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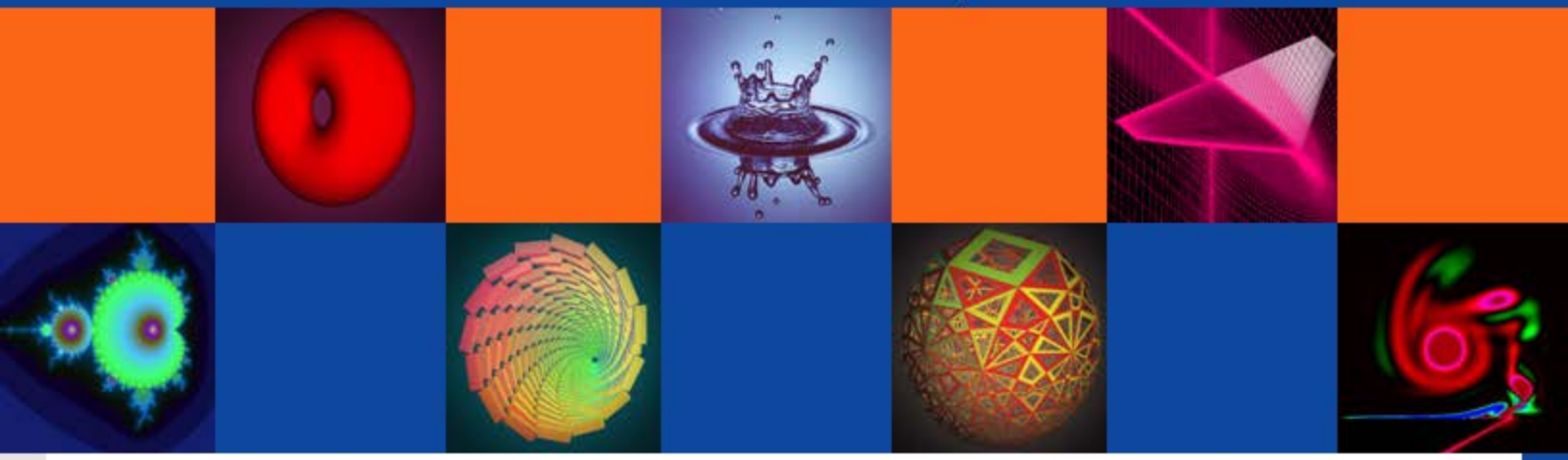

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Abstract

Visceral Leishmaniasis (VL) is a potentially fatal disease caused by the protozoan parasite *Leishmania donovani*. This disease is a health problem for the very poor because it results in thousands of deaths and illnesses every year. Some countries, such as India and Bangladesh, have started programs to reduce the occurrences of VL by focusing on early diagnosis and complete treatment of VL. Post-Kala-azar Dermal Leishmaniasis (PKDL) is a cutaneous manifestation of Leishmaniasis that can occur following the incomplete treatment of VL. Some treatments for PKDL are available such as intravenous Stibogluconate and oral Miltefosine. This study develops a mathematical model of the relationship between the level of PKDL treatment and the incidences of VL during a given period. The results indicate a nearly linear relationship between PKDL treatment rates and the percent reduction of VL incidences. With the current treatments available and considering achievable levels of treatment, the model predicts that up to 20% of VL cases could be prevented by treating new PKDL cases. Hypothetical combined treatment initiatives including bed nets and insecticide spraying are also considered. Results suggest that the population of individuals with Post Kala-azar Dermal Leishmaniasis is certainly a significant factor in the transmission of *L. donovani* infection and treatment should be pursued at the highest level sustainable with particular focus on treating new cases.

Introduction

Visceral Leishmaniasis (VL), also known as Kala-azar, is a fatal disease caused by the *Leishmania donovani* protozoan parasite and is characterized by fever, weight loss, hepatosplenomegaly, and pancytopenia[9]. The parasite is transmitted by the bite of the vector *Phlebotomus argentipes*, commonly known as the sandfly. For the model presented herein, animals are not considered a significant reservoir in India[34]. VL is a health problem among the very poor; 90% of VL cases arise in Bangladesh, Nepal, Sudan, and India, where the disease is dire in the eastern and more rural parts of the country, causing the deaths of thousands and the severe sickening of hundreds of thousands every year[9]. Post-Kala-azar Dermal Leishmaniasis (PKDL) is a cutaneous manifestation of Leishmaniasis following treatment of VL, characterized by skin lesions and nodules or papules which are often to be found on the face[12]. PKDL is not a

life threatening disease and the treatment of this disease is considered to be a burden by many of the affected. For example, in Bangladesh, current treatment guidelines call for 120 intramuscular injections of sodium Stibogluconate. Hence, many patients remain undiagnosed and untreated[1].

In India, humans are considered the primary reservoir for the *L. donovani* parasite due to the high population density making the transmission from human to human via sandflies (anthroponosis) common. According to the American Society for Microbiology, the promastigote form of *L. donovani* is transmitted into the skin by female phlebotomine sandflies. Once transmitted, the parasites are internalized by dendritic cells and macrophages in the dermis where they lose their flagella, transforming into the amastigote form. The amastigotes multiply, destroy the host cell and infect other phagocytic cells. The amastigotes disseminate through the lymphatic and vascular systems, eventually infiltrating the bone marrow, liver and spleen[3]. Similar to India, a major reservoir in Sudan for the parasite is in humans; however, the findings of infected flies in the uninhabited Dinder Park strongly suggest the presence of a reservoir other than man. *L. donovani* has been detected in dogs and some other animals including livestock[13].

In 2005, the Indian, Nepalese, and Bengali governments initiated a plan to reduce the occurrence of VL to less than 0.01% by 2015. They planned to do this by focusing on early diagnosis and complete treatment (treatment-related control strategies) and spraying insecticides in homes (vector-related control strategy)[1]. Four drugs are available to treat VL. These drugs include pentavalent antimonials, which have been the "first-line" treatment for 70 years, but are said to be toxic and accompanied by failure rates due to drug resistance; Miltefosine, which is the first oral treatment against VL, but is said to lead to resistance because of its long half-life; Amphotericin B, used in conventional and liposomal formulations, yet too expensive and complex to be used on a large scale; and Paromomycin (PMM), which is currently being tested in a Phase IV trial in India[1].

Diagnosis of PKDL is based on a history of VL, distribution and appearance of lesions, and by parasitological confirmation when the diagnosis is doubtful[2]. Even though there is some controversy with diagnosing and treating PKDL, some trials have been made to find better treatments. In Sudan, some patients that were diagnosed with PKDL underwent treatment with intravenous sodium stibogluconate[12]. The result of the study showed a complete disappearance of any indication of PKDL. Treatment with intravenous sodium stibogluconate varied among patients due to their reaction or prior diseases. Some patients were treated as planned for 30 days and were healed, some patients needed to be treated with ketoconazole for 30 days and then put back on treatment with sodium stibogluconate before they were healed, and for some patients, even after being returned to regular treatment received a higher dose of the treatment[12]. Another study was reported with a 26 year old Ethiopian man (patient 1) and a 42 year old Ethiopian man (patient 2). Both patients were given treatment options: intravenous sodium stibogluconate or oral miltefosine. The patients chose to try miltefosine. Patient 1 was cured after six months of treatment with side effects during the elapsed time. Patient 2 was cured after three months of treatment with no experienced side effects[4]. This was the first reported use of miltefosine in the treatment of PKDL; according to Belay et al. (2006) "Miltefosine appears to be a promising

treatment for PKDL, and its use in this context merits further investigation" (226). These treatments of PKDL can serve to reduce the reservoir for the VL disease.

