Control strategies and sensitivity analysis of anthroponotic visceral leishmaniasis model

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ABSTRACT
This study proposes a mathematical model of Anthroponotic visceral leishmaniasis epidemic with saturated infection rate and recommends different control strategies to manage the spread of this disease in the community. To do this, first, a model formulation is presented to support these strategies, with quantifications of transmission and intervention parameters. To understand the nature of the initial transmission of the disease, the reproduction number $R_0$ is obtained by using the next-generation method. On the basis of sensitivity analysis of the reproduction number $R_0$, four different control strategies are proposed for managing disease transmission. For quantification of the prevalence period of the disease, a numerical simulation for each strategy is performed and a detailed summary is presented. Disease-free state is obtained with the help of control strategies. The threshold condition for globally asymptotic stability of the disease-free state is found, and it is ascertained that the state is globally stable. On the basis of sensitivity analysis of the reproduction number, it is shown that the disease can be eradicated by using the proposed strategies.

1. Introduction

Leishmaniasis is a family of infectious diseases. This disease is transmitted by different species of phlebotomize sandflies. Anthroponotic visceral leishmaniasis (AVL) is caused by Leishmania donovani and is transmitted by sandfly. Human is the main reservoir of the virus. The clinical symptoms of AVL include fatigue, prolonged fever, losing weight, bleeding tendency and enlargement of both spleen and liver. The average incubation period of visceral leishmaniasis (VL) is 2–6 months; however, longer and shorter periods (from 10 days to 1 year) \cite{1, 26}. The latency period of sandfly is assumed roughly to be 3–7 days \cite{21, 22}. Post-kala azar dermal leishmaniasis (PKDL) is the complication of VL in a patient who has recovered from VL. The interval between PKDL and VL is observed from 0 to

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6 months in Sudan and from 2 to 3 years in India [27]. Somalia, Yemen, Saudi Arabia, Ethiopia, Kenya and Uganda are the countries highly suffering with AVL [14, 19]. For more details and related literature of Leishmaniasis, the readers can refer to [2, 3, 8, 16, 17, 25, 26].

In this paper, we consider the work of Stauch et al. [23] by incorporating some new biological features related to develop a mathematical model. To do this, we introduce the system of nonlinear differential equations to represent the dynamics of the disease. We show that the model is epidemiologically and mathematically well posed. To understand the nature of the initial transmission of the disease, the reproduction number $R_0$ is obtained by using the next-generation method. On the basis of sensitivity analysis of $R_0$, we propose control strategies for disease transmission. To understand the dynamical behaviour and stability analysis, we use the Routh–Hurwitz criteria and stability analysis theory of nonlinear systems of differential equations. The threshold condition for globally asymptotic stability of the disease-free state is presented and shown that this state is globally stable. Numerical simulations are carried out to justify the effect of control strategies on the prevalence period of AVL.

The paper is organized as follows. Some basic ideas of the related problem are presented in Section 2. A mathematical model of the interaction between the human and the vector is presented in Section 3. Section 4 presents stability and sensitivity analysis of the proposed model. Section 5 is concerned with numerical simulations of the control strategies, with quantifications of transmission and intervention parameters. Finally, we present our conclusion.

2. Preliminaries

In this section, we present some definitions related to the present work [5, 12, 23].

**Definition 2.1:** The matrix $M_{m \times m}$, for $m > 2$, is said to be irreducible if for any proper sub-set $N$ of $\{1, 2, \ldots, m\}$. $\exists i \in N$ and $j \notin N$ such that $A_{ij} \neq 0$.

Irreducibility of the model means that none of the class of the model is isolated.

**Definition 2.2:** The matrix $M$ is said to be the Metzler matrix if $A_{ij} \geq 0$ for $i \neq j$.

**Definition 2.3:** PCR (polymerase chain reaction): This test is used to determine whether the bacteria are present in DNA.

DAT (direct agglutination test): This test is used to determine the presence of antibodies to a specific antigen.

LST (leishmanin skin test): This test is used to measure the cellular immunity against VL.

**Theorem 2.1 ([12]):** *If the hypothesis $H_1$–$H_5$ are satisfied, then disease-free equilibrium is globally asymptotically stable for the system:

\[
\dot{X}_1 = A_1(X) \cdot (X - X^*_1) + A_{12}(X) \cdot X_2,
\]

\[
\dot{X}_2 = A_2(X) \cdot X_2,
\]

where
(H1) : The system is defined on a positively invariant set $X$ of the nonnegative orthant. The system is dissipative on $X$. That $X$ is the region, where the model has biological sense, well posed and all its trajectories are forward bounded.

