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A Multi-Host Transmission Dynamics of Cutaneous Leishmaniasis

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Abstract: We present a multi-host deterministic model for the transmission dynamics of cutaneous leishmaniasis (*CL*). The model includes three hosts, namely, an incidental host for human, a primary reservoir host for rodent, and a secondary reservoir host for sandfly. In addition to involved hosts in the dynamic transmission of the disease, we incorporated into the model the deaths due to use of insecticides and rodenticides as control measures.
The conditions for the stability of the model are determined. The model has two equilibria; one disease free equilibrium and one endemic equilibrium. The basic reproduction number, $\mathcal{R}_0$, computed using the next generation operator, do not explicitly include parameters relating to the dynamic transmission in the incidental host and is influenceable by the control values consisting of the use of insecticides and rodenticides. The local and global stability of equilibria are established, moreover, the threshold conditions for disease persistence are completely determined by the basic reproduction number. Sensitivity analyses of $\mathcal{R}_0$ with respect to the model parameters were carried out. We find that the rodenticide death rate followed by insecticide death rate, are the highly sensitive parameters. Moreover, the use of rodenticides as control measure can be successful in controlling *CL*.

Keywords: *Control Measure, Deterministic Model, Leishmaniasis, Reproduction Number, Sensitivity Analysis, Stability Analysis*

Introduction:
Leishmaniasis is a vector-borne disease caused by protozoan parasites and is transmitted by the bite of female sandflies. The sandfly acquires leishmania parasites in the blood meal intake on an infected host. The two broad categories of leishmaniasis according to the source of human infection are: zoonotic leishmaniases, in which the reservoir hosts are wild or domestic animals, and anthroponotic leishmaniases, in which reservoir hosts are humans. The main forms of the disease are: cutaneous leishmaniasis (*CL*), mucocutaneous leishmaniasis (*MCL*), and visceral leishmaniasis (*VL*), also known as kala-azar, the only life-threatening form [7].
Leishmaniasis is spread over four continents and is endemic over 98 countries and territories. Approximately between 0.7 and 1.2 million of new cases of *CL* and between 0.2 and 0.4 million of new cases of *VL* are estimated to occur yearly worldwide. Visceral leishmaniasis causes an estimated 50.000 deaths yearly, a rate surpassed among parasitic diseases only by malaria. More than 90% of global cases of *VL* occur in Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan. Cutaneous leishmaniasis is more widely distributed and the highest estimated cases occur in Afghanistan, Algeria, Brazil, Colombia, Costa Rica, Ethiopia, Iran, Peru, Sudan and Syria [7].
No vaccine or drugs to prevent the infection by the parasites are currently available. In endemic regions, the protection from sandfly bites remains the best way to prevent the infection at human level. Among the recommended personal protective measures in endemic regions: minimize nocturnal outdoor activities from dawn to dusk, wear protective clothing, apply insect repellent to exposed skin, and use of proper bed nets.
Cutaneous leishmaniasis is endemic in Algeria and represents an actual public health problem. The disease, used to be mainly endemic in the sub-Saharan steppe, is experiencing a geographical spread towards the north. The notification of leishmaniasis became mandatory in the country in 1976. The health authorities have implemented in 2006 a national leishmaniasis control program with the aim to reduce the annual incidence [2]. Despite the undertaken actions, the number of reported cases remains high with a yearly average of 12161 cases, i.e., 36 cases per 100000 inhabitants at national level. Three *CL* outbreaks happened between 2000 and 2014, with 14822 reported cases in 2004, 25511 cases in 2005 and 14714 cases in 2010 [5]. The preventive strategies set up in Algeria need therefore to be evaluated and improved. In the aim to reduce the incidence of human *CL*, control measures against sandflies along with animal reservoir hosts should be evaluated while also taking into account the local contexts. To this end, a refined multi-host deterministic model for the transmission dynamics of the disease of the one presented by Selmane is presented and analysed [6]. The model incorporates the deaths due to the application of insecticides and rodenticides.
The paper is organized as follows. In the second section, a multi-host deterministic model to describe the transmission dynamics of *CL* is presented. The model includes three hosts, namely, an incidental

host for human, a primary reservoir host for involved animal, and a secondary reservoir host for sandfly. The determination of equilibria, the computation of basic reproduction number, the local and global stability of equilibria of the model are undertaken in the third section. In the fourth section, the sensitivity analyses of the basic reproduction number with respect to the model parameters are performed. The last section is devoted to the analysis and consequences of obtained results.

