Abstract

In this work we focus on the transmission dynamics of Visceral strains of leishmania, using mathematical model with two latent compartments in human. From the governing differential equations of the model, we find the reproductive number $R_0$, the number of secondary infection and its biological interpretation. Using Routh- Hurwitz criteria on upper bound matrix, the threshold condition, for stability of the Disease Free State, is calculated. Finally we show that the disease free equilibrium is globally asymptotically stable if $R_0<\xi_{11}$.

Keywords: Leishmaniasis; Basic reproductive number; Mathematical model; Local and global stability

Introduction

Visceral leishmaniasis is a vector-borne disease of humans and other mammals. This disease is caused by parasites of the Leishmania donovani complex. There are two main forms of visceral leishmania: (1) zoonotic visceral leishmaniais (ZVL), which affects mainly young children and the domestic dog as its principal reservoir and (2) anthroponotic visceral leishmaniais (AVL), this affects people of all ages, and infectious sand y transmit it from human to human via biting [1]. Visceral leishmaniasis (VL) is severe and fatal. The average incubation period is 2-6 months; however it may vary from 10 days to one year [2,3]. Some of the patients recovered from VL, develops Post kala-Azar dermal leishmania with in the interval of 6 months to 3 years [4]. The vector latent period is assumed roughly to be 3 to 7 days [5,6].

No doubt leishmania control is challenging because the control of both sandflies and the reservoir is di cult. The failure rate of treatment is high due the two factors. Clinical structure of disease, the response of human immune system and the drug resistance acquired by the species [7].

Motivated from Hashim et al. [8] and Shillor et al. [9], the authors did not consider Homogenous population. We in our work have considered the homogenous mixing of the population. The Reproductive number so calculated, depends upon the densities of humans, reservoirs and vectors, which highlights the importance of homogenous mixing. Also we have applied new concept for calculating threshold condition, for disease free state as developed by Kamgang and Sallet [10].

In this paper, we present a mathematical model for the transmission dynamic of leishmaniasis. The model of 10 compartments includes 2 exposed classes of human infected with visceral leishmaniasis and PKDL. These exposed classes were not considered previously in the models. We find positive invariant region and use next generation matrix method to find the basic reproduction number $R_0$. Using upper bound matrix $A_r(X)$ of the matrix $A_r(X)$ of the infected classes, the threshold number is found. Comparing $R_0$ and we find three values for $R_0$. On the basis of these values, we discuss the dynamical behavior of the model. Finally we show the global stability of the disease free equilibrium, and the existence of endemic equilibrium.

Model Formulation

In this section we present the formulation of the model. We divide the compartmental model of human, reservoir and vector populations into different classes. The human population consist of sub-classes $S_h$, $E_1$, $I_1$, $P_2$, $R_1$, $E_{12}$. Here $S_h$ represent the class of susceptible human, $E_1$ is the VL infected class, $E_{12}$ is the class recovered from VL and exposed to PKDL, $P_2$ is the human class with PKDL and $R_1$ is the human recovered class. $I_1$ is the human class infectious with VL.

The total human population $N_h$ is

$$N_h = S_h + E_1 + I_1 + E_{12} + P_2 + R_1$$

The vector population is divided into two sub-classes $S_v(t)$ and $I_v(t)$, also the reservoir class is divided into $S_v(t)$ and $I_v(t)$.

After susceptible person, being bitten by infectious vector, he/she can’t transmit leishmania virus immediately. We call this person as infected (exposed). When a susceptible vector $S_v(t)$, bite the infectious person, the vector moves from susceptible compartment to the infectious compartment $I_v(t)$ [11].

The interaction of human, reservoir and vector population is represented in the flowchart as shown in Figure 1.

Figure 1: The interaction of human, reservoir and vector population.

