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Study on the Threshold Conditions for Infection of *Visceral Leishmaniasis*

M. ZAMIR, R. SULTANA[++]*, R. ALI**, W. A. PANHWAR*, S. KUMAR*

Department of Mathematics, University of Science and Technology, Bannu, Khyber Pakhtunkhwa, Pakistan

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In this work, we have focused on the transmission dynamics of visceral strains of leishmania, by using mathematical model that includes human, reservoir and vector population. Threshold conditions for persistence of infection are obtained using Routh-Hurwitz criteria and Next generation method. Both the thresholds conditions agree on the same parameters. The biological sense of threshold is discussed and found meaningful. At the end results of numerical simulation are given, which shows that the disease is eradicable and the infected classes are inter-dependent. Simulation also shows the effect of treatment.

Keywords: Leishmaniasis, Basic reproductive number, Mathematical model, Routh-Hurwitz criteria.

1. INTRODUCTION

Visceral leishmaniasis is a vector-borne disease of humans and other mammals. This disease is caused by parasites of the *Leishmania donovani c*omplex. There are two main forms of visceral leishmania: (1) zoonotic visceral leishmaniasis (ZVL), which affects mainly young children and the domestic dog as its principal reservoir and (2) anthroponotic *visceral leishmaniasis* (AVL), this affects people of all ages, and infectious sandfly transmit it from human to human via biting. There are an estimated 0.5 million cases of visceral leishmaniasis per year, concentrated in India, Nepal, Bangladesh, Sudan and Brazil. Both the forms are important public health problems (Molina *at al.,* 2003). Some of the patients of Vl develops Post kala-Azar dermal *leishmania* with in the interval of 6 months to 3 years (Lowth 2014). No doubt *leishmania* control is challenging because the control of both sandflies and the reservoir is difficult. 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 (Porrozzi *at al.,* 2004). Inspiring from (Fialho *at al.,* 1995, Coutinho *et al.,* 2005), in this paper, we present a mathematical model for the transmission dynamic of visceral leishmaniasis. Threshold conditions for transmission are calculated by different methods. The threshold so calculated is biologically analyzed, and is found meaningful. Numerical simulations regarding the inter-dependence of infected classes and effect of treatment rate are presented.

2. MODEL FORMULATION

The human population consists of sub-classes, S_h, I_1, R. S_h represent the class of susceptible human, I_t is the human class infectious with V_L and R is the recovered class. The total human population N_h is, $N_h(t) = S_h(t) + I_1(t)$ The vector population is divided into two sub-classes $S_v(t)$ and $I_v(t)$, also the reservoir class is divided into $S_r(t)$ and $I_r(t)$ so that

$$N_v(t) = S_v(t) + I_v(t), \qquad N_r(t) = S_r(t) + I_r(t)$$

After susceptible persons, being bitten by infectious vectors, they move to the compartment I_1 at the rate λ_h. The infected humans are treated at the rate γ_1, with effective medicine of effect rate σ, the rest die with the disease at the rate δ_1. The humans recovered from the disease move to the compartment R at the rate $\gamma_1\sigma$. The susceptible reservoirs after contact with infected sand flies get infected at the rate λ_r and move to the compartment I_r. The sandflies are recruited to the susceptible class at the rate Γ_v. Sandflies contact both infected reservoirs and humans and get infected at the rate λ_v.

The terms of interaction λ_h, λ_r and λ_v are as under $\lambda_h = \frac{ab_2 I_v}{N_h+N_r}$ is the average rate of infection of human with Vl from infected sand fly.

$\lambda_r = \frac{ab\, I_v}{N_h+N_r}$ is the average rate of infection of reservoir from infected sand fly, and b is the transmission probability of Vl to reservoir from sand fly.

$\lambda_v = \frac{a}{N_h+N_r}(c_2 I_1 + cI_r)$ is the average rate of infection of sand fly with Vl from human/reservoir.

It is to be noted that both sandfly and reservoir never die with infection but the natural death.