Model Formulation:

The proposed multi-host model is a refined model of the one previously introduced by Selmane [6]. In this paper, the use of insecticides and rodenticides are taken into account and their impact on the human incidence are evaluated.

The model is made up of three hosts. Human host is modelled using susceptible-infected-recovered *(SIR)* scheme, whereas sandfly host and rodent host are modelled using susceptible-infected *(SI)* scheme. In the sequel, we give a brief description each host's model and we specify the interaction between them. The epidemiological states are indexed by H for humans, by S for sandflies, and by R for rodents.

- ***SI* model for sandfly population**

The adult life span being 2 to 3 weeks, which is relatively short, so, we can assume that an infected sandfly remains infective until its death. The sandfly population can therefore be described by a *SI* model, where the adult sandfly population at time t is subdivided into susceptible $(\tilde{S}_S)$ and infectious $(\tilde{I}_S)$ such that $N_S(t) = \tilde{S}_S(t) + \tilde{I}_S(t)$. Only female sandflies are considered because they are the only proven vectors of human disease. Susceptible female sandflies become infected when they bite an infectious rodent. The per capita incidence rate among sandflies depends on the fraction of infectious rodents $\frac{\tilde{I}_R}{N_R}$ where $N_R(t) = \tilde{S}_R(t) + \tilde{I}_R(t)$ is the total rodent population size and β_{RS} the contact rate which is related to the frequency of bites, and is given by $\beta_{RS}\frac{\tilde{I}_R}{N_R}$. We incorporate into this *SI* model the death rate c_S due to the use of insecticides as control measure. The sandfly population dynamics is, therefore described by the following system of differential equations:

$$\begin{cases} \dot{\tilde{S}}_S = b_S N_S - \beta_{RS}\frac{\tilde{I}_R}{N_R}\tilde{S}_S - (c_S + \mu_S)\tilde{S}_S \\ \dot{\tilde{I}}_S = \beta_{RS}\frac{\tilde{I}_R}{N_R}\tilde{S}_S - (c_S + \mu_S)\tilde{I}_S \end{cases} \quad (1)$$

- **SIR model for human population**

The human population is described by a susceptible-infective-recovered *SIR* model. Susceptible humans become infected when they are bitten by infectious sandflies. The per capita incidence rate among susceptible humans is given by $\beta_{SH}\frac{\tilde{I}_S}{N_S}$; it depends on the fraction of infectious sandflies $\frac{\tilde{I}_S}{N_S}$ and the contact rate β_{SH} which is related to the frequency of bites. The infected humans move to the recovered state at rate γ_H, and we suppose that they acquire immunity. We assume the total human population size N_H is constant, i.e., $N_H(t) = \tilde{S}_H(t) + \tilde{I}_H(t) + \tilde{R}_H(t)$ at any time t. Based on the above assumptions, the human population dynamics is described by the following system of ordinary differential equations:

$$\begin{cases} \dot{\tilde{S}}_H = b_H N_H - \beta_{SH}\frac{\tilde{I}_S}{N_S}\tilde{S}_H - \mu_H\tilde{S}_H \\ \dot{\tilde{I}}_H = \beta_{SH}\frac{\tilde{I}_S}{N_S}\tilde{S}_H - (\gamma_H + \mu_H)\tilde{I}_H \\ \dot{\tilde{R}}_H = \gamma_H\tilde{I}_H - \mu_H\tilde{R}_H \end{cases} \quad (2)$$

- ***SI* model for rodent population**

The dynamics of transmission is bi-directional between sandfly population and rodent population, i.e., they are both source and sink of infection. The per capita incidence rate among susceptible rodents is given by $\beta_{SR}\frac{\tilde{I}_S}{N_S}$; it depends on the fraction of infectious sandflies $\frac{\tilde{I}_S}{N_S}$ and the contact rate β_{SR} which is related to the frequency of bites. We incorporate into this *SI* model the death rate c_R due to the use of rodenticides as control measure. The rodent population is described by the following *SI* model:

$$\begin{cases} \dot{\tilde{S}}_R = b_R N_R - \beta_{SR}\frac{\tilde{I}_S}{N_S}\tilde{S}_R - (c_R + \mu_R)\tilde{S}_R \\ \dot{\tilde{I}}_R = \beta_{SR}\frac{\tilde{I}_S}{N_S}\tilde{S}_R - (c_R + \mu_R)\tilde{I}_R \end{cases} \quad (3)$$

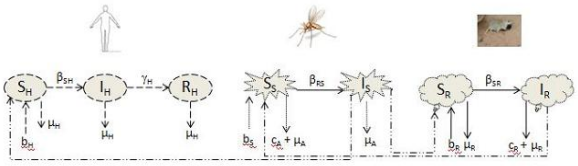

Figure 1: The interplay between hosts in the transmission dynamics of cutaneous leishmaniasis.