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The dynamical system for human, reservoir and vector population is given by

\[
\begin{align*}
\dot{S} &= \Gamma_h - (\lambda_h + \mu_h)S_h \\
\dot{E}_1 &= \lambda_h S_h - (k_2 + \mu_h)E_1 \\
\dot{I}_1 &= k_2E_1 - (\gamma_1 + \delta_h + \mu_h)I_1 \\
\dot{E}_{12} &= (1 - a_1)\gamma_1I_1 - (k_3 + \mu_h)E_{12} \\
\dot{P}_2 &= k_3E_{12} - (\gamma_2 + \beta_h + \delta_v + \mu_h)P_2 \\
\dot{R} &= a_1\gamma_1I_1 + (\gamma_2 + \beta_h)P_2 - (\mu_h)R \\
\dot{S}_v &= \Gamma_v - \lambda_v S_v - \mu_v S_v \\
\dot{I}_v &= \lambda_v S_v - \mu_v I_v \\
\dot{S}_r &= \Gamma_r - \lambda_r S_r - \mu_r S_r \\
\dot{I}_r &= \lambda_r S_r - \mu_r I_r \\
\dot{P}_v &= \gamma vI_v - \delta_vP_v
\end{align*}
\]  

(1)

Mathematical Analysis of the Model

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

Invariant region

We have assumed all the parameters as nonnegative. Since the model is concerned with living population, therefore the state variables are assumed to be nonnegative at $t=0$. The dynamic of overall population is given by the following differential equations.

\[
\begin{align*}
\dot{N}_h &= \Gamma_h - \mu_h N_h - \delta_h I_1 - \delta_p P_2 \\
\dot{N}_r &= \Gamma_r - \mu_r N_r, \\
\dot{N}_v &= \Gamma_v - \mu_v N_v.
\end{align*}
\]  

If the human population is disease free, i.e. $I_1 = P_2 = 0$, then equation (2) reduces to the form;

\[
\dot{N}_h = \Gamma_h - \mu_h N_h.
\]

Equilibrium in this case is

\[
N_{h}^* = \frac{\Gamma_h}{\mu_h}.
\]

From equation (2) and the fact that $(\delta_h + \delta_p)N_h \geq \delta_h I_1 + \delta_p (P_2)$, we have

\[
\Gamma_h - \mu_h N_h - (\delta_h + \delta_p)N_h \leq N_{h}^* \leq \Gamma_h - \mu_h N_h
\]

The lower bond for equation (7) is given by

\[
N_h = \Gamma_h - \mu_h N_h - (\delta_h + \delta_p)N_h.
\]

The equilibrium of equation (8) is

\[
N_{h}^* = \frac{\Gamma_h}{\mu_h + \delta_h + \delta_p}
\]

With the initial condition

Notation | Value | Resource |
---|---|---|
$c_2$ | Progression rate of VL in sandfly (from human) | 0.22 | [14] |
$a$ | Sandflies biting rate | 0.2856 day$^{-1}$ | [14] |
$\Gamma_h$ | Recruitment rate of human | 0.0015875 day$^{-1}$ | [15] |
$\Gamma_v$ | Recruitment rate of sandfly | 0.299 day$^{-1}$ | [16] |
$\Gamma_r$ | Recruitment rate of reservoir | 0.073 day$^{-1}$ | Assumed |
$c_1$ | Natural mortality rate of human | 0.00004 day$^{-1}$ | [16] |
$\mu_v$ | Natural mortality rate of Sandflies | 0.189 day$^{-1}$ | [16] |
$\mu_r$ | Natural mortality rate of Reservoirs | 0.000274 day$^{-1}$ | Assumed |
$\gamma_2$ | PKDL recovery rate after treatment | 0.033 day$^{-1}$ | [17] |
$\beta_1$ | PKDL induced death rate | 0.0056 day$^{-1}$ | [17] |
$l - \alpha_1$ | Developing PKDL rate after treatment | 0.36 day$^{-1}$ | [17] |
$c$ | Progression rate of VI in sandfly (from reservoir) | Variable | Variable |
$b$ | Progression rate of VI in reservoir (from sandfly) | Variable | Variable |
$\gamma_1$ | Treatment rate of VL | Variable | Assumed |
$\delta_1$ | VL induced death rate | 0.011 day$^{-1}$ | [18] |
$k_2$ | $1/k_2$ is Incubation period of vi | 0.006555 day$^{-1}$ | [19] |
$k_3$ | $1/k_3$ is Incubation period of PKDL | 0.004925925 day$^{-1}$ | [2,20] |
$\delta_2$ | PKDL induced death rate | Assumed | Assumed |
$b_2$ | Progression rate of VL in human (from sandfly) | 0.0714 day$^{-1}$ | [21] |