(H2) : The sub-system $\dot{X}_1 = A_1(X_1,0)(X_1 - X^*_1)$ is globally asymptotically stable at the equilibrium $X^*_1$ on the canonical projection of $\Omega$ on $R^{n1}$. That is, when there is no disease, the whole population will be stable at diseases free equilibrium.

(H3) : The matrix $A_2(X)$ is Metzler and irreducible for any given $X \in \Omega$. That is, no block (compartment) of the model is isolated from others.

(H4) : There exists an upper bound matrix $\bar{A}_2$ for $M = \{A_2(X), X \in \Omega\}$ with the property that either $\bar{A}_2 \notin M$ or if $\bar{A}_2 \in M$ (i.e. $\bar{A}_2 = \max_{\Omega} M$), then for any $\bar{x} \in \Omega$ such that $\bar{A}_2 = A_2(\bar{x}), \bar{x} \in R^{n1} \times \{0\}$.

(H5) : $\alpha(\bar{A}_2) \leq 0$.

3. Mathematical formulation

Stauch et al. [23] studied the biological behaviour of the disease, while we present a mathematical formulation of the model. Our newly developed model represents the dynamics of visceral strains of Leishmania in two different populations, human population $N_h$ and sandfly population $N_v$. The total population is distributed in 14 compartments:

- $S_h$ : Susceptible human population, PCR, DAT and LST negative ($P^-, D^-, L^-$).
- $E_1$ : Early latent period VL in human population and is ($P^+, D^-, L^-$).
- $E_2$ : The Second stage of VL – latency in human population and is ($P^+, D^+, L^-$).
- $I_1$ : Early symptomatic and diagnosis stage of VL in human class and is ($P^+, D^+, L^-$).
- $I_2$ : The second stage of symptomatic kala azar, under first—line treatment and is ($P^+, D^+, L^-$).
- $I_3$ : The third stage of symptomatic kala azar, under second — line treatment and is ($P^+, D^+, L^-$).
- $E_3$ : The dormant period, before developing PKDL.
- $I_4$ : The human class with PKDL.
- $R_1$ : The human class recovered from the latent stage $E_2$ and is ($P^-, D^+, L^-$).
- $R_2$ : The human class recovered with immunity ($P^-, D^-, L^+$).
- $R_3$ : The human class recovered in response of first — line and second – line treatment and is ($P^-, D^-, L^+$).
- $S_v$ : The susceptible sandfly population.
- $E_v$ : The exposed sandfly population.
- $I_V$ : The infectious sandfly population.

The total human population $N_h$ is $N_h = S_h + E_1 + E_2 + I_1 + I_2 + E_3 + I_3 + I_4 + R_1 + R_2 + R_3.$
Total vector population $N_v(t)$ is, $N_v(t) = S_v(t) + E_v(t) + I_v(t)$.

The susceptible humans become latent at the rate $\lambda_h$, after contact with infected sand fly. After completing sojourn time, the patient develop second latent stage $E_2$, at the rate $\xi_1$. The fraction $\gamma_1 \xi_2$ of the patients at $E_2$ develops symptomatic Kala Azar, the fraction $\gamma_2 \xi_2$ enter the dormant period of PKDL and the fraction $\gamma_3 \xi_2$ recover and get $PCR^-$. The fraction $\alpha_3$ of these recovered individuals become $(P^-, D^-, L^+)$. Some of these recovered individuals lose their cellular immunity at the rate $\alpha_1$, getting $(P^-, D^-, L^-)$ and become susceptible again.

After diagnosis, the symptomatic infectious individuals at $I_1$ are put on first-line treatment at the rate $\xi_3$. After the first-line treatment, these infectious individuals can be divided into six subgroups:

- Fraction $\mu_k$ of these infectious human dies due to toxicity of medicines.
- Fraction $\mu_T$ dies due to VL-induced death.
- Fraction $\mu_h$ dies due to natural death.
- Fraction $p_1 \tau_1$ does not show +ve response to first-line treatment and is put on second-line treatment.
- Fraction $p_2 \tau_1$ enters the dormant period before the development of PKDL.
- Fraction $p_3 \tau_1$ is recovered.

After completing a sojourn time at $R_3$, the person further improves and become $(P^-, D^-, L^+)$, and enters the class $R_2$. After second-line treatment, infectious individuals can be divided into three subgroups:

- A group passes away due to, toxicity of second-line treatment, $\mu_T$, natural mortality $\mu_k$ and disease death $\mu_k$.
- A group $p_5 \tau_2$ is recovered and enters the recovered class $R_3$.
- A group $p_4 \tau_2$ enters the dormancy period of PKDL.