The full model for the transmission dynamics of *CL* is schematically illustrated in Figure 1, and is described by the systems (1), (2), and (3). The corresponding normalized system is given by:

$$\begin{cases} \dot{S}_H = b_H - \beta_{SH} I_S S_H - \mu_H S_H \\ \dot{I}_H = \beta_{SH} I_S S_H - (\gamma_H + \mu_H) I_H \\ \dot{R}_H = \gamma_H I_H - \mu_H R_H \\ \dot{S}_S = b_S - \beta_{RS} I_R S_S - (c_S + \mu_S) S_S \\ \dot{I}_S = \beta_{RS} I_R S_S - (c_S + \mu_S) I_S \\ \dot{S}_R = b_R - \beta_{SR} I_S S_R - (c_R + \mu_R) S_R \\ \dot{I}_R = \beta_{SR} I_S S_R - (c_R + \mu_R) I_R \end{cases} \quad (I)$$

where $S_H = \frac{\tilde{S}_H}{N_H}$, $I_H = \frac{\tilde{I}_H}{N_H}$, $R_H = \frac{\tilde{R}_H}{N_H}$, $S_S = \frac{\tilde{S}_S}{N_S}$, $I_S = \frac{\tilde{I}_S}{N_S}$, and $S_R = \frac{\tilde{S}_R}{N_R}$, $I_R = \frac{\tilde{I}_R}{N_R}$.

Analysis of the Model:

- **Equilibria**

The equilibria are obtained by setting the right hand sides of equations of the system (I) equal to zero, and by solving the corresponding algebraic system. The system has two equilibria:
a disease free equilibrium (*DFE*):

$$E_0^* = \left(1,0,0,\frac{b_S}{c_S+\mu_S},0,\frac{b_R}{c_R+\mu_R},0\right)$$

and a unique endemic equilibrium

$$E^* = (S_H^*, I_H^*, R_H^*, S_S^*, I_S^*, S_R^*, I_R^*)$$

where

$$S_H^* = \frac{1}{1+k_1 I_S^*}$$
$$I_H^* = \frac{\mu_H}{a_1}\frac{k_1}{1+k_1 I_S^*} I_S^*$$
$$R_H^* = \frac{\gamma_H}{a_1}\frac{k_1}{1+k_1 I_S^*} I_S^*$$
$$S_R^* = \frac{b_R}{c_R+\mu_R}\frac{1}{1+k_2 I_S^*}$$
$$I_R^* = \frac{b_R}{c_R+\mu_R}\frac{k_2}{1+k_2 I_S^*} I_S^*$$
$$S_S^* = \frac{b_S}{c_S+\mu_S} - I_S^*$$
$$I_S^* = \frac{(c_R+\mu_R)^2(c_S+\mu_S)}{\left((c_R+\mu_R)(c_S+\mu_S)+\beta_{RS}b_R\right)\beta_{SR}}(\mathcal{R}_0^2-1)$$

where $k_1 = \frac{\beta_{SH}}{\mu_H}, k_2 = \frac{\beta_{SR}}{c_R+\mu_R}$, and $a_1 = \gamma_H + \mu_H$ and where $\mathcal{R}_0$ is the basic reproduction number computed using the next generation operator [3]:

$$\mathcal{R}_0^2 = \frac{b_S\beta_{SR}}{(c_S+\mu_S)^2}\frac{b_R\beta_{RS}}{(c_R+\mu_R)^2}.$$