Table 1: Description of the parameters.
\(N_0(0) = N_s\) \hspace{1cm} (10)

If \(N_s\) and \(N_v\) denote the solution of equation (5) and equation (8), then any solution of equation (2), satisfy
\[N_s \leq N_s \leq N_v.\] \hspace{1cm} (11)

Consider the biological feasible region \(\Omega\) given by:
\[\Omega = (S_h, E_1, I_1, P_2, R_1, S_r, I_r, S_v, I_v, 0) \in \mathbb{R}^{10}.\]

From equation (2), using standard comparison theorem, we have
\[N_h \leq N_h(0)e^{-\mu t} + \frac{\Gamma_h}{\mu_h}(1 - e^{-\mu t})\].

So
\[N_h \rightarrow \frac{\Gamma_h}{\mu_h} \text{ as } t \rightarrow \infty.\]

Similarly
\[N_r \rightarrow \frac{\Gamma_r}{\mu_r} \text{ and } N_v \rightarrow \frac{\Gamma_v}{\mu_v}\] \text{ and } t \rightarrow \infty.

Hence is positively invariant domain, and the model is epidemiologically and mathematically well posed.

Let us define a new region \(G\) as
\[G = \{X \in \Omega; N_h \leq N_h; N_r \leq \frac{\Gamma_r}{\mu_r}; N_v \leq \frac{\Gamma_v}{\mu_v}\}.
\]

where
\[X = (S_h, E_1, I_1, E_1, P_2, R_1, S_r, I_r, S_v, I_v, 0).\]

Clearly \(G\) is the sub region of \(\Omega\). In light of equation (3), equation (4) and equation (11), it is reasonable to work on \(G\) instead of \(\Omega\).

**Disease free equilibrium**

The disease free equilibrium of the model (1) is given by:
\[X_0 = (\frac{\Gamma_h}{\mu_h}, 0, 0, 0, 0, 0, 0, 0, 0, 0).\]

**Reproductive number**

The number of secondary infections occurring in completely susceptible population by introducing an infectious individual to the population is called reproductive number \(R_0^{[12]}\). In order to find the susceptible population by introducing an infectious individual to the population we use next generation method for \(R_0 = \sqrt{R_a + R_b}\).

The term \(R_1\) indicates that if sandfly is infectious and the reservoir is susceptible, the contact would result the transmission of Vl from sand y to reservoir. The term \(R_2\) indicates the transmission of Vl from reservoir to sand y. So the term \(R_1\) indicate the transmission of Vl between sandly and reservoir. Similarly the term \(R_3\) indicates the transmission of VI between human and sand fly. The term \(R_4\) and \(R_5\) both denote the transmission of visceral strains of leishmania. There is no term representing the transmission of PKDL because it is the silent complication of Vl. When a susceptible vector bites human/reservoir infected with PKDL, the vector does not transmit PKDL but transmit VI to the next victim. So \(R_0\) is biologically sensible.

**Stability Analysis**

In this section, we discuss the relation between additional threshold number and basic \(\xi\) reproductive number \(R_0\) to find the global stability of the disease free equilibrium, and existence of endemic equilibrium of the system (1).

**Proposition:** The disease free equilibrium is locally asymptotically stable if \(R_0<1\) and unstable if \(R_0>1\).

**Proof:** For the proof of this result verify the reference [13].

**Global stability of the disease free equilibrium**

To find the global stability of the disease free equilibrium of the system (1), we state some definitions [9,10].