In this study, we will use a dynamical system model to investigate the question: What is the relationship between VL incidence during a given period and the level of PKDL treatment during the same period? We assume that the infection reaches an endemic state and define the proportion of PKDL cases treated as the ratio of PKDL cases treated to the incidences of PKDL over the time period. VL has a SIRS infection cycle structure in hosts, since recovery confers temporary immunity, with some recovered hosts spontaneously developing PKDL. Vectors undergo an SEI cycle with a significant latent period during which the parasite reproduces in the gut. Due to elapsed time for the parasite to grow in the gut and be transmitted, in addition to the SIR model, a vector category will include an exposed (E) vector category.

Mathematical Model

The model's dynamics are based on the epidemiologically pertinent stages of the disease. Diagnostically the stages of VL can be separated by corresponding levels of parasitemia[1]. The model is compartmentalized into five human classes and three classes of sandflies listed in Table 1 related to *L. donovani* infection as summarized in the flow chart (Fig 1). The flow chart reflects the natural cycle of the disease with the arrows between each state variable representing per capita rates of transition between categories. Spontaneous development of PKDL by asymptomatic individuals was neglected from the model because the reported incidences are insignificantly low.

The model is a system of ordinary differential equations with one equation representing each class or state variable. Each transition rate from the flow chart represents a term in the respective equations. Though India is experiencing roughly exponential growth, birth rates into the susceptible classes are represented as constant rates[14]. This simplifying assumption is made since the time period to be simulated is short and to allow the system to reach an endemic equilibrium at which the efficacy of PKDL treatment can be evaluated. A synthetic birth rate also allows maintenance of a realistic fly to human density ratio and provides conditions consistent with vector dependent transmission as indicated by the literature[15]. The infection rates were developed assuming that the transmission of the disease is dependent on the density of the sandfly population and not the human population[15]. Thus the terms are a product of the contact rate (c), probability of infection per contact ($\beta_V, \sigma_A, \sigma_P, \sigma_S$), density of sandflies involved for the respective transmission (susceptible or infected), and the proportion of humans in the state variable involved. The rate of PKDL treatment (ψ) is a parameter varied in the numerical simulations. The other simple per capita rates ($\omega, \theta, \gamma, \phi, \rho$) are derived as the inverse of the average time spent in a state before the respective transition or as the product of the inverse of the average time spent in a state regardless of the transition out and the fraction of individuals in that state who will make that particular transition.

The last three equations ($\frac{dT}{dz}, \frac{dZ}{dt}, \& \frac{dV}{dt}$) are used for tallying the number of cases of PKDL treated (**T**), the new incidences of PKDL (Z), and the new incidences of VL (V) respectively. Totaling the number of new VL cases and the proportion of new PKDL cases treated over the simulated time period allows for evaluation of a relationship between the cases treated and VL incidences prevented as presented in the results section.

State Variables	Definition
S	Susceptible human
I_S	Infected Symptomatic VL
I_A	Infected Asymptomatic VL
R	Recovered
P	Infected with PKDL
S_V	Susceptible vectors
E_V	Exposed vectors
I_V	Infected vectors

Table 1. Human and sandfly state variables

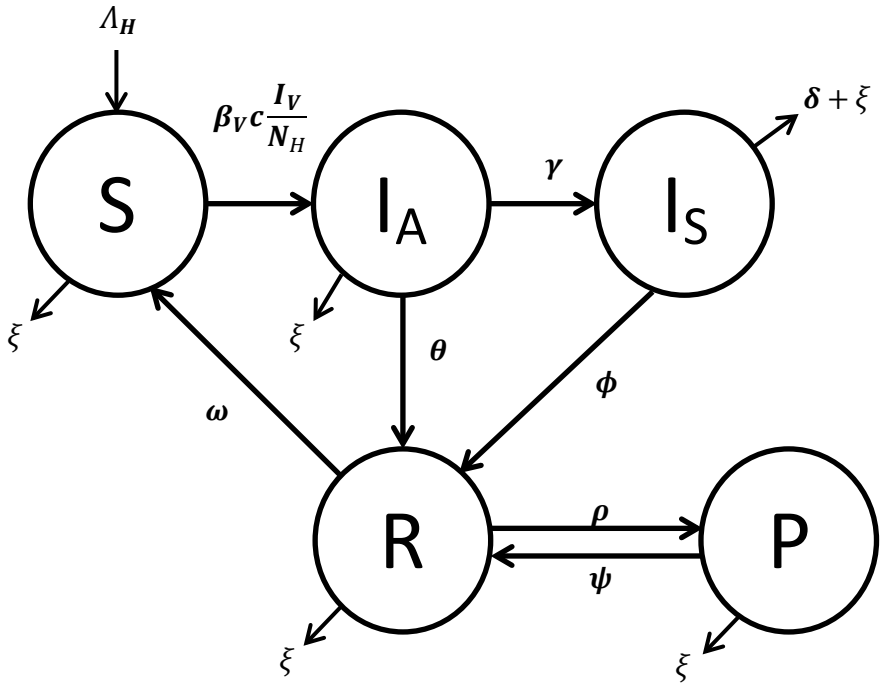

Figure 1. Flow chart depicting five state variables relating to *L. donovani* transmission.

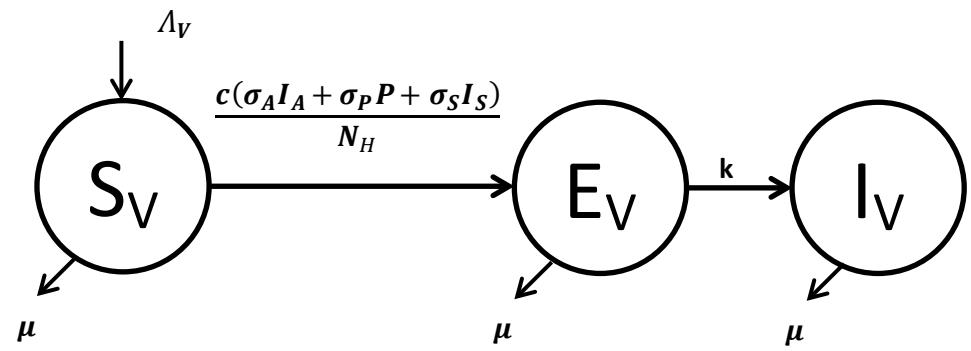

Figure 2- Flow chart depicting vectors in three state variables.