- **Stability of equilibria**

The local asymptotic stability of equilibria can be achieved through the determination of the eigenvalues of the jacobian matrix, J_{E^*}, of the system (I) evaluated at an equilibrium E^*. The eigenvalues of J_{E^*} are the roots of the polynomial $\det(J_{E^*} - \lambda I) = 0$ where the matrix J_{E^*} is

$$J_{E^*} = \begin{pmatrix} M_1 & M_2 \\ O & M_3 \end{pmatrix}$$

and

$$M_1 = \begin{pmatrix} -\beta_{SH}I_S^* - \mu_H & 0 & 0 \\ \beta_{SH}I_S^* & -a_1 & 0 \\ 0 & \gamma_H & -\mu_H \end{pmatrix}$$

$$M_2 = \begin{pmatrix} 0 & -\beta_{SH}S_H^* & 0 & 0 \\ 0 & \beta_{SH}S_H^* & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$M_3 = \begin{pmatrix} -\beta_{RS}I_R^* - a_2 & 0 & 0 & -\beta_{RS}S_S^* \\ \beta_{RS}I_R^* & -a_2 & 0 & \beta_{RS}S_S^* \\ 0 & -\beta_{SR}S_R^* & -\beta_{SR}I_S^* - a_3 & 0 \\ 0 & \beta_{SR}S_R^* & \beta_{SR}I_S^* & -a_3 \end{pmatrix}$$

and where $a_2 = c_S + \mu_S$ and $a_3 = c_R + \mu_R$.
The disease free equilibrium $E_0^* = \left(1,0,0,\frac{b_S}{a_2},0,\frac{b_R}{a_3},0\right)$ is locally asymptotically stable. Indeed, five eigenvalues of the jacobian matrix of system (I) evaluated at E_0^* are negative $\lambda = -\mu_H, -\mu_H, -a_1, -a_2, -a_3$ and the remaing eigenvalues are roots of the following polynomial:

$$\lambda^2 + (a_2+a_3)\lambda + a_2a_3\left(1-\mathcal{R}_0^2\right)$$

$a_2 + a_3 > 0$, thus using the Routh-Hurwitz Criterion, we conclude that the roots are with negative real parts for $\mathcal{R}_0 < 1$ and consequently the *DFE* is locally asymptotically stable when $\mathcal{R}_0 < 1$, otherwise the *DFE* is unstable and an epidemic is triggered.
The determination of the eigenvalues of the jacobian matrix J_{E^*} evaluated at the endemic equilibrium E^* shows that five eigenvalues are straightforwardly determined : $\lambda = -\mu_H, -a_1, -\beta_{SH}I_S^* - \mu_H, -a_3, -a_2$ and they are negative since $I_S^* > 0$, and the two remaining eigenvalues satisfy the equation:

$$\lambda^2 + a\lambda + b = 0$$

where

$$a = \beta_{RS}I_R^* + a_2 + \beta_{SR}I_S^* + a_3 > 0$$
$$b = \beta_{RS}\beta_{SR}S_R^*S_S^*(\mathcal{R}_0^2 - 1)$$

As $S_R^* > 0$ and $S_S^* > 0$, the coefficient b is positive for $\mathcal{R}_0 > 1$, thus according to the Routh-Hurwitz Criterion, the roots are with negative real parts and consequently the endemic equilibrium is locally asymptotic stable for $\mathcal{R}_0 > 1$.
To prove the global stability for *DFE* when $\mathcal{R}_0 < 1$, we used a theorem in [3]. The conditions (H1) and (H2) of the theorem [3] are met; hence the *DFE* is globally asymptotically stable.
The global asymptotic stability of the endemic equilibrium was established using the following Lyapunov function

$$V(S_H,I_H,R_H,S_S,I_S,S_R,I_R) = \left(S_H - S_H^* - S_H^* log\frac{S_H}{S_H^*}\right) + \left(I_H - I_H^* - I_H^* log\frac{I_H}{I_H^*}\right) + \left(R_H - R_H^* - R_H^* log\frac{R_H}{R_H^*}\right) + \left(S_S - S_S^* - S_S^* log\frac{S_S}{S_S^*}\right) + \left(I_S - I_S^* - I_S^* log\frac{I_S}{I_S^*}\right) + \left(S_R - S_R^* - S_R^* log\frac{S_R}{S_R^*}\right) + \left(I_R - I_R^* - I_R^* log\frac{I_R}{I_R^*}\right).$$