**Definition 1:** An \(m \times m\) matrix, for \(m>2\) is called irreducible if for any proper sub-set I of \{1, 2, …, m\}, \(\in \mathbb{N}\) and \(q \in I\) such that \(A_{p,q} \neq 0\).

**Definition 2:** The matrix \(M\) is said to be Metzler matrix if \(A_{p,q} \geq 0\) for \(p \neq q\).

**Definition 3:** The compact set \(M \subset \Omega\) is called stable for the dynamical system defined on \(M\) if for every trajectory initiated from a point in \(M\) is in \(W\), for all \(t \geq 0\). Here \(U\) and \(W\) are neighborhoods of \(M\).

**Definition 4:** A compact set \(N \subset D\) is called an attractor for a dynamical system defined on \(D\) if there exist a nbhds \(X\) and \(Y\) of \(N\) such that for every point \(x \in X\), there exists a time \(T > 0\), such that every trajectory initiated at \(x\), belongs to \(Y\) for \(t \geq T\). The largest set \(X\) is called a basin of attraction.

If \(X=D\) the set \(N\) is then called global attractor. A set \(N\) which is both stable and a global attractor is called globally asymptotically stable.

**Theorem:** The set \(G\) is globally asymptotically stable for the dynamical system (1) defined on \(\Omega\).
be the non-infected class of the total population, and let $\varepsilon \subset \Omega$ be globally asymptotically stable. Let $M$ be the largest invariant subset of $\mathcal{E}$. Then $M$ is globally asymptotically stable on $\Omega$. Particularly if $M = \{x^*\}$ where $X^*$ is equilibrium point of the system with basin of attraction containing $\mathcal{E}$. Then $X^*$ is GAS for the system on $\Omega$.

**Proof:** For the proof of the theorem verify the reference [9] theorem (5). To prove the global stability of the disease free equilibrium, we use theorem (4.3) of [10].

For this let

$$X = (S_h, S_I, I_1, e_1, I_2, P_2, I_x, I_y)^T.$$  

Now for global asymptotic stability of the disease free equilibrium of the system (1) on smaller set $G$, we decompose $X$ as, $X_S$ and $XI$ of noninfected and infected, humans reservoirs and sandies, such that

$$X_G = (S_h, S_I, I_1, e_1, I_2, P_2, I_x, I_y)^T.$$

**Theorem:** Let $X^*$ be the non-infected class of the total population, then

$$X^* = (S_h^*, R_h^*, S_r^*, I_1^*, I_2^*, P_2^*, I_x^*, I_y^*)^T.$$

So the model can now be written as

$$\dot{X} = A(X) + E_X \rightarrow \begin{bmatrix} \dot{X}_S = A_S(X)X_S + E_S \\ \dot{X}_I = A_I(X)X_I \end{bmatrix}$$

where

$$A_S = \begin{pmatrix} (1 - \mu_h)(1 - \lambda_h) & 0 & 0 & 0 \\ 0 & -\mu_h & 0 & 0 \\ 0 & 0 & (1 - \mu_I)(1 - \lambda_I) & 0 \\ 0 & 0 & 0 & (1 - \mu_I + \lambda_I) \end{pmatrix} \quad A_S = \begin{pmatrix} (\gamma_h + \beta_h)(\gamma_h + \beta_h) & 0 & 0 & 0 \\ 0 & -\mu_h & 0 & 0 \\ 0 & 0 & (1 - \mu_I)(1 - \lambda_I) & 0 \\ 0 & 0 & 0 & (1 - \mu_I + \lambda_I) \end{pmatrix}$$

And the matrix $A_S(X)$ is given by

$$A_S(X) = \begin{pmatrix} -a_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & k_1 & -a_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_r & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_r & 0 \end{pmatrix} \frac{a_h S_h}{N_h + N_r}$$

We restrict the domain of the system (1) from $G$ to $G$, to ensure the irreducibility of $A_S(X)$, such that $G = \{X, X \in G, X_S = 0\}$.

The set $\Omega$ is positively invariant because only the initial point of any trajectory can have $X_0 = 0$. Putting $S_h = R_h = S_r = S_I = 0$, in the system (1), we have $S_h > 0, R_h > 0, S_r > 0, S_I > 0$.