After completing the sojourn period (dormancy period) $\alpha_2$ at $E_3$, the victimized individuals develop PKDL, subject to their survival. Some of these individuals are recovered due to treatment (180 days = $\tau_3$) and some recover naturally at the rates $\beta_2$ and $\beta_1$, getting $(P^-, D^-, L^+)$. After completing the sojourn period $\alpha_4$, these recovered individuals enter the recovered class $R_2$. A susceptible vector, after contact with a person in latent or infectious states, gets infected and enters the exposed class $E_v$ at the rate $\lambda_v$. After completing the incubation period $\sigma_v$ at $E_v$, the vector becomes infectious and enters the class $I_v$.

Figure 1 represents the flow of the disease in susceptible population. The dynamical system for human and vector population is given by

\[
\begin{align*}
\dot{S}_h &= \Gamma_h + \alpha_1 R_2 - \left(\frac{a \beta (1 - \nu_1) b I_v}{N_h}\right) S_h - (\mu_h) S_h, \\
\dot{E}_1 &= \left(\frac{a \beta (1 - \nu_1) b I_v}{N_h}\right) S_h - (\xi_1 + \mu_h) E_1, \\
\dot{E}_2 &= \xi_1 E_1 - ((\omega_1 + \omega_2 + \omega_3) \xi_2 + \mu_h) E_2,
\end{align*}
\]
Figure 1. Flow chart representing the dynamics of the disease. The blue lines represent the interaction between susceptible and infected populations.

Here, $\mu_1 = \mu_h + \mu_k$, $\mu_2 = \mu_h + \mu_k + \mu_T1$ and $\mu_3 = \mu_h + \mu_k + \mu_T2$. The description of the parameters is given in the following table:
Table of parameters

| Notation | Parameter definition | Value            | Resource |
|----------|----------------------|------------------|----------|
| $\Gamma_h$ | Humans' recruitment rate | 0.0015875 day$^{-1}$ | [9]      |
| $\Gamma_v$ | Sandflies' recruitment rate | 0.299 day$^{-1}$ | [13]    |
| $\mu_h$ | Humans' natural mortality rate | 0.00004 day$^{-1}$ | [13]    |
| $\mu_v$ | Sandflies' natural mortality rate | 0.189 day$^{-1}$ | [13]    |
| $\delta_1$ | Inverse of sojourn period at $E_1$ | 0.0166666 | [11]    |
| $\delta_2$ | Inverse of sojourn period at $I_2$ | 0.0833333 | [23]    |
| $\delta_3$ | Inverse of sojourn period at $I_3$ | 1 | [23]    |
| $r_1$ | Inverse of first-line treatment period | 0.0333333 day$^{-1}$ | [10]    |
| $r_2$ | Inverse of second-line treatment period | 0.0333333 day$^{-1}$ | [10]    |
| $r_3$ | Inverse of treatment period of PKDL | 0.0055555 day$^{-1}$ | [20]    |
| $\alpha_2$ | Inverse of relapse period to PKDL | 0.0015873 day$^{-1}$ | [20, 27] |
| $\alpha_3$ | Inverse of sojourn period at $R_1$ | 0.013513 | [23]    |
| $\alpha_4$ | Inverse of sojourn period at $R_2$ | 0.003257 | [23]    |
| $\beta_1$ | Inverse of sojourn period at $R_3$ | 0.003257 | [23]    |
| $p_1$ | Fraction not responding to first-line treatment | 0.05 | [10]    |
| $p_2$ | Fraction developing PKDL after first-line treatment | 0.03 | [23]    |
| $p_3$ | Fraction of VL recovering with first-line treatment | 0.92 | [23]    |
| $p_4$ | Fraction developing PKDL after second-line treatment | 0.03 | [23]    |
| $p_5$ | Fraction recovering from VL with second-line treatment | 0.97 | [23]    |
| $\sigma_v$ | Inverse of incubation period at $E_v$ | 0.2 | [22]    |
| $a$ | Sandflies biting rate | 0.2856 day$^{-1}$ | [7]    |
| $\mu_{r_1}$ | Excess in mortality due to first-line treatment toxicity | 0.00167 | [23]    |
| $\mu_{r_2}$ | Excess in mortality due to second-line treatment toxicity | 0.00167 | [23]    |
| $\mu_k$ | VL-induced death rate | 0.011 day$^{-1}$ | [24]    |
| $\omega_1$ | Fraction of $E_2, E_3$ entering state $I_1$ | 0.0033 | [23]    |
| $\omega_2$ | Fraction of $E_2, E_3$ entering state $I_2$ | 0.0001 | [23]    |
| $\omega_3$ | Fraction of $E_2, E_3$ entering state $I_3$ | 0.0066 | [23]    |
| $\beta_1$ | Inverse of feeding cycle period of sandfly | 0.25 | [23]    |
| $\beta_2$ | Fraction recovering from PKDL due to treatment | 0.981 | [17] |

4. Replace model analysis by model analysis

In this section, we discuss invariant region, the disease-free equilibrium point and reproduction number $R_0$ of the system (1).