Using system (I) and substituting: $S_H = S_H - S_H^*$, $S_S = S_S - S_S^*$, $S_R = S_R - S_R^*$, $I_H = I_H - I_H^*$, $I_S = I_S - I_S^*$, $I_R = I_R - I_R^*$, $R_H = R_H - R_H^*$ we obtain the Lyapunov derivative $\frac{dV}{dt} \leq 0$. Moreover, the largest compact invariant set in

$$\left\{(S_H, I_H, R_H, S_S, I_S, S_R, I_R) \in \Omega: \frac{dV}{dt} \leq 0\right\}$$

is the singleton $\{E^*\}$ and hence E^* is globally asymptotically stable in the region :

$$\Omega = \left\{ \begin{matrix} (S_H, I_H, R_H, S_S, I_S, S_R, I_R) \in \mathbb{R}_+^7: \\ S_H + I_H + R_H = S_S + I_S = S_R + I_R = 1 \end{matrix} \right\}.$$

Sensitivity analysis:

In determining how best to reduce human morbidity due to *CL*, it is necessary to know the relative importance of the different factors responsible for its transmission. As the initial disease transmission is directly related to reproduction number $\mathcal{R}_0$, we perform sensitivity analyses to discover parameters that have a high impact on $\mathcal{R}_0$, and should be targeted by intervention strategies.

The relative change in a state variable when a parameter changes can be measured through sensitivity indices. The normalized forward sensitivity index of a variable to a parameter is defined as the ratio of the relative change in the variable to the relative change in the parameter. So, the normalized forward sensitivity index of $\mathcal{R}_0$ is given by:

$$Ind_{\wp}^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial \wp} \times \frac{\wp}{\mathcal{R}_0}$$

where $\wp$ is a parameter of $\mathcal{R}_0$.

We have

$$Ind_{b_S}^{\mathcal{R}_0} = Ind_{b_R}^{\mathcal{R}_0} = Ind_{\beta_{SR}}^{\mathcal{R}_0} = Ind_{\beta_{RS}}^{\mathcal{R}_0} = 0.5$$

that is, the sensitivity index of $\mathcal{R}_0$ with respect to the parameter b_S (respectively b_R, β_{SR} and β_{RS}) does not depend on any parameter values. The sensitivity index of $\mathcal{R}_0$ with respect to the parameter c_R (respectively μ_R, c_S, μ_S) depends on the parameter value of μ_R (respectively c_R, μ_S, c_S).

For $\mu_S = \frac{1}{21}, \mu_R = \frac{1}{3*365}$ the values of the normalized forward sensitivity index of $\mathcal{R}_0$ are displayed in Table 1. The most sensitive parameter is the death rate c_R due to the use of rodenticides followed by the death rate c_S due to the use of insecticides, and the least sensitive parameter is the rodent death rate μ_R.

Table 1

(c_S, c_R)	(0.5,0.5)	(0.01,0.01)	(0.9,0.01)
$Ind_{c_R}^{\mathcal{R}_0} = -\frac{c_R}{c_R + \mu_R}$	-0.99	-0.91	-0.91
$Ind_{\mu_R}^{\mathcal{R}_0} = -\frac{\mu_R}{c_R + \mu_R}$	-0.0018	-0.083	-0.083
$Ind_{c_S}^{\mathcal{R}_0} = -\frac{c_S}{c_S + \mu_S}$	-0.91	-0.17	-0.94
$Ind_{\mu_S}^{\mathcal{R}_0} == -\frac{\mu_S}{c_S + \mu_S}$	-0.087	-0.82	-0.05

Results and Discussion:

The threshold conditions for disease persistence are completely determined by the basic reproduction number $\mathcal{R}_0$:

$$\mathcal{R}_0 = \sqrt{\frac{b_S \beta_{SR}}{(c_S+\mu_S)^2} \frac{b_R \beta_{RS}}{(c_R+\mu_R)^2}}.$$

This threshold does not explicitly include parameters related to the dynamic transmission in human population; which is expected in view of the fact that incidental hosts will not cause infections in susceptible sandflies, and therefore will not generate new infections. Consequently, the disease becomes endemic if it persists endemically in the primary reservoir hosts. Note that the threshold $\mathcal{R}_0$ is influenceable by the parameters c_S and c_R, corresponding to deaths of sandflies and rodents respectively due to use of insecticides and rodenticides, and this in a similar way. Therefore, the control measures should be directed towards both primary and secondary reservoir hosts. Moreover, the performed sensitivity analyses showed that the most sensitive parameter is the death rate c_R due to the use of rodenticides followed by the death rate c_S due to the use of insecticides. Consequently, the use of rodenticides as control measure can be successful in controlling *CL*.

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