So all of the diagonal entries of $A_S(X)$ are nonnegative, hence $A_S(X)$ is metzler and irreducible $\forall X \in \mathcal{G}$.

Since diagonal entries of $A_S(X)$ are negative. So we state the following result

**Proposition:** Let $X^*_I$ be the non-infected class of the total population, then

$$X^*_I = (S_h^*, R_h^*, S_r^*, I_1^*, I_2^*, P_2^*, I_x^*, I_y^*)^T.$$
Proof:

Since

\[
\frac{1}{N_h + N_r} \leq \frac{1}{N_h + N_r},
\]

So the upper bond of \( A_I(X) \) denoted by \( \overline{A}_I \) is given by

\[
\overline{A}_I(X) = \begin{pmatrix}
-a_1 & 0 & 0 & 0 & 0 & \frac{ab_2 S_0^0}{N_h + N_r} \\
-k_2 & -a_2 & 0 & 0 & 0 & 0 \\
0 & 0 & d_2 & -a_3 & 0 & 0 \\
0 & 0 & -k_3 & -a_4 & 0 & 0 \\
0 & 0 & 0 & 0 & -\mu_r & \frac{ab_2 S_0^0}{N_h + N_r} \\
0 & \frac{ac_2 S_0^0}{N_h + N_r} & 0 & \frac{ac_2 S_0^0}{N_h + N_r} & \frac{ac_2 S_0^0}{N_h + N_r} & -\mu_r \\
\end{pmatrix},
\]

and

Clearly \( A_I(X) \leq \overline{A}_I(X) \) as \( \frac{1}{N_h + N_r} \leq \frac{1}{N_h + N_r} \).

And

\( A_I(X) = \overline{A}_I(X) \) only if; \( S_h = S_0^0, R_1 = R_0^0, S_r = S_0^0, S_r = S_0^0 \).

Thus \( H_1 \) of theorem (4.3) holds [10], equivalently equation (15) and equation (16), hold.

To show that \( H_1 \) or equation (18) holds, we state the following theorem.

Theorem: The metzler matrix satisfy the axiom \( H_5: \alpha(\overline{A}_I) \leq 0 \) if the basic reproductive number \( R_0 \) satisfy the inequality; \( R_0 \leq \xi \), where \( \xi \) is the additional threshold number given by

\[
\xi = a^2 \left( c + \frac{\mu_r}{\mu_k} \right) \left( \mu_k + \alpha_1 + \alpha_2 \right) \left( \mu_k + \alpha_1 + \alpha_2 \right) + a^2 \left( \mu_k + \alpha_1 + \alpha_2 \right) \left( \mu_k + \alpha_1 + \alpha_2 \right).
\]

Proof: We decompose the matrix \( \overline{A}_I \) in the blocks such that

\[
\overline{A}_I = \begin{pmatrix}
L & M \\
P & Q
\end{pmatrix},
\]

where \( L, M, P, Q \) are \( 3 \times 3 \) sub-matrices. The matrix \( \overline{A}_I \) is stable if \( S \) and \( Q - PL^{-1}M \) are metzler stable. Here \( S \) is metzler stable, because all its off diagonal entries are nonnegative, and all the eigen values are negative.

Let

\[
Y = Q - PL^{-1}M
\]

Then \( \overline{A}_I \) is stable if \( Y \) is stable.

And \( Y \) is stable if \( det(Y) \geq 0 \)

This means that \( \alpha(\overline{A}_I) \leq 0 \) only if

\[
\frac{2n_2}{\mu_k^2} + \frac{k_2 n_3}{\mu_k^2 \mu_r} + \frac{d_2^2 k_2 n_4}{\mu_k^2 \mu_r^2 g_2^2 \mu_r} - 1 < 0, \quad \frac{2n_2}{\mu_k^2} + \frac{k_2 n_3}{\mu_k^2 \mu_r} + \frac{d_2^2 k_2 n_4}{\mu_k^2 \mu_r^2 g_2^2 \mu_r} < 1,
\]

where

\[
m_1 = \frac{ab_2 S_0^0}{N_h + N_r}, \quad n_2 = \frac{ab_2 S_0^0}{N_h + N_r}, \quad n_3 = \frac{ac_2 S_0^0}{N_h + N_r}, \quad n_4 = \frac{ac_2 S_0^0}{N_h + N_r}, \quad n_5 = \frac{ac_2 S_0^0}{N_h + N_r}.
\]