4.1. Invariant region

The proposed model is concerned with living population; therefore the state variables are nonnegative. The dynamic of overall population is obtained by adding all the classes concerned with humans ($N_h$) and adding all the classes concerned with vector ($N_v$) and is given by the following differential equations:

$$\dot{N}_h = \Gamma_h - \mu_h N_h - \delta_1 I_1 - \delta_2 I_2 - \delta_3 I_3,$$

$$\dot{N}_v = \Gamma_v - \mu_v N_v,$$
where \( \delta_1 = \mu_k, \delta_2 = \mu_k + \mu T_1 \) and \( \delta_3 = \mu_k + \mu T_2 \). If the human population is disease-free, then \( (N_h \rightarrow \Lambda_h / \mu_h, N_v \rightarrow \Lambda_v / \mu_v) \) as \( t \rightarrow \infty \). This shows that the biological feasible region \( \Psi \) is given by

\[
\Psi = \left( (S_h, E_1, E_2, I_1, I_2, I_3, R_1, R_2, R_3, I_4, E_3, S_v, E_v, I_v) \in R_+^{14}, 0 \leq S_h, E_1, E_2, I_1, I_2, I_3, R_1, R_2, R_3, I_4, E_3, S_v, E_v, I_v; N_h \leq \frac{\Gamma_h}{\mu_h}; N_v \leq \frac{\Gamma_v}{\mu_v} \right),
\]

which is a positively invariant domain. The model is epidemiologically and mathematically well posed [6] and all the trajectories are forward bounded.

### 4.2. Disease-free equilibrium and reproduction number

For the disease-free equilibrium, we equate the right-hand sides of all the equations in Equation (1) to zero; also, we assume that initially, there is no infection. Then, the disease-free equilibrium of the model (1) is

\[
X_0 = \left( \frac{\Gamma_h}{\mu_h}, 0, 0, 0, 0, 0, 0, 0, 0, 0 \right).
\]

The number of secondary infections caused in completely susceptible population by introducing an infectious individual to the population is called reproduction number \( R_0 \) [4]. In order to find the basic reproduction number, we use the next-generation method [5]. \( R_0 = \rho(-FV^{-1}) \), where \( \rho \) is the spectral radius. Here

\[
R_0 = \left( \frac{m_1 m_2 \sigma_v}{a_1 a_1 a_1 \mu_v (1 + \nu_2)} + \frac{\xi_1 m_1 m_3 \sigma_v}{a_1 a_2 a_1 a_1 \mu_v (1 + \nu_2)} + \frac{a_8 a_2 \xi_1 m_1 m_7 \sigma_v}{a_1 a_2 a_1 a_1 a_1 a_1 \mu_v (1 + \nu_2)} \right)^{1/2},
\]

which can be written as

\[
R_0 = \sqrt{R_a + R_b + R_c},
\]

where

\[
\begin{align*}
m_1 &= a_1(1 - \nu_1)b, & m_2 &= \frac{a_1(1 - \nu_1)c_1 \Gamma_v \mu_h}{\mu_v (1 + \nu_2) \Gamma_h}, & m_3 &= \frac{a_1(1 - \nu_1)c_2 \Gamma_v \mu_h}{\mu_v (1 + \nu_2) \Gamma_h}, \\
m_4 &= \frac{a_1(1 - \nu_1)c_3 \Gamma_v \mu_h}{\mu_v (1 + \nu_2) \Gamma_h}, & m_5 &= \frac{a_1(1 - \nu_1)c_3 \Gamma_v \mu_h}{\mu_v (1 + \nu_2) \Gamma_h}, & m_6 &= \frac{a_1(1 - \nu_1)c_3 \Gamma_v \mu_h}{\mu_v (1 + \nu_2) \Gamma_h}, \\
m_7 &= \frac{a_1(1 - \nu_1)c_4 \Gamma_v \mu_h}{\mu_v (1 + \nu_2) \Gamma_h},
\end{align*}
\]

\[
\begin{align*}
a_1 &= \xi_1 + \mu_h, & a_2 &= (\omega_1 + \omega_2 + \omega_3) \xi_2 + \mu_h, & a_3 &= \omega_1 \xi_2, & a_4 &= \xi_3 + \mu_1, \\
a_5 &= p_1 \tau_1 + p_2 \tau_1 + p_3 \tau_1 + \mu_2, & a_6 &= p_1 \tau_1, & a_7 &= p_4 \tau_2 + p_5 \tau_2 + \mu_3, & a_8 &= \omega_2 \xi_2, \\
a_9 &= p_2 \tau_1, & a_{10} &= p_2 \tau_2, & a_{11} &= \alpha_2 + \mu_h, & a_{12} &= \beta_2 \tau_3 + \beta_1 + \mu_h, \\
a_{13} &= \sigma_v + \mu_v (1 + \nu_2)
\end{align*}
\]
and
\[
R_a = (ab)(ac_1) \left( \frac{\Gamma_v \mu_h \sigma_v (1 - v_1)^2}{(\mu_v)^2 \Gamma_h a_1 a_1 a_1 (1 + v_2)^2} \right),
\]
\[
R_b = (ab)(ac_2) \left( \frac{\Gamma_v \mu_h \xi_1 (1 - v_1)^2}{(\mu_v)^2 \Gamma_h a_1 a_2 a_1 a_1 (1 + v_2)^2} \right),
\]
\[
R_c = (ab)(ac_4) \left( \frac{a_8 a_2 \xi_1 \sigma_v \Gamma_v \mu_h (1 - v_1)^2}{(\mu_v)^2 \Gamma_h a_1 a_2 a_1 a_1 a_1 a_1 a_1 (1 + v_2)^2} \right).
\]

4.3. Biological interpretation and sensitivity of $R_0$

$R_a = (ab)(ac_1)(\beta^2 \Gamma_v \mu_h \sigma_v (1 - v_1)^2/(\mu_v)^2 \Gamma_h a_1 a_1 a_1 (1 + v_2)^2)$, where $a$ is the sandfly biting rate, $b$ is the transmission probability of VL infection to human from sandfly and $c_1$ is the transmission probability of VL infection to sandfly from human in state $E_1$. If human is susceptible and the sandfly is infected with VL, then the term $ab$ confirms the transmission of VL infection from sandfly to human. If human is in the latency period, stage $E_1$ and the sandfly is susceptible, then $ac_1$ confirms the transmission of VL infection from human to sandfly. So, the term $R_a$ denotes VL transmission, between human and sandfly.

$R_b = (ab)(ac_2)(\beta^2 \Gamma_v \mu_h \xi_1 (1 - v_1)^2/(\mu_v)^2 \Gamma_h a_1 a_2 a_1 a_1 (1 + v_2)^2)$, where $c_2$ is the transmission probability of VL infection to sandfly from human in state $E_2$. If human is susceptible and the sandfly is infected with VL, then the term $ab$ confirms the transmission of VL infection from sandfly to human. If human is in the latency period, stage $E_2$ and the sandfly is susceptible, then $ac_2$ confirms the transmission of VL infection from human to sandfly. So, the term $R_b$ denotes VL transmission, between human and sandfly. Similarly, the term $R_c$ denotes VL transmission, with involvement of state $I_4$. Thus, $R_0$ is biologically meaningful.

4.3.1. Sensitivity analysis of $R_0$

Definition 4.1 ([18]): The normalized forward sensitivity index of a variable, $x$, that depends differentiably on a parameter $y$ is defined as
\[
\gamma^x_y = \frac{\partial x}{\partial y}.
\]

To reduce the rate of disease transmission, it is important to know the role of different parameters involved in its transmission. Since initial disease transmission depends on basic reproduction number $R_0$. Therefore, we find the sensitivity indices of the parameters involved in reproduction number $R_0$. These indices allow us to measure the relative change in $R_0$ with the change in a parameter. With the help of these indices, we find the parameters that are highly effective in disease transmission, and need to be targeted by intervention strategies. Table 1 shows the sensitivity indices of the parameters involved in the initial disease transmission.

Sandfly biting rate $a$ and duration of feeding cycle $\beta$ have got highest sensitivity indices 1. This means that the decrease in biting rate by 10% would decrease $R_0$ by 10%. The second highest index $-1$ is that of sandfly’s mortality rate $\mu_v$. That is, increasing $\mu_v$ by 10% will decrease $R_0$ by 10%. The fraction of exposed human in the class $E_2$ which
Table 1. The sensitivity indices of parameters.

| Parameter | Index | Parameter | Index |
|-----------|-------|-----------|-------|
| a         | +1    | b         | +0.5  |
| c₁        | +0.0000088 | c₂       | +0.499 |
| c₄        | +0.00002 | σᵥ       | +0.49 |
| ξ₁        | +0.00003 | ξ₂       | −0.997 |
| ω₁        | −0.65  | ω₂       | −0.004 |
| ω₃        | −0.334  | µᵥ       | 0.0000006 |
| β₂        | −0.0000007 | µᵥ       | 0.498 |
| μᵥ        | −1     | Γᵥ       | +0.5 |
| Γₕ        | −0.5   | ν₁       | −0.42 |
| ν₂        | −0.17  | β        | 1     |

Develop symptomatic kala azar is denoted by $\omega_1 \cdot \omega_1$; has got a sensitivity index of $−0.65$. The transmission probabilities of infection between human and sandfly have got a sensitivity index of 0.5. The parameter $\Gamma_v$; birth rate of sandflies, have got a sensitivity index of 0.5. Decrease of 10% in the birth rate of sandflies will decrease $R_0$ by 5%. $\Gamma_h$ have got a sensitivity index of $−0.5$. Increase in human’s birth rate causes a decrease in $R_0$. The sensitivity index of death rate of human $\mu_h$ is 0.49. Increase in treatment rate of human will cause a decrease in human’s death rate, which will reduce $R_0$. We develop four different control strategies which touch, directly or indirectly, the parameters effecting the initial transmission rate $R_0$ of ACL.

4.4. Stability of disease-free state

For global stability of the disease-free equilibrium, we proceed as follows:

Let

$$X = (S_h, R_1, R_2, R_3, S_v, E_1, E_2, I_1, I_2, I_3, I_4, E_v, I_v)^T.$$

$$X_s = (S_h, R_1, R_2, R_3, S_v)^T$$ and $$X_I = (E_1, E_2, I_1, I_2, I_3, I_4, E_v, I_v)^T.$$

**Theorem 4.1:** The sub-system $\dot{X_s} = A_s(X_s)(X_s) + E_s$ is globally asymptotically stable at $G = \{X \in \Psi; X_I = 0, X_s \neq 0\}$.

**Proof:** The above sub-system in accordance with Theorem 2.1 is equivalent to

$$\dot{X}_1 = A_1(X) \cdot (X - X_1^*) + A_{12}(X) \cdot X_2.$$

The system can be written as follows, on the domain $G = \{X \in \Psi; X_I = 0, X_s \neq 0\}$:

$$\dot{S}_h = \Gamma_h - \mu_h S_h,$$

$$\dot{R}_1 = -(\alpha_3 + \mu_h) R_1,$$

$$\dot{R}_2 = -(\alpha_1 + \mu_h) R_2,$$

$$\dot{R}_3 = -(\alpha_4 + \mu_h) R_3,$$

$$\dot{S}_v = \Gamma_v - (\mu_v) S_v.$$

The system (4) is a linear system. This system is globally asymptotically stable at the equilibrium $(\Gamma_h/\mu_h, 0, 0, 0, \Gamma_v/\mu_v)$, corresponding to the disease-free equilibrium where the hypotheses $H_1$ and $H_2$ are satisfied.
The sub-system $\dot{X}_2 = A_2(X)X_2$ can be written as

$$
\dot{E}_1 = \left( \frac{a\beta(1 - v_1)bI_v}{N_h} \right) S_h - (\xi_1 + \mu_h)E_1,
$$

$$
\dot{E}_2 = \xi_1 E_1 - ((\omega_1 + \omega_2 + \omega_3)\xi_2 + \mu_h)E_2,
$$

$$
\dot{I}_1 = (\omega_1\xi_2)E_2 - (\xi_3 + \mu_1)I_1,
$$

$$
\dot{I}_2 = \xi_3 I_1 - (p_1\tau_1 + p_2\tau_1 + p_3\tau_1 + \mu_2)I_2,
$$

$$
\dot{I}_3 = (p_1\tau_1)I_2 - (p_4\tau_2 + p_5\tau_2 - \mu_3)I_3,
$$

$$
\dot{E}_3 = (\omega_2\xi_2)E_2 + (p_2\tau_1)I_2 + (p_4\tau_2)I_3 - (\alpha_2 + \mu_h)E_3
$$

$$
\dot{I}_4 = \alpha_2E_3 - (\beta_2\tau_3 + \beta_1 + \mu_h)I_4,
$$

$$
\dot{E}_v = \left( \frac{a\beta(1 - v_1)(c_1E_1 + c_2E_2 + c_3(I_1 + I_2 + I_3) + c_4I_4)}{N_h} \right) S_v
$$

$$
- (\sigma_v + \mu_v(1 + v_2))E_v,
$$

$$
\dot{I}_v = \sigma_vE_v - \mu_v(1 + v_2)I_v.
$$

Theorem 4.2: For the sub-system (5), $A_2$ is Metzler and irreducible $\forall X \in \Psi$, and there exists a matrix $\tilde{A}_2$ such that

$$
A_2(X) \leq \tilde{A}_2 \quad \text{for } X \in \Psi,
$$

and

$$
\tilde{A}_2 \notin M = \{A_2(X), X \in \Psi\},
$$

$$
\alpha(\tilde{A}_2) \leq 0,
$$

where $\alpha$ is the stability modulus of $\tilde{A}_2$.

Proof: We can write the sub-system (5) as

$$
\dot{X}_2 = A_2(X)X_2.
$$

Here, $A_2(X)$ is given by the following matrix:

$$
\begin{pmatrix}
-a_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{a\beta(1 - v_1)bI_v}{N_h} \\
\xi_1 & -a_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & a_3 & -a_4 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \xi_3 & -a_5 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & a_6 & -\alpha_7 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & a_9 & -a_11 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & a_9 & -a_11 & 0 & 0 \\
\frac{a\beta(1 - v_1)c_1S_h}{N_h} & \frac{a\beta(1 - v_1)c_2S_h}{N_h} & \frac{a\beta(1 - v_1)c_3S_h}{N_h} & \frac{a\beta(1 - v_1)c_4S_h}{N_h} & 0 & 0 & 0 & \frac{a\beta(1 - v_1)c_4S_h}{N_h} & \frac{-a_{12}}{N_h} \\
\frac{a\beta(1 - v_1)c_2S_h}{N_h} & \frac{a\beta(1 - v_1)c_3S_h}{N_h} & \frac{a\beta(1 - v_1)c_4S_h}{N_h} & 0 & 0 & 0 & 0 & 0 & -\frac{a_{13}}{N_h} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_v & -\mu_v(1 + v_2)
\end{pmatrix}.
$$

All the off-diagonal entries of the matrix $A_2(X)$ are nonnegative, on the domain $G$. Hence, $A_2(X)$ is Metzler and irreducible $\forall X \in G$. 
The upper bond matrix of the matrix $A_2(X)$ is denoted by $\tilde{A}_2$ and is given by

$$
\tilde{A}_2(X) = \begin{pmatrix}
-a_1 & 0 & 0 & 0 & 0 & 0 & 0 & ab \\
ξ_1 & -a_2 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & a_3 & -a_4 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & ξ_3 & -a_5 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & a_6 & -a_7 & 0 & 0 & 0 \\
0 & a_8 & 0 & a_9 & a_{10} & -a_{11} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & a_2 & -a_{12} & 0 \\
ac_1 & ac_2 & ac_3 & ac_3 & ac_3 & 0 & ac_4 & -a_{13} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & σ_v \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -μ_v
\end{pmatrix}.
$$

This upper bound is not attained in $Ψ$, and particularly not realized for the Jacobian at the disease-free equilibrium. Thus, we can have sufficient condition. So $H_4$ of Theorem 2.1 equivalent to Equations (6) and (7) holds.

Finally, we show that $H_5$ or Equation (8) holds; we state the following theorem.

**Theorem 4.3:** The Metzler matrix satisfy the axiom '$α(\tilde{A}_2) ≤ 0' if $Π < 1$, where $Π$ is the additional threshold number given by

$$
Π = \frac{a^2bc_1}{a_1a_3μ_v} + \frac{a^2bc_2ξ_1σ_v}{a_1d_1a_3μ_v} + \frac{a^2bc_4a_8k_2σ_vξ_1}{a_1d_1a_12d_13μ_v}.
$$

**Proof:** We decompose the matrix $\tilde{A}_2$ in four blocks, such that

$$
\tilde{A}_2 = \begin{pmatrix}
B & C \\
D & E
\end{pmatrix},
$$

where $B, C, D$ and $E$ are $7 \times 7$, $7 \times 2$, $2 \times 7$ and $2 \times 2$ sub-matrices, respectively. We know that the matrix $\tilde{A}_2$ is stable if and only if $B$ and $E - DB^{-1}C$ are Metzler stable [12]. Here, $B$ is Metzler stable because all its off-diagonal entries are nonnegative, and all the eigenvalues are negative. To show that $E - DB^{-1}C$ is stable, we proceed as follows:

Let

$$
Y = E - DB^{-1}C
$$

$$
⇒ \tilde{A}_2\text{is stable if } Y \text{ is stable.}
$$

From [15], $α(\tilde{A}_2) ≤ 0$ only if

$$
\left(\frac{n_1n_2σ_v}{a_1a_3μ_v} + \frac{ξ_1n_1n_3σ_v}{a_1d_1a_3μ_v} + \frac{a_8k_2ξ_1n_1n_7σ_v}{a_1d_1a_12d_13μ_v} - 1\right) < 0. \quad (9)
$$

Here $n_1 = ab$, $n_2 = ac_1$, $n_3 = ac_2$, $n_4 = ac_3$, $n_5 = ac_3$, $n_6 = ac_3$, $n_7 = ac_4$. By putting these values in Equation (9), we have

$$
\frac{a^2bc_1σ_v}{a_1a_3μ_v} + \frac{a^2bc_2ξ_1σ_v}{a_1d_1a_3μ_v} + \frac{a^2bc_4a_8k_2σ_vξ_1}{a_1d_1a_12d_13μ_v} < 1.
$$

We name this value as $Π$. Thus, $H_5$ or (8) holds, if $Π < 1$. ■
Thus, we have shown that axioms $H_1 \ldots H_5$ of Theorem 2.1 do hold. Now, we are in a position to claim the following result.

**Theorem 4.4:** If the parameters used in the model satisfy the condition $\alpha(\tilde{A}_2) \leq 0$, then the disease-free equilibrium of the system (1) is globally asymptotically stable.

## 5. Simulation results of the model

We use four different control strategies and generate numerical simulation for each, using Matlab software. In these strategies, we focus on treatment of human class and control of sandfly class. $\tau_1, \tau_2, \xi_3$ are interventions by treatment of human class, where $v_1, v_2$ are vector-related interventions (Table 2). The ratio of human and sandfly is taken as 100:527.

In the following numerical simulations, $E_1$ denotes early latent period of VL in human population, $E_2$ is the second stage of VL-latency in human population, $E_3$ is the dormant period before development of PKDL, $I_1$ is the early symptomatic and diagnosis stage of VL in human, $I_2$ is the second stage of symptomatic kala azar, $I_3$ is the third stage of symptomatic kala azar and $I_4$ denotes the human class with PKDL. $E_f$ is the class of exposed

| Strategy | $\tau_1$ | $\tau_2$ | $\tau_3$ | $\xi_3$ | $v_1$ | $v_2$ | $\Pi$ |
|----------|--------|--------|--------|-------|------|------|------|
| 1        | 30 days | 30 days | 180 days | 5 days | 0.09 | 0.06 | 0.0416965936 |
| 2        | 15 days | 15 days | 90 days  | 1 day  | 0.09 | 0.06 | 0.0416965936 |
| 3        | 30 days | 30 days | 180 days | 5 days | 0.5  | 0.3  | 0.00896962611 |
| 4        | 15 days | 15 days | 90 days  | 1 day  | 0.5  | 0.09 | 0.01204364265 |

**Figure 2.** The time spent in elimination of infectious classes, using control strategy No. 1.
Figure 3. The time spent in elimination of infectious classes, using control strategy No. 2.

Figure 4. The time spent in elimination of infectious classes, using control strategy No. 3.
sandflies and $I_f$ denotes the infectious class of sandflies. We apply control strategies to these infectious classes to eliminate the disease. Figures 2–5 present the time spent in eradication of each infectious class.

In Table 3, we compile the summary of the results of the control strategies, obtained from numerical simulations. The table presents the time spent (TS) in elimination of each infectious class. ($E_1$, TS) means the time spent (unit days) in elimination of exposed class $E_1$.

### Table 3. Results of control strategies.

| Strategy | $E_1$, TS | $E_2$, TS | $E_3$, TS | $I_2$, TS | $I_3$, TS | $I_4$, TS | $E_v$, TS |
|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 1        | 580       | 500       | 2400      | 200       | 130       | 2600      | 65        | 57        |
| 2        | 460       | 457       | 2400      | 130       | 70        | 2400      | 65        | 57        |
| 3        | 350       | 320       | 2700      | 180       | 130       | 2700      | 25        | 15        |
| 4        | 580       | 570       | 2400      | 180       | 140       | 2700      | 55        | 65        |

### 6. Discussion and conclusion

In this work, a mathematical model of Anthroponotic leishmania transmission was developed. On the basis of sensitivity analysis of the reproduction number, we presented four control strategies. For quantification of prevalence period of the disease, we performed numerical simulations. The results shown that the disease can be eradicated by using the proposed strategies. Control strategy 2 and strategy 3 take comparatively small time in the elimination of the disease. Since the prolonged prevalence of PKDL may cause the new outbreaks of VL, we recommend control strategy 2, where the prevalence period of PKDL
is comparatively low. The reproduction number of the model is most sensitive to $a$, sandfly biting rate; $\beta$, the feeding period of sandfly and $\mu_v$, the mortality rate of sandfly. So along with treatment of human’s infectious classes, we need to focus control variables $\nu_1$ and $\nu_2$, using different measures to control phlebotomize sandflies and its biting rate. This includes residual spraying of dwellings, insecticide-treated nets and application of repellents/insecticides to skin. Sandfly is susceptible to all the major insecticidal groups. The main intervention for vector control is reduction in sandfly life expectancy, which lowers the size of vector population and hence reducing the biting pressure of vector on humans. By reducing sandfly life expectancy, the vector is less likely to survive long enough to bite twice – once to acquire infection and again to infect a host, and the vector spends small time as infected. The extinction of PKDL states, $I_4$ and $E_3$, takes comparatively a long time. Although, both, theorems and numerical simulations agree with the global stability of disease-free equilibrium yet the long prevalence of state $I_4$ in the population works as a reservoir and hence cannot be neglected.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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