$$\frac{dS}{dt} = R_H + \omega R - S(\beta_V c \frac{I_V}{N_H} - \xi) \quad (1)$$

$$\frac{dI_A}{dt} = S\beta_V c \frac{I_V}{N_H} - I_A(\theta - \gamma) - \xi I_A \quad (2)$$

$$\frac{dI_S}{dt} = \gamma I_A - I_S(\phi - (\delta + \xi)) \quad (3)$$

$$\frac{dR}{dt} = \theta I_A + \phi I_S + \psi P - R(\omega - \rho - \xi) \quad (4)$$

$$\frac{dP}{dt} = \rho R - P(\psi - \xi) \quad (5)$$

$$\frac{dS_V}{dt} = R_V - c(\sigma_A I_A + \sigma_P P + \sigma_S I_S)\frac{S_V}{N_H} - \mu S_V \quad (6)$$

$$\frac{dE_V}{dt} = c(\sigma_A I_A + \sigma_P P + \sigma_S I_S)\frac{S_V}{N_H} - E_V(k - \mu) \quad (7)$$

$$\frac{dI_V}{dt} = kE_V - \mu I_V \quad (8)$$

$$\frac{dT}{dt} = \psi P \quad (9)$$

$$\frac{dZ}{dt} = \rho R \quad (10)$$

$$\frac{dV}{dt} = \gamma I_A \quad (11)$$

Parameters	Definition	Units	Est. Value	Source
ξ	Natural death rate for humans	$\frac{1}{\text{day}}$	0.0079	26
Λ_H	Reproductive rate of humans	$\frac{1}{day}$	0.0309	26
N_H	Population density of Bihar, India	$\frac{Humans}{sq.km}$	1102.39	33
γ	Rate of progression from asymptomatic to symptomatic	$\frac{1}{day}$	0.0006	6
θ	Spontaneous recovery from asymptomatic	$\frac{1}{day}$	0.0139	30, 31, Estimated by Stauch et al.
ϕ	Rate of recovery with treatment for VL	$\frac{1}{day}$	0.0306	32, Estimated by Stauch et al.
ρ	Rate of development to PKDL	$\frac{1}{day}$	0.0028	20
ω	Loss of immunity	$\frac{1}{day}$	0.0135	1
ψ	Rate of treatment of PDKL	$\frac{1}{day}$	98.1%	17
δ	Death rate due to VL (*with treatment)	$\frac{1}{day}$	13%	16
Λ_V	Reproductive rate of vectors	$\frac{1}{day}$	195.6003	24,25
N_V	Relative Density of Female Sandflies	$\frac{Flies}{sq.km}$	987.63	24, 25, Estimated by Stauch et al.
σ_A	Probability of sandflies becoming infected after biting asymptomatic VL infected human.		0.01458	1
σ_P	Probability of sandflies of PKDL infected humans		1	Assumed
σ_S	Relative infectivity of symptomatic VL infected humans		1	Assumed
μ	Natural death rate of vectors	$\frac{1}{day}$	0.0714	21
K	Rate of becoming infectious after exposure	$\frac{1}{day}$	0.2	22
c	Biting rate of flies	$\frac{1}{day}$	0.25	23
β_V	Infectivity of vectors	$\frac{1}{day}$	1	Assumed
	Ratio of sandflies to humans		527:100	Estimated by Stauch et al.

Table 2. State variables and estimates of current values in the study area

Table 2 summarizes the model parameters and their estimated values (for further details see the appendix).

Analysis

Disease-Free Equilibrium

We first consider the two disease-free classes, which are the susceptible human (S) and susceptible vector (S_V) classes, along with the total human population N_H and total sandfly population N_V.

$$\frac{dS}{dt} = \Lambda_H + \omega R - c\beta_V S\frac{I_V}{N_H} - \xi S \quad (1)$$

$$\frac{dS_V}{dt} = \Lambda_V - c(\sigma_A I_A + \sigma_P P + \sigma_S I_S)\frac{S_V}{N_H} - \mu S_V \quad (7)$$

$$N_H = S + I_A + I_S + R + P \quad (13)$$

$$N_V = S_V + E_V + I_V \quad (14)$$

At the disease-free equilibrium all non-susceptible classes will have zero as their value ($I_A = I_S = R = P = E_V = I_V = 0$). Solving for S and S_V gives us the following equilibrium.

$$S = \frac{\Lambda_H}{\xi} \quad (15)$$

$$S_V = \frac{\Lambda_V}{\mu}$$

These two expressions also represent the equilibrium values of the total populations N_H and N_V respectively.

Finding R_C using Next Generation Operator

The control reproductive number R_c provides a measure of the persistence of *L. donovani* infection or lack thereof, with a theoretical PKDL treatment rate in the model. By evaluating at the disease-free equilibrium it can be determined whether transmission of the infection will be sustained when the number of infected individuals is close to zero. This condition is equivalent to the infection persisting at some endemic level in the population. When the value of R_c is 1 or greater the infection will persist in the population.

To find the R_c value, we used the Next Generation Operator, or NGO. The NGO reduces the dimension of the calculation down to just the number of infectious classes. In this case, we were able to reduce a size eight matrix to a size four square matrix. We started by finding the equilibrium of the two infected noninfectious classes, which are the recovering class of human R and exposed class of vectors E_V in term of the susceptible and infected classes. To find the equilibrium for these two classes, we performed the same steps as we did for the disease-free equilibrium previously.

$$\theta I_A + \phi I_S + \psi P - \omega R - \rho R - \xi R = \frac{dR}{dt} = 0$$

$$\rightarrow R = \frac{\psi P + \theta I_A + \phi I_S}{(\xi + \rho + \omega)}$$

$$c(\sigma_A I_A + \sigma_P P + \sigma_S I_S)\frac{S_V}{N_H} - kE_V - \mu E_V = \frac{dE_V}{dt} = 0$$

$$\rightarrow E_V = \frac{cS_V(\xi + \rho + \omega)(\sigma_A I_A + \sigma_P P + \sigma_S I_S)}{((S + P + I_A + I_S)(\xi + \rho + \omega) + I_A\theta + I_S\phi + P\psi)(k + \mu)}$$

These expressions for R and E_V in terms of other variables will be substituted into the four infectious infected equations, which are $I_A, I_A, P,$ and I_V. These are the equations which drive the transmission of the disease. Also, (13) was substituted for N_H for the purpose of taking derivatives because it contains state variables, which is essential to the next step.

$$\frac{dI_A}{dt} = \frac{I_V c\beta_V S}{\left(S + I_A + I_S + \left(\frac{\psi P + \theta I_A + \phi I_S}{(\xi + \rho + \omega)}\right) + P\right)} - I_A(\theta + \gamma + \xi)$$

$$\frac{dI_S}{dt} = \gamma I_A - (\phi + \delta + \xi)I_S$$

$$\frac{dP}{dt} = \rho\left(\frac{\psi P + \theta I_A + \phi I_S}{(\xi + \rho + \omega)}\right) - P(\xi + \psi)$$

$$\frac{dI_V}{dt} = \frac{kcS_V(\xi + \rho + \omega)(\sigma_A I_A + \sigma_P P + \sigma_S I_S)}{((S + P + I_A + I_S)(\xi + \rho + \omega) + I_A\theta + I_S\phi + P\psi)(k + \mu)} - \mu I_V$$

From the differential equations above, we solve for the subsystem Jacobian matrix (**K**) at the disease-free equilibrium found previously. Likewise, the values of $I_A, I_A, P,$ and I_V will be evaluated as zero. We then separate the matrix **K** into **K**=**M**-**D** where **M** has only non-negative terms and **D** is a diagonal Matrix with all positive terms.

$$\mathbf{K} = \begin{pmatrix} \frac{\partial}{\partial I_A}\left(\frac{dI_A}{dt}\right) & \frac{\partial}{\partial I_S}\left(\frac{dI_A}{dt}\right) & \frac{\partial}{\partial P}\left(\frac{dI_A}{dt}\right) & \frac{\partial}{\partial I_V}\left(\frac{dI_A}{dt}\right) \\ \frac{\partial}{\partial I_A}\left(\frac{dI_S}{dt}\right) & \frac{\partial}{\partial I_S}\left(\frac{dI_S}{dt}\right) & \frac{\partial}{\partial P}\left(\frac{dI_S}{dt}\right) & \frac{\partial}{\partial I_V}\left(\frac{dI_S}{dt}\right) \\ \frac{\partial}{\partial I_A}\left(\frac{dP}{dt}\right) & \frac{\partial}{\partial I_S}\left(\frac{dP}{dt}\right) & \frac{\partial}{\partial P}\left(\frac{dP}{dt}\right) & \frac{\partial}{\partial I_V}\left(\frac{dP}{dt}\right) \\ \frac{\partial}{\partial I_A}\left(\frac{dI_V}{dt}\right) & \frac{\partial}{\partial I_S}\left(\frac{dI_V}{dt}\right) & \frac{\partial}{\partial P}\left(\frac{dI_V}{dt}\right) & \frac{\partial}{\partial I_V}\left(\frac{dI_V}{dt}\right) \end{pmatrix}_{Disease-Free\ Equilibrium}$$

$$\Rightarrow \mathbf{K} = \begin{pmatrix} -(\xi+\gamma+\theta) & 0 & 0 & c\beta_V \\ \gamma & -(\xi+\delta+\phi) & 0 & 0 \\ \dfrac{\theta\rho}{\xi+\rho+\omega} & \dfrac{\phi\rho}{\xi+\rho+\omega} & -\left(\xi+\dfrac{\psi(\xi+\omega)}{\xi+\rho+\omega}\right) & 0 \\ \dfrac{kc\xi\Lambda_V\sigma_A}{\Lambda_H\mu(k+\mu)} & \dfrac{kc\xi\Lambda_V\sigma_S}{\Lambda_H\mu(k+\mu)} & \dfrac{kc\xi\Lambda_V\sigma_P}{\Lambda_H\mu(k+\mu)} & -\mu \end{pmatrix}$$

$$\Rightarrow \mathbf{M}-\mathbf{D} = \begin{pmatrix} 0 & 0 & 0 & c\beta_V \\ \gamma & 0 & 0 & 0 \\ \dfrac{\theta\rho}{\xi+\rho+\omega} & \dfrac{\phi\rho}{\xi+\rho+\omega} & 0 & 0 \\ \dfrac{kc\xi\Lambda_V\sigma_A}{\Lambda_H\mu(k+\mu)} & \dfrac{kc\xi\Lambda_V\sigma_S}{\Lambda_H\mu(k+\mu)} & \dfrac{kc\xi\Lambda_V\sigma_P}{\Lambda_H\mu(k+\mu)} & 0 \end{pmatrix} - \begin{pmatrix} \xi+\gamma+\theta & 0 & 0 & 0 \\ 0 & \xi+\delta+\phi & 0 & 0 \\ 0 & 0 & \xi+\dfrac{\psi(\xi+\omega)}{\xi+\rho+\omega} & 0 \\ 0 & 0 & 0 & \mu \end{pmatrix}$$

Finding the dominant eigenvalues of the matrix MD^{-1} will give us the control reproductive number (R_C).

$$\mathbf{MD^{-1}} = \begin{pmatrix} 0 & 0 & 0 & c\beta_V \\ \gamma & 0 & 0 & 0 \\ \dfrac{\theta\rho}{\xi+\rho+\omega} & \dfrac{\phi\rho}{\xi+\rho+\omega} & 0 & 0 \\ \dfrac{kc\xi\Lambda_V\sigma_A}{\Lambda_H\mu(k+\mu)} & \dfrac{kc\xi\Lambda_V\sigma_S}{\Lambda_H\mu(k+\mu)} & \dfrac{kc\xi\Lambda_V\sigma_P}{\Lambda_H\mu(k+\mu)} & 0 \end{pmatrix} \begin{pmatrix} \dfrac{1}{\xi+\gamma+\theta} & 0 & 0 & 0 \\ 0 & \dfrac{1}{\xi+\delta+\phi} & 0 & 0 \\ 0 & 0 & \dfrac{1}{\xi+\dfrac{\psi(\xi+\omega)}{\xi+\rho+\omega}} & 0 \\ 0 & 0 & 0 & \dfrac{1}{\mu} \end{pmatrix}$$

$$= \begin{pmatrix} 0 & 0 & 0 & \dfrac{c\beta_V}{\mu} \\ \dfrac{\gamma}{\xi+\gamma+\theta} & 0 & 0 & 0 \\ \dfrac{\theta\rho}{(\xi+\rho+\omega)(\xi+\gamma+\theta)} & \dfrac{\phi\rho}{(\xi+\rho+\omega)(\xi+\delta+\phi)} & 0 & 0 \\ \dfrac{kcS_V\sigma_A}{\Lambda_H\mu(k+\mu)(\xi+\gamma+\theta)} & \dfrac{kc\xi\Lambda_V\sigma_S}{\Lambda_H\mu(k+\mu)(\xi+\delta+\phi)} & \dfrac{kc\xi\Lambda_V\sigma_P}{\Lambda_H\mu(k+\mu)(\xi+\dfrac{\psi(\xi+\omega)}{\xi+\rho+\omega})} & 0 \end{pmatrix}$$

The dominant eigenvalue of this matrix is the control reproductive number (R_C). This matrix is used to generate R_C values during numerical simulation.

4.1 Stability Analysis.

The steps for determining the stability of the disease-free equilibrium also involve calculating a subsystem Jacobian matrix; however, this subsystem involves all 8 equations that

represent rates of change for state variables eq.(1)-eq.(8). The value of N_H and N_V will again be expanded for the purpose of taking partial derivatives. We will call this resulting matrix **J**.

$$\boldsymbol{J} = \begin{pmatrix} -\xi & 0 & 0 & \omega & 0 & 0 & 0 & -c\beta_V \\ 0 & -(\xi+\gamma+\theta) & 0 & 0 & 0 & 0 & 0 & c\beta_V \\ 0 & \gamma & -(\xi+\gamma+\phi) & 0 & 0 & 0 & 0 & 0 \\ 0 & \theta & \phi & -(\xi+\rho+\omega) & \psi & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho & -(\xi+\psi) & 0 & 0 & 0 \\ 0 & -\frac{cS_V\sigma_A}{S} & -\frac{cS_V\sigma_S}{S} & 0 & -\frac{cS_V\sigma_P}{S} & -\mu & 0 & 0 \\ 0 & \frac{cS_V\sigma_A}{S} & \frac{cS_V\sigma_S}{S} & 0 & \frac{cS_V\sigma_P}{S} & 0 & -(k+\mu) & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & k & -\mu \end{pmatrix}$$

We proceed to find all the eigenvalues for the matrix **J** because they will tell us whether the disease-free equilibrium is stable or unstable. After inputting all the parameter estimates (see Table 2), we obtained two imaginary, one positive, and five negative eigenvalues. The one positive eigenvalue is conclusive to prove instability of the disease-free equilibrium in the given scenario, suggesting the infection will not die out under current conditions.

Numerical Simulation

Simulations and graphics were produced in MATLAB version 7.0.4.365 using the built in ordinary differential equation solver ode45. Initial conditions were calculated using the prevalence for each category based on parasitemia level and population density given in Table 2. The treatment rate of PKDL varies from none to $0.0333(\text{day})^{-1}$ a rate which corresponds to an average time of seeking treatment and becoming non-infectious of 30 days. This range was chosen based on the treatment duration of PKDL which lasts 30 days so scenarios are considered in which the average time to receive treatment ranges from never(infinity) to 30 days. We realize that patients may be treated to the point of non-infectivity sooner than 30 days, however we assume 30 days to be a reasonable lower bound considering any delay in receiving treatment.

Preliminary results indicated that values of the state variables reached within one tenth of one percent of their equilibrium values within two years of simulation. All simulations presented in the results were run for two years. This condition functions well under the assumption of a constant population density since the density of Bihar is not likely to increase significantly over two years.

Scenarios with hypothetical sandfly control measures were also simulated. These simulations were performed at ψ=0.025/day which corresponds to an average time of treatment until noninfectious of 40 days. This value showed the typical dynamics of the treatment rates considered and is still an optimistic estimate, but not unreasonably so. For these simulations two parameters were varied: the contact rate(c) and the death rate of sandflies (μ). These represent varying levels of implementation of bed nets and indoor residual insecticide spraying respectively.

One measure of the level of treatment presented is the proportion of new incidences of PKDL treated over the two year simulation. This reflects a hypothetical treatment initiative where individuals who develop PKDL either seek treatment or are reexamined at regular intervals for PKDL following treatment for VL.

Results

Numerical exploration indicated that when an endemic equilibrium of the system existed it was unique.

Two series of simulations are presented. In the first series (Figures 3 through 7), the simulation is run with the treatment rate of PKDL (ψ) varying each simulation from none to $0.0333(day)^{-1}$. In the second series (Figure 8) the rate of treatment, ψ=0.025/day, is held constant, and the parameters representing the biting rate of sandflies (c) and their death rate(μ) are varied for each simulation instead.

Figures 4 and 5 represent the level of treatment as the proportion of new incidences of PKDL treated over the two year simulation. These reflect the impact of the hypothetical treatment initiative. Figures 3 and 6 represent the treatment rate as it is in the equations of the model, the per capita rate ψ.

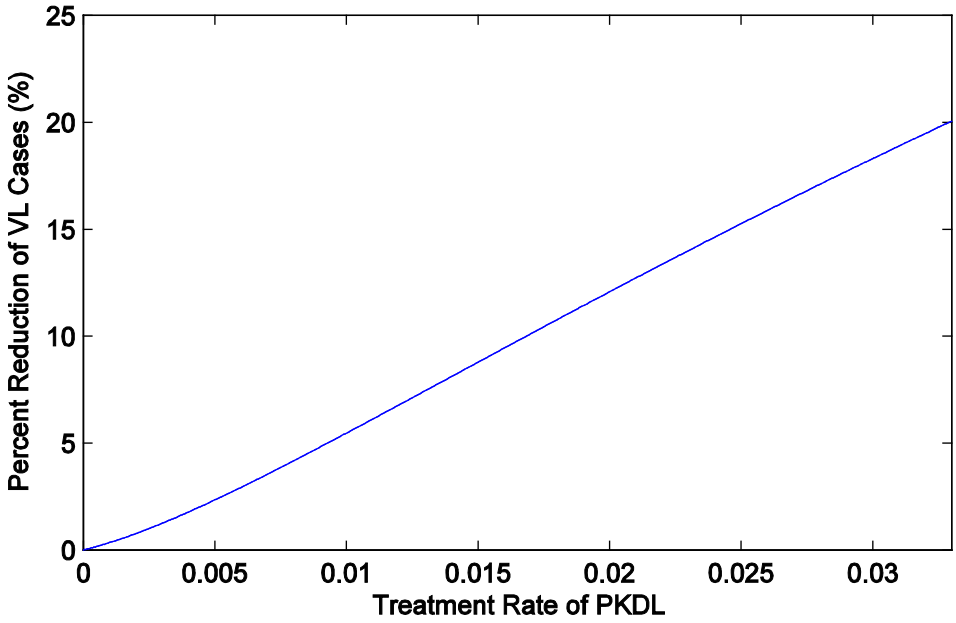

Figure 3 Treatment Rate vs Percent Reduction of VL Cases

Figure 3 graphs the treatment rate ψ against the percent reduction of total VL cases. Though this curve may appear roughly linear at these values the change in concavity is not numerical error and for a larger range of treatment rates the curve assumes a more pronounced sigmoid shape.

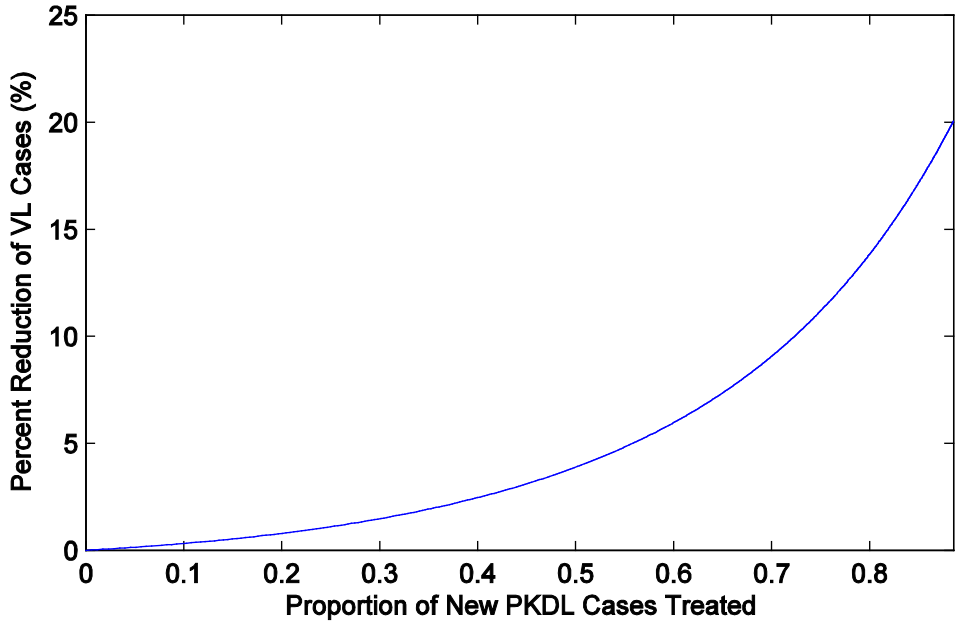

Figure 4 Proportion of PDKL Cases Treated vs Percent Reduction of VL Cases

Figure 4 shows the proportion of new PKDL cases treated plotted against the percent of total VL incidences averted over the two years (referred to as percent reduction) for each treatment level. This curve would level off at extremely high treatment rates, however for in the range of reasonable treatment rates considered the relationship is roughly exponential.

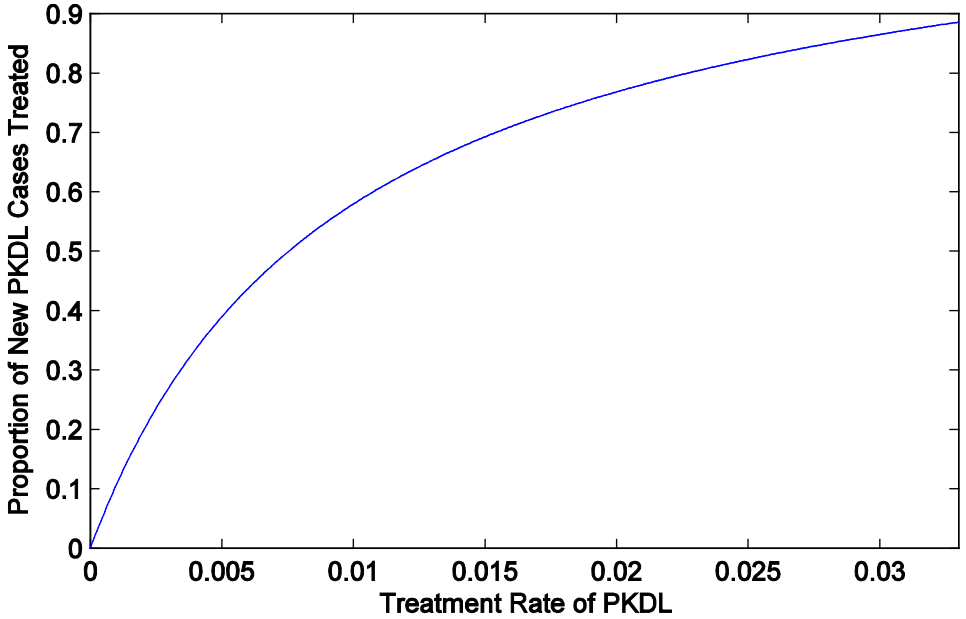

Figure 5 Proportion of PKDL Cases Treated vs Control Reproductive Number

Figure 5 plots the proportion of new incidences of PKDL cases that were treated into remission during the two year period against the control reproductive number, R_C, the value of which actually depends on the value of ψ for each simulation (see matrix $\mathbf{MD}^{-1}$).

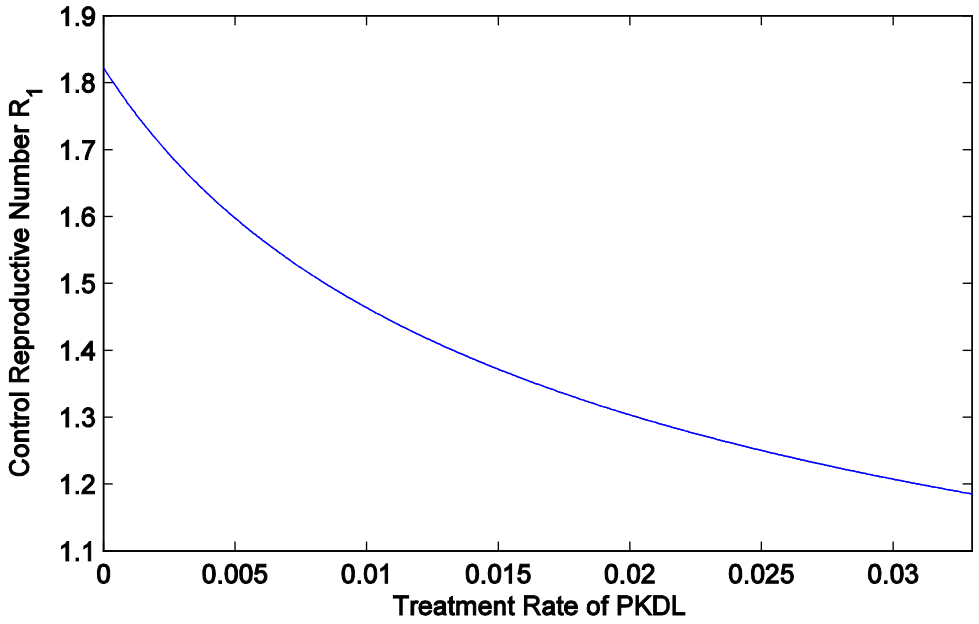

Figure 6 shows the treatment rate ψ graphed against the control reproductive number R_C. The calculation of R_C directly depends on ψ not the proportion of new PKDL cases treated (see matrix $\mathbf{MD}^{-1}$).

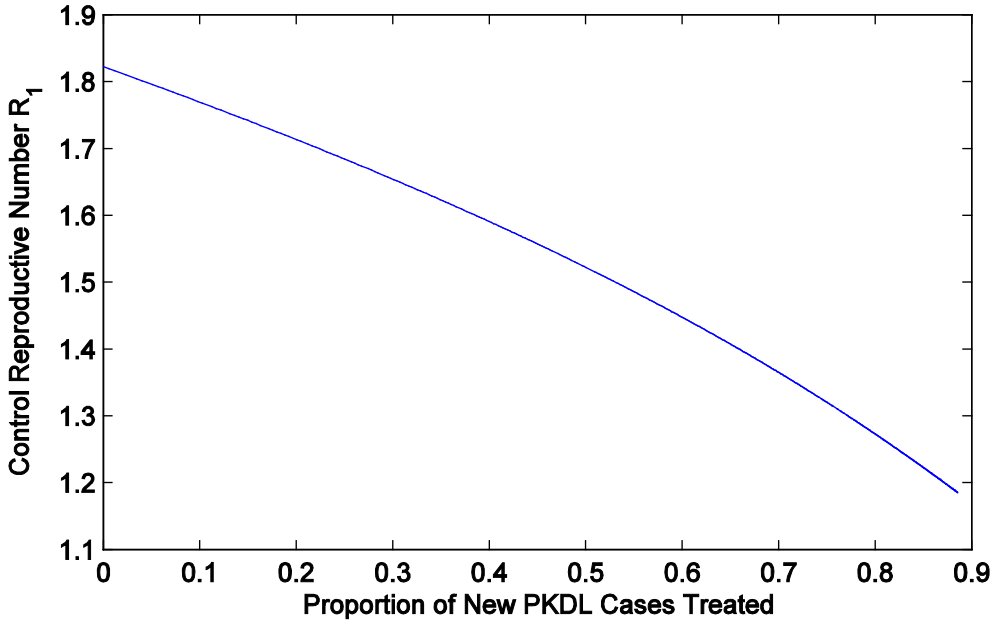

Figure 3 Treatment Rate vs Proportion of PKDL Cases Treated

Figure 7 demonstrates the effect of the treatment rate on the proportion of new PKDL cases treated.

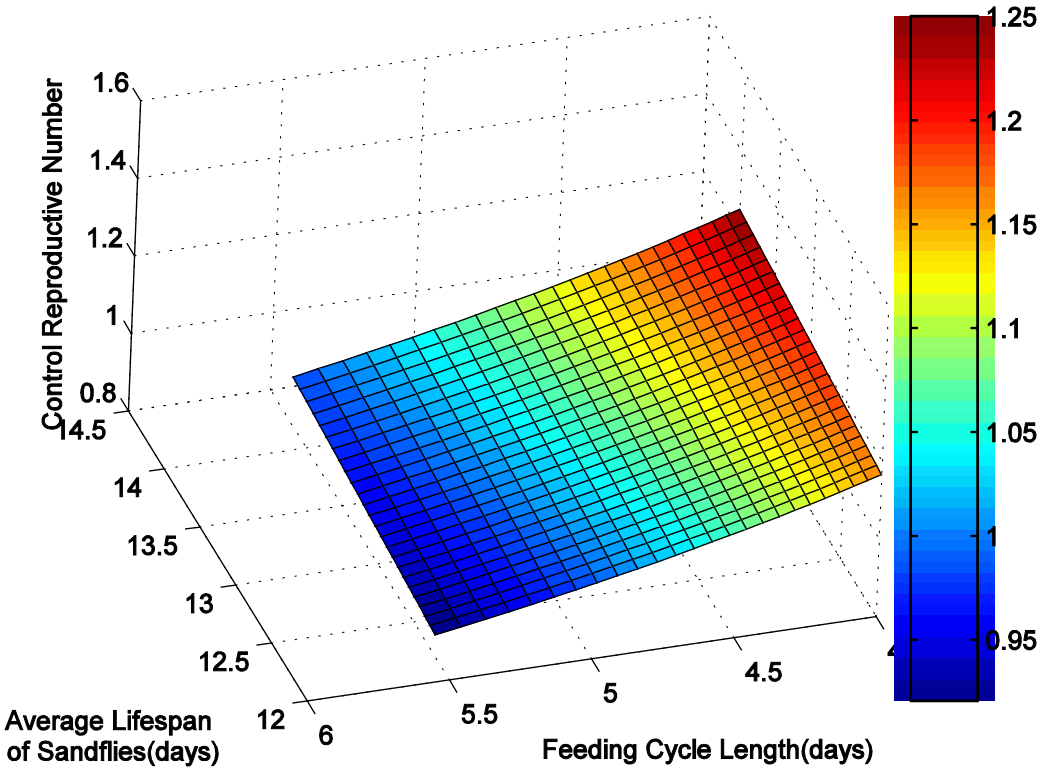

Figure 4 Effect of Sandfly Control Measures on Control Reproductive Number

Figure 8 illustrates the effect of varying rates of sandfly control measures on the value of RC. Hypothetical controls were simulated deviating from the natural values of contact rate(c) and the death rate of sandflies(μ). These values correspond to the average amount of time between bites per sandfly (feeding cycle duration) which is normally 4 days and the average lifespan of sandflies which is naturally 14 days.

In the first series of simulation a treatment rate of ψ =0.08 yielded R_C=0.9999, however this level of treatment corresponds to an average time of treatment to the point of non-infectivity of 12.5 days which not possible given current treatments considered for PKDL.

They also show based on our parameter estimates the maximum percent reduction possible assuming treatment is sought immediately after developing symptoms and takes 30 days to complete is 20.2% (figure 5). Likewise, with PKDL treatment alone the most optimistic reduction of R_C was to a value of 1.18.

In the second series the simulations of sandfly control measures (figure 8) showed that as little as a 24.7% increase in the feeding cycle duration(from 4 to 5 days) and a 13.2% reduction in the average lifespan of a sandfly (from 14 to 12.14 days) could result in effecting the spread of L.donovani infection.

Discussion

Conclusions

Figure 3 illustrates an important result of the model, showing that with the current treatments available and considering only achievable levels of treatment the impact of treating more new PKDL cases on VL cases does not diminish at higher proportions of cases treated. Likewise, the graph of R_C vs. the proportion of new PKDL cases treated (Fig. 6) indicates that effect of treatment on the spread of the disease within the range considered will continue to increase within reasonable treatment ranges.

Conversely, Figures 4 and 5 show that thought effect of PKDL treatment on VL incidence increases at the higher proportions of new PKDL cases treated there is a diminishing return of this proportion with increased treatment rate ψ indicating how high the actual treatment rate would have to be to capture a large proportion of new PKDL cases. The opposite concavities of Figures 6 and 7 display the same effect. The effect of an increasing proportion of cases treated on R_C produces increasingly higher reduction of R_C whereas the effect of higher treatment rates diminishes.

These results indicate that public health initiatives aimed at preventing or decreasing the spread of *L.donovani* will be more effective when focusing on new cases by both raising awareness about the epidemiological effect of seeking treatment and keeping track of individuals who received treatment for VL

The series of sandfly control simulations indicated that PKDL treatments in tandem with achievable vector control initiatives may produce even more pronounced effects on the transmission of *L.donovani* even to the point reducing the spread of the disease into decline.

Limitations

The particular values reported may not accurately reflect the actual results if these treatments were implemented the large number of parameters estimated from independent sources certainly produced some numerical inaccuracies in the simulations, though these inaccuracies should not extend into the general behavior of the model assuming these estimate are close to the actual values. However, the results certainly produce meaningful insight into the relationship between PKDL treatment and VL incidence and corroborate the conclusion that high levels of PKDL treatment will significantly impact the rate of *L. donovani* infection.

Many assumptions may have distorted the accuracy of the model. It should be noted that among other limiting assumptions this model is only applicable to regions where *L.donovani* infection has no substantial nonhuman reservoir, such as the endemic areas of India where human population is high.

Further study

This study suggests that there is a significant epidemiological impact on *L.donovani* infection in humans by treating PKDL, but more research is required to determine the precise

level of treatment necessary. Further study is required to fit models like this to actual data involving varying treatment levels of PKDL to determine both goodness of fit and fit the model to real rates of impact. Clinical studies to determine how infectious PKDL patients are may improve understanding of how significant of a reservoir for transmission PKDL is.

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Appendix. Parameter Estimates

The PCR (polymerase chain reaction) and DAT (direct agglutination test) tests proved to determine the values of the several categories. The PCR test is used to replicate a small segment of DNA into larger amounts; this is then used to determine whether or not the bacteria are present. The test will result positive if the bacteria are present. The DAT test is used to determine the presence of antibodies to a specific antigen. If the DAT test results positive the antibodies are present and if it results negative the antibodies are not present.

The value for susceptible human hosts, which is denoted on Figure1 as S, was taken from reference one. They justified the value by testing a chosen population for VL by using the tests PCR and DAT. The percentage of cases in which both tests resulted negative were put into this susceptible category, in this case 76%.

The value for asymptotic infected individuals, which is denoted on Figure 1 as I_A, was taken from reference one. They justified the value of asymptomatic infected individuals by taking the percentage of individuals tested for Visceral Leishmaniasis and taking those who tested positive for PCR and negative for DAT and those who tested positive for both PCR and DAT and placing them into the asymptomatic infected individual category, in this case 11.985%.

The value for symptomatic individuals, which is denoted on Figure 1 as I_S, was taken from reference one. They justified the value of symptomatic infected individuals by taking the percentage of individuals tested for Visceral Leishmaniasis and taking those who tested positive for PCR or DAT while showing symptoms and placing them into the symptomatic infected individual category, in this case 0.015%.

The value for recovered individuals, which is denoted on Figure 1 as R, was taken from reference one. They justified the value of recovered individual hosts by taking the cases that resulted PCR negative and DAT positive and placing them into the recovered category. The PCR test with negative results determines the current status of infection of the individual, as to where the DAT test resulting positive indicates the antibodies are present. This means that the individual does not currently have visceral leishmaniasis but did at one point.

The value for the prevalence of recovered individuals who will develop PKDL, which is denoted on Figure 1 as P, was taken from reference one. They justified this value of prevalence

by simply adding the total percentage of prevalence from individuals treated with the first line treatment to the total percentage of prevalence from individuals treated with the second line treatment, which amounted to 6%.

The value for susceptible vectors, which is denoted on Figure 2 as S_V, was taken from reference 28. They justified the value of susceptible vectors by taking the total percentage of vectors already infected with Visceral Leishmaniasis and subtracting it from 100%, which resulted to 96.6%. The remaining vector population is Visceral Leishmaniasis free and is therefore susceptible to the disease.

The value for the relative density of female sandflies, which is denoted as N_V, was calculated with information from references 1, 25, 26, and 34. We took the total population density of individuals in Bihar, India (34) and multiplied it times the ratio of vectors per person found in reference (1). This value gave us the vector population density in Bihar, India; we then multiplied that value by the proportion of male to female sandflies, which was found in reference 26, which yielded 987.63 as the relative population density of female sandflies.

The value for the prevalence of exposed sandflies, which is denoted on Figure 2 as E_V, was calculated with information from reference 28. We took the prevalence of infectious vectors and subtracted that amount from the total percentage of vectors infected with Visceral Leishmaniasis, which amounted to 2.9%.

The value for the prevalence of infectious vectors, which is denoted on Figure 2 as I_V, was taken from reference 29. The value for I_V was concluded to be 0.5%.

The value for the death rate of an individual, which is denoted on Figure 1 as ζ, was calculated with information from reference 27. The value taken from reference 27 indicated the death rate per 1,000 individuals, in order to obtain the death rate per individual we divided the death rate per 1,000 individuals by 1,000, which amounted to 0.0079.

The value for the birth rate of an individual, which is denoted on Figure 1 as Λ_H , was calculated from reference 27. The value taken from reference 27 indicated the birth rate per 1,000 individuals, in order to obtain the birth rate per individual we divided the birth rate per 1,000 individuals by 1,000, which amounted to 0.0309.

The value of population density of individuals in Bihar, India, which is denoted on Figure 1 as N_H, was calculated with information from reference 34. We took the total population of Bihar, India and divided it by the area in squared kilometers, which amounted to 1,102.39.

The value of progression from asymptomatic cases to symptomatic cases, which is denoted on Figure 1 asγ, was calculated from reference 6. The value of the rate of cases that progressed from asymptomatic to symptomatic was given in terms of 1,000 people per months. In order to obtain the value in one person per day we took the value given in reference 6 and divided it by 1,000, we then multiplied it by the number of months in a year. We then took that number and divided it by the total number of days in one year, which yielded 0.0006.

The value for the fraction of individuals, who will spontaneously recover from asymptomatic Visceral Leishmaniasis, which is denoted on Figure 1 as θ is calculated with information from reference 1. First we added the sojourn time in the early asymptomatic stage to

the sojourn time in the late asymptomatic stage to get the total time an individual spends in the asymptomatic stage. We then took the inverse of the time spent in the asymptomatic stage and multiplied it by the fraction of cases that spontaneously recover from asymptomatic Visceral Leishmaniasis, which amounted to 0.0139.

The value for the rate of recovery with treatment for Visceral Leishmaniasis, which is denoted on Figure 1 by Φ, was calculated with information from reference 33. We multiplied the fraction of individuals who respond to treatment against Visceral Leishmaniasis to the inverse time of duration of treatment for Visceral Leishmaniasis, which yielded 0.0306.

The value for the rate of development to PKDL, which is denoted on Figure 1 as Ƥ, was calculated with information from reference 21. The rate of development to PKDL was given in terms of per 180 days. In order to obtain the value in per one day we divided the value given by 180, which amounted to 0.0028.

The value for the rate of loss of immunity, which is denoted on Figure1 as ω, was taken from reference one. In order to obtain the rate at which loss of immunity occurs we simply took the inverse of the time of duration spent in the period where the DAT tests are positive, which yielded 0.0135.

The value for the cure rate for treatment of PKDL, which is denoted on Figure 1 as φ, was taken from reference 18. The percentage of PKDL cases that were cured after treatment resulted in 98.1% of the cases.

The value for the death rate due to Visceral Leishmaniasis when treated, which is denoted on Figure 1 as δ, was taken from reference 16. The percentage of cases that result in death due to Visceral Leishmaniasis when treated resulted to be 13%.

The value for the reproductive rate of vectors, which is denoted on Figure 2 as Λ_V, was calculated with information from references 1, 26, 34, and 35. First we multiplied the population density of individuals in Bihar, India (34) by the ratio of vectors per person (1). We then took the population density of vectors and multiplied it by the percentage of female vector population (26). Lastly, we took the number of the female population density and divided it by the lifespan of vectors (35), which resulted in 195.6003.

The value of the probability of the vector becoming infected after biting and asymptomatic Visceral Leishmaniasis infected human, which is denoted on Figure 2 as σ_A, was calculated with information from reference one. First, we multiplied the probability that a susceptible vector becomes infected when feeding on a human host in the early asymptomatic stage by the amount of time spent in the early asymptomatic stage. We then took the probability that a susceptible vector becomes infected when feeding on a human host in the late asymptomatic stage and multiplied it by the amount of time spent in the late asymptomatic stage. We then added both probabilities and lastly, we divided the result of the sum by the total number of time spent in the asymptomatic stage, which yielded 0.0146.

The value of the probability of vectors becoming infected after biting a PKDL infected human, which is denoted on Figure 2 as σ_P, was taken from reference one. This value is assumed to be 1.0.

The value of the relative infectivity of symptomatic Visceral Leishmaniasis infected humans, which is denoted in Figure 2 as σ_S, was taken from reference one. This value is assumed to be 1.0.

The value of the natural death rate of vectors, which is denoted on Figure 2 as μ, was calculated with information from reference 22. In order to obtain the death rate of vectors we took the inverse of the lifespan of the vectors, which yielded 0.0714.

The value of the rate of becoming infectious after exposure, which is denoted on Figure 2 as k, was calculated with information from reference one. We took the inverse of the duration of time spent in the exposed vector stage, which is calculated to be 0.20.

The value of the biting rate of vectors, which is denoted as c, was obtained from reference 24. The given rate at which vectors bite is 0.25. The value of the infectivity of vectors, which is denoted in Figure 2 as βv, was assumed by reference 1. This value is assumed to be 1.0.

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