At the disease free equilibrium,

\[
S_h = S_r = 0, \quad S_r = 0, \quad R_1 = R_0^0 = \frac{\Gamma_h}{\mu_k}, \quad R_0 \leq 0, \quad N_h + N_r = 0.
\]

By putting these values in above equation, we have

\[
\frac{a^2 h c (\mu_k + \alpha_1 + \alpha_2)^2 \Gamma_k \Gamma_r}{\mu_k^2 (\mu_k + \alpha_1 + \alpha_2)^2} + \frac{a^2 k_2^2 (\mu_k + \alpha_1 + \alpha_2)^2 \Gamma_k^2 \Gamma_r^2}{\mu_k^2 (\mu_k + \alpha_1 + \alpha_2)^2}, \quad a^2 \left( \frac{2n_2}{\mu_k^2} + \frac{k_2 n_3}{\mu_k^2 \mu_r} + \frac{d_2^2 k_2 n_4}{\mu_k^2 \mu_r^2 g_2^2 \mu_r} \right) \geq 1.
\]

We take this value as \( \xi \). Thus \( H_1 \) or equation (17) holds, if \( \xi \geq 1 \).

Also \( R_0 < \xi \). So using theorem (4.3) of [10], we claim the following result.

Theorem: If the parameters of the model satisfy the condition \( \alpha(\overline{A}_I) \leq 0 \), then the disease free equilibrium of the system (1) is globally asymptotically stable.

Simulation results of the model

In the Figure 2 below, we have reduced the treatment rate of both VL infected and PKDL infected humans, in the sense that we have used drugs other than sodium stibogluconate (expensive medicine) or that the hospital is far away or that the case is not properly diagnosed leading to wrong treatment. No mass awareness program is lunched for vector control. Taking \( y_1 = 0.023, \ a = 0.2856 \) (normal); and \( a_2 = 0.064 \).
The graph shows that it takes long time to eradicate the diseases.

In Figure 3 we have increased the treatment rate for both V1 and PKDL and also a proper arrangement for vector control. Taking $\gamma_v=0.5$, $\gamma_c=0.4$, biting of sandfly $a=0.1856$ medicine effectiveness $a=0.74$. The graph shows that with in short time the disease can be eradicated.

**Conclusion**

In this work a mathematical model of leishmania transmission was presented. The novelty of the model is the homogenous mixing of human, reservoir and vector. The basic reproduction number $R_0$ so calculated, depends upon the density of human, vectors and reservoirs, which highlights the importance of homogenous mixing. $R_0$ is most sensitive to $a$; $b$ and $c$ and can have value greater than 1 (endemic state), if $a$; sand y biting rate, $b$; transmission probability of either strain in reservoir from sand y and $c$, transmission probability of either strain in sand y from reservoir, were not controlled. For this, different measures to control phlebotomine sandflies, like residual spraying of dwellings and animal shelters, insecticide treated nets; application of repellents/ insecticides to skin or to fabrics and impregnated dog collars may be taken. Sand y is susceptible to all the major insecticidal groups. In ZVL foci, where dogs are the unique domestic reservoir, a reduction in Leishmania transmission would be expected if we could combine an effective mass treatment of infected dogs with a protection of both healthy and infected dogs from the sand y bites. Since sand y can up to the range of 1km, so leishmania transmission in dogs can be controlled, if they were kept away at least by 1km, from villages and cities. The disease can be controlled in human within a short time, however in reservoir class; the disease control takes long time. It is suggested to cull PCR+ dogs; this strategy gives imminent results in disease control.

**References**