[++]Corresponding author E-mail: Email : riffatumer@hotmail.com

*Department of Zoology, University of Sindh Jamshoro, Sindh, Pakistan

**Department of Mathematics, University of Malakand Lower dir, KPK, Pakistan

3. THRESHOLD CONDITIONS FOR INFECTION:

The interaction of human, reservoir and vector population is represented in the flowchart as shown in **(Fig..1).**

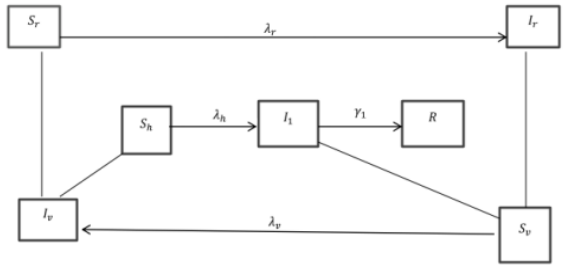

Figure 1: flow chart

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

$$\begin{cases} \dot{S}_h = \Gamma_h - (\lambda_h + \mu_h)S_h \\ \dot{I}_1 = \lambda_h S_h - (\gamma_1\sigma + \delta_1 + \mu_h)I_1 \\ \dot{R} = (\gamma_1\sigma)I_1 - \mu_h R \\ \dot{S}_r = \Gamma_r - \lambda_r S_r - \mu_r S_r \\ \dot{I}_r = \lambda_r S_r - \mu_r I_r \\ \dot{S}_v = \Gamma_v - \lambda_v S_v - \mu_v S_v \\ \dot{I}_v = \lambda_v S_v - \mu_v I_v. \end{cases} \quad (1)$$

The description of the parameters are given in table below.

Notation	Parameter definition	Value	Resource
Γ_h	Recruitment rate of human	$0.0015875day^{-1}$	[6]
Γ_r	Recruitment rate of reservoir	$0.073day^{-1}$	Assumed
Γ_v	Recruitment rate of sandfly	$0.299day^{-1}$	[7]
μ_h	Natural mortality rate of human	$0.00004day^{-1}$	[7]
μ_r	Natural mortality rate of Reservoirs	$0.00274day^{-1}$	Assumed
μ_v	Natural mortality rate of Sandflies	$0.189day^{-1}$	[7]
a	Sandflies biting rate	$0.2856day^{-1}$	[8]
γ_1	Treatment rate of VL	$0.03day^{-1}$	Assumed
δ_1	VL induced death rate	$0.011day^{-1}$	[9]
σ	effectiveness of medicine	0.64	Assumed
c_2	Progression rate of VL in sandfly(from human)	0.22	[12]
b_2	Progression rate of VL in human (from sandfly)	$0.0714day^{-1}$	[11]
c	Progression rate of Vl in sandfly(from reservoir)	Variable	Variable
b	Progression rate of Vl in reservoir(from sandfly)	Variable	Variable

4. THRESHOLD CONDITIONS FOR INFECTION:

4.1. 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 (Deikmann *at al.*, 1990). In order to find the basic reproductive number, we use next generation method as given by (Lainson *et al.*, 1987, Sundar *et al.*, 2001, Zaman *at al.*, 2012).

$$R_0 = \rho(FV^{-1})$$

Where ρ is spectral radius.
Here

$$f = \begin{pmatrix} f_1 \\ f_2 \\ f_3 \end{pmatrix} = \begin{pmatrix} \lambda_h S_h \\ \lambda_r S_r \\ \lambda_v S_v \end{pmatrix}$$

where f_1, f_2 , f_3 are the entries coming into the infected classes I_1, I_r , I_v only from susceptible classes S_h, S_r , S_v .And

$$F = \begin{pmatrix} \frac{\delta f_1}{\delta I_1} & \frac{\delta f_1}{\delta I_r} & \frac{\delta f_1}{\delta I_v} \\ \frac{\delta f_2}{\delta I_1} & \frac{\delta f_2}{\delta I_r} & \frac{\delta f_2}{\delta I_v} \\ \frac{\delta f_3}{\delta I_1} & \frac{\delta f_3}{\delta I_r} & \frac{\delta f_3}{\delta I_v} \end{pmatrix} = \begin{pmatrix} 0 & 0 & m_1 \\ 0 & 0 & m_2 \\ m_3 & m_4 & 0 \end{pmatrix}$$

Similarly

$$V = \begin{pmatrix} \frac{\delta v_1}{\delta I_1} & \frac{\delta v_1}{\delta I_r} & \frac{\delta v_1}{\delta I_v} \\ \frac{\delta v_2}{\delta I_1} & \frac{\delta v_2}{\delta I_r} & \frac{\delta v_2}{\delta I_v} \\ \frac{\delta v_3}{\delta I_1} & \frac{\delta v_3}{\delta I_r} & \frac{\delta v_3}{\delta I_v} \end{pmatrix} = \begin{pmatrix} -a_1 & 0 & 0 \\ 0 & -\mu_r & m_2 \\ m_3 & m_4 & -\mu_v \end{pmatrix}$$

Where v_1 denote the sum of entries coming in or going out of the infected class I_1, excluding those coming from susceptible class. Similarly v_2 and v_3 denote the sum of entries coming in or going out of the infected classes I_r and I_V excluding those coming from susceptible classes.

