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Analyzing the Impact of Control Strategies on Visceral Leishmaniasis: A Mathematical Modeling Perspective

Fathelrhman EL Guma[1,2], Mohamed A. Abdoon[3,4], Ahmad Qazza[5], Rania Saadeh[5,*], Mohammed Ali Arishi[6], Abdoelnaser M. Degoot[7]

[1] *Department of Mathematics, Faculty of Science and Arts, Al Baha University, Baljurashi 1988, Saudi Arabia*
[2] *Department of Statistical Study, Alsalam University, Alfula, Sudan*
[3] *Department of Basic Sciences, Common First Year Deanship, King Saud University, P.O. Box 1142, Riyadh 12373, Saudi Arabia*
[4] *Department of Mathematics, Faculty of Science, Bakht Al-Ruda University, Sudan*
[5] *Department of Mathematics, Zarqa University, Zarqa 13110, Jordan*
[6] *Ministry of Health, King Khalid Hospital in Tabuk, Faculty of Laboratory , Department of Histopathology, 71411, Saudi Arabia*
[7] *African Institute for Mathematical Sciences, Kigali, Rwanda*

Abstract. Visceral Leishmaniasis remains a significant public health challenge in eastern Sudan despite extensive control efforts. This study employs MCMC Bayesian inference techniques to fit a mathematical model for studying visceral Leishmaniasis transmission dynamics with interventions. The research focuses on evaluation of control programs to adapt to the dynamic nature of visceral Leishmaniasis transmission. We analyze 22 years of cumulative visceral Leishmaniasis cases from eastern Sudan, an endemic region for visceral Leishmaniasis, and assessed the effectiveness of interventions implemented thus far.

The results reveal that visceral Leishmaniasis is prevalent, with reported cases representing less than 20% of community infections. Improved surveillance and diagnostics are necessary for accurately estimating the disease burden. The effectiveness of intervention strategies for vector control for reducing VL transmission in the region is found to be limited. Furthermore, the model predicts visceral Leishmaniasis cases will continue to increase in the near future, underscoring the need adaptable initiatives to reduce the disease burden.

2020 Mathematics Subject Classifications: AMS classification codes

Key Words and Phrases: Visceral Leishmaniasis, mathematical analysis, disease dynamics, parameters estimation, reproductive number, interventions.

*Corresponding author.
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Email addresses: fathyelrhman@gmail.com (F. EL Guma), Moh.abdoon@gmail.com (M. A. Abdoon), aqazza@zu.edu.jo (A. Qazza), rsaadeh@zu.edu.jo (R. Saadeh), Mohmmedam@moh.gov.sa (M. A. Arishi), degoot@aims.ac.za (A. M. Degoot)

1. Introduction

Visceral Leishmaniasis (VL), also known as Al Kala-azar, has been a longstanding issue in Sudan, with its initial documented instance dating back to 1908 [7]. The disease has been observed in various parts of the country, including the Darfur region in western Sudan, the Nuba Mountains in Kordofan, and along the banks of the White Nile, among others [19]. However, it is the eastern region that has experienced the highest incidence of VL, making it a focal point for public health efforts due to the significant concern it poses in those areas [4]. Despite considerable intervention programs aimed at controlling and eliminating VL, particularly in the eastern region.

The utilization of mathematical modeling has become indispensable in comprehending the intricate dynamics and transmission patterns of infectious diseases, as exemplified in references [1, 25, 26]. By employing equations that delineate the interactions among populations and infections, as well as the routes of transmission, researchers can gain profound insights into disease dynamics. However, the complexity of these models and the presence of unforeseen variables often hinder the attainment of analytical solutions. Hence, crucial parameters and approximate solutions are frequently derived through numerical approaches [5, 9, 14]. Numerical models enable scientists to predict treatment outcomes, evaluate medication efficacy, and refine strategies for managing clinical cases. These methodologies play a pivotal role in enhancing public health measures, optimizing vaccination programs, and advancing the understanding of epidemiological factors contributing to disease transmission [12, 13, 28]. Various mathematical models have been proposed to analyze the dynamics of VL transmission, typically based on SