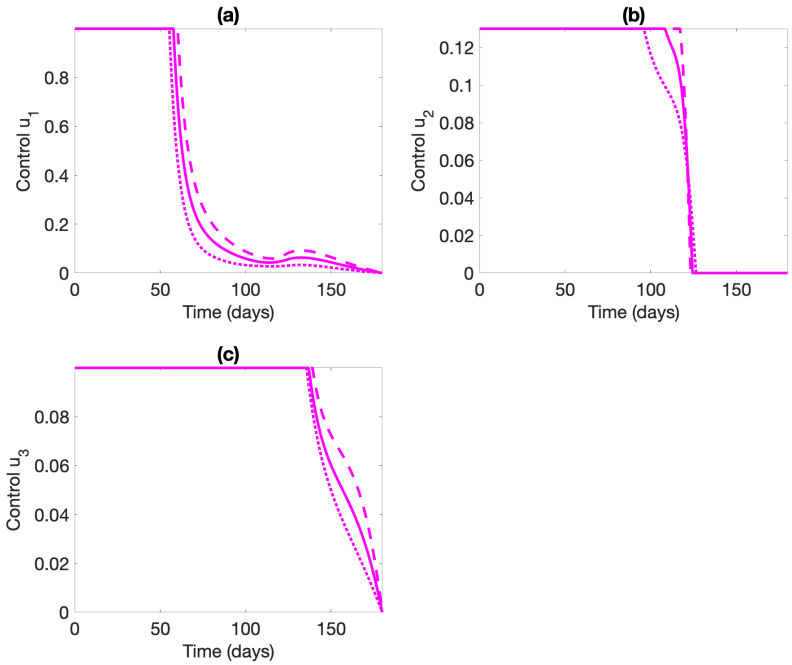

FIGURE 6. Optimal controls of the leishmaniasis model (4.1) in the $\pm 50\%$ uncertainty interval of parameters Λ_R, Λ_S and b_{SR} for: (a) Personal protection control; (b) Sandflies insecticide control; (c) Reservoir culling control. The parameters Λ_R, Λ_S and b_{SR} are set within $\pm 50\%$ interval of their baseline values given in Table 2 and all other parameters are taken in their baseline values. In all plots, the solid curves represent the plot for baseline values of all parameters, the dotted curves represent the plot for lower bound of the three parameters and the dashed curves represent the plot for upper bound of these three parameters.

6. Conclusions and discussion

In this article, a new deterministic model is designed and used to study the transmission dynamics of leishmaniasis model. The model includes the transmission dynamics in humans and canine reservoirs. The study shows that the disease-free equilibrium of the model is locally- and globally-asymptotically stable whenever the associated reproduction number ($\mathcal{R}_0$, an epidemiological threshold quantity that measures the spreading capacity of the disease), is less than unity and unstable otherwise.

This study identifies (via sensitivity analysis) the significant parameters using as model outcome the reproduction number. The parameters with the largest impact are the natural death rate of sandflies (μ_S), sandflies biting rate on the canine reservoir (b_{SR}), transmission probability *per* contact for susceptible sandflies (β_S), recruitment rate of sandflies (Λ_S), sandflies biting rate in humans (b_S), transmission probability *per* contact for susceptible canine reservoir (β_R), transmission probability *per* contact for susceptible humans (β_H), vaccination efficacy in canine reservoir

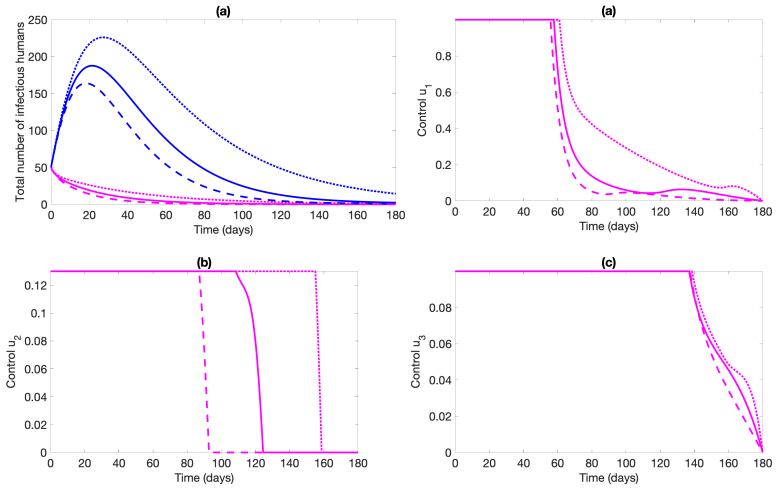

FIGURE 7. Optimal controls of the leishmaniasis model (4.1) in the $\pm 50\%$ uncertainty interval of τ_H for: (a) Total number of infected humans; (b) Personal protection control; (c) Sandflies insecticide control; (d) Reservoir culling control. All of the other parameters are in their baseline values given in Table 2. In all plots, the solid curves represent the plot for baseline values of all parameters, the dotted curves represent the plot for lower bound of the three parameters and the dashed curves represent the plot for upper bound of these three parameters.

(ε), recruitment rate of canine reservoir (Λ_R), and the disease-induced death rate of infected reservoir (δ_R).

The identification of these key parameters is vital to the formulation of effective control strategies for combating the spread of the disease. Thus, following the results obtained from the sensitivity analysis, we introduce three time dependent controls into system (2.1). The time dependent controls represent the use of personal protection such as insect repellant, door and window screens against sand flies in the bid to reduce human contact with the flies, insecticide spraying with insecticide such as pyrethroids are effective against sandflies both indoors and outdoors and culling of infected canine reservoir. Results from the numerical simulations indicates that that leishmaniasis can be controlled in the community by the application of these time dependent controls.

Hence, in this article, we formulated and analyzed a system of ordinary differential equations for leishmaniasis in humans and canine reservoirs. Some of theoretical and epidemiological findings of this study are summarized below:

(i) The leishmaniasis model (2.1) is locally-and globally-asymptotically stable (LAS) when $\mathcal{R}_0 < 1$ and unstable when $\mathcal{R}_0 > 1$;
(ii) The sensitivity analysis of the model shows that the significant parameters are the natural death rate of sandflies (μ_S), sandflies biting rate on the canine reservoir (b_{SR}), transmission probability *per* contact for susceptible sandflies (β_S), recruitment rate of sandflies (Λ_S), sandflies biting rate in humans (b_S), transmission probability *per* contact for susceptible canine

reservoir (β_R), transmission probability *per* contact for susceptible humans (β_H), vaccination efficacy in canine reservoir (ε), recruitment rate of canine reservoir (Λ_R), and the disease-induced death rate of infected reservoir (δ_R)

(iii) Numerical simulations indicates that that leishmaniasis can be controlled in the community by the application of time dependent controls representing personal protection ($u_1(t)$), insecticide spraying ($u_2(t)$) and culling infected canine reservoir ($u_3(t)$) respectively.

(iv) The control profiles were approximately the same for all parameter values chosen within the uncertainty interval of these parameters (Λ_R, Λ_S and b_{SR}).

(v) In the uncertainty interval for parameter τ_H, more control efforts are required when humans recover more slowly.

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