The dominant Eigen value of $(-FV^{-1})$ is

$$\left[\frac{m_2 m_4}{\mu_v \mu_v} + \frac{m_1 m_3}{a_1 \mu_v}\right]^{\frac{1}{2}}$$

So

$$R_0 = \left[\frac{m_2 m_4}{\mu_v \mu_v} + \frac{m_1 m_3}{a_1 \mu_v}\right]^{\frac{1}{2}}$$

$$m_1 = ab_2 \frac{\Gamma_h \mu_r}{\mu_r \Gamma_h + \mu_h \Gamma_r},\ m_2 = ab \frac{\Gamma_r \mu_h}{\mu_r \Gamma_h + \mu_h \Gamma_r},\ m_3 = ac_2 \frac{\mu_r \mu_h \Gamma_v}{\mu_v(\mu_r \Gamma_h + \mu_h \Gamma_r)}$$

$$m_4 = = ac \frac{\mu_r \mu_h \Gamma_v}{\mu_v(\mu_r \Gamma_h + \mu_h \Gamma_r)} \quad a_1 = \gamma_1 + \delta_1 + \mu_h$$

And at disease free equilibrium

$$S_h = \frac{\Gamma_h}{\mu_h} = N_h, S_r = \frac{\Gamma_r}{\mu_r} = N_r, S_v = \frac{\Gamma_v}{\mu_v} = N_v$$

4.2. THRESHOLD CONDITIONS USING STABILITY ANALYSIS, ROUTH-HURWITZ CRITERIA:

Let M be the jacobian matrix of the infected class of model (1). Then

$$M = \begin{pmatrix} \frac{\delta I_1}{\delta I_1} & \frac{\delta I_1}{\delta I_r} & \frac{\delta I_1}{\delta I_v} \\ \frac{\delta I_r}{\delta I_1} & \frac{\delta I_r}{\delta I_r} & \frac{\delta I_r}{\delta I_v} \\ \frac{\delta I_v}{\delta I_1} & \frac{\delta I_v}{\delta I_r} & \frac{\delta I_v}{\delta I_v} \end{pmatrix} = \begin{pmatrix} -a_1 & 0 & m_1 \\ 0 & -\mu_r & m_2 \\ m_3 & m_4 & -\mu_v \end{pmatrix}$$

The characteristic equation of M is

$\det(M - \lambda I = 0)$

$\Longrightarrow A_0 \lambda^3 + A_1 \lambda^2 + A_2 \lambda + A_3 = 0$

Where

$A_0 = 1, \quad A_1 = \mu_v + \mu_{r+} a_1$,

$A_2 = a_1 \mu_r + a_1 \mu_v + \mu_v \mu_r - m_1 m_3 - m_2 m_4$,

$A_3 = a_1 \mu_v \mu_r - m_1 m_3 \mu_r - a_1 m_2 m_4$

According to Routh-Hurwitz criteria the disease free equilibrium is stable if;

A_1, A_2, A_3 *are greater than zero,*

$A_1 A_2 - A_3 > 0$ *and* $A_3(A_1 A_2 - A_3) > 0$

Here

$A_1 A_2 = a_1((\mu_r + \mu_v)^2 + \mu_v)\mu_r\ D_2 + D_3 + D_1 > D_1 = A_3$

Where

$D_1 = a_1 \mu_v \mu_r - m_1 m_3 \mu_r - a_1 m_2 m_4$,

$D_2 = \mu_v \mu_r - m_1 m_3 - m_2 m_4$,

$D_3 = {a_1}^2 \mu_v \mu_r - a_1 m_1 m_3 \mu_r - \mu_r m_2 m_4$

Since $D_1 < D_2 < D_3$ so if $D_1 > 0$ then both D_2 and D_3 are greater than zero.

Hence all the conditions of Routh-Hurwitz criteria hold only if

$$D_1 = a_1 \mu_v \mu_r - m_1 m_3 \mu_r - a_1 m_2 m_4 > 0$$

$$\Longrightarrow \frac{m_2 m_4}{\mu_v \mu_v} + \frac{m_1 m_3}{a_1 \mu_v} < 1$$

Thus the disease free equilibrium is stable only if

$$\Longrightarrow \frac{m_2 m_4}{\mu_v \mu_v} + \frac{m_1 m_3}{a_1 \mu_v} < 1 \qquad (2)$$

If condition (2) does not hold then non-trivial equilibrium is globally stable and trivial equilibrium is unstable.

4.3 THE BIOLOGICAL SENSE OF THRESHOLD CONDITION:

Sandfly interact both with human and reservoir and all the three species can have one of the two states at a time, susceptible or infectious. Accordingly four cases arises.

Case (1); Human and sandfly interaction, when human is susceptible and sandfly is infectious:

$$m_1 = ab_2 \frac{\Gamma_h \mu_r}{\mu_r \Gamma_h + \mu_h \Gamma_r}$$

a is biting rate of sandfly and b_2 is progression rate of V_L in human from sandfly. So the biological function of m 1 is the transmission of V_L from sandfly to human.

Case (2); Human and sandfly interaction, when sandfly is susceptible and human is infectious:

$$m_3 = ac_2 \frac{\Gamma_v \mu_r \mu_h}{\mu_v(\mu_r \Gamma_h + \mu_h \Gamma_r)}$$

a is the biting rate and c_2 is the progression rate of V_L in sandfly. So the biological function of m_3 is the transmission of V_L from human to sandfly. The combined effect of case (1) and case (2) is equivalent to a single term $\frac{m_1 m_3}{a_1 \mu_v}$ which represents the inter-transmission of V_L strains of leishmania between human and sandfly.

Similarly case (3) and case (4), represent the interaction between sandfly and reservoir. The net effect of both the cases is equivalent to a single term $\frac{m_2 m_4}{\mu_v \mu_v}$ .Which represent the inter-transmission of V_L strains of leishmania between reservoir and sandfly. Hence the threshold condition is biological meaningful.

5. RESULTS OF NUMERICAL SIMULATION

We use fourth order Runge-Kutta Method for numerical simulations and consider the time of six months, when the sandfly growth rate is at the peak. We assume the initial susceptible populations as S_0 = 20000, Sr_0 = 1000, Sv0 = 100000 and the initial infections I_1 = 8000,

Ir = 300, I_V = 50000. In fig (2), the treatment is as high as γ_1 = 0.8 and sandfly biting rate
a = 0.2856. In fig (3), biting rate is the same but we have decreased the treatment rate as γ_1 = 0.2. In fig (4), γ_1 = 0.2 but we have decreased the biting rate as a = 0.0856.In fig (5), biting rate a = 0.2856 and the treatment rate γ_1 = 0.03.

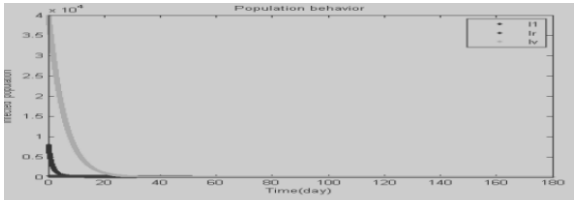

Figure 2: High treatment rate and max biting rate

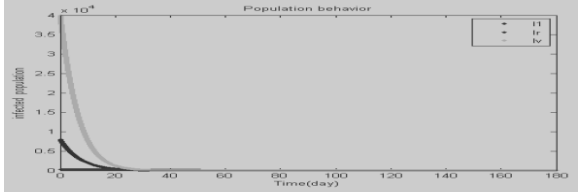

Figure 3: medium treatment rate and max biting rate

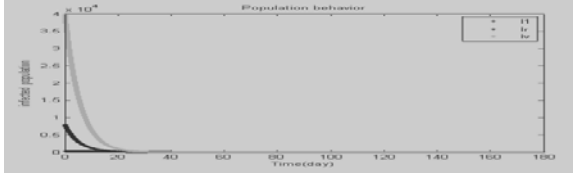

Figure 4: medium treatment rate and low biting rate

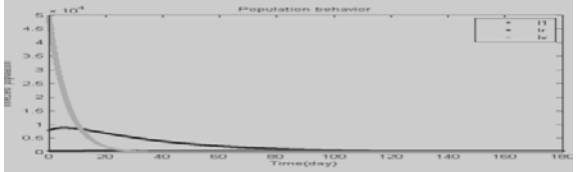

Figure 5: low treatment rate and high biting rate

6. CONCLUSION

The threshold conditions so found contain the same parameters relating to the transmission dynamics of I_r, I_v *and* I_1 So the endemic establishment threshold conditions depend upon the dynamic transmission of all the infected classes. Numerical simulations show that all the infected classes are interrelated, increase or decrease in any infected class, and effects other infected classes. It is important to note that treatment of infected human causes decrease in both, the infected classes of vector and reservoir. Though the treatment is expensive yet it leads to disease Free State earlier than by other tools. The disease is eradicable. The value of Threshold in all the above cases is less than one, so the disease Free State is stable. Inhibition effect due to mass alertness and behavioral changes in human can be included as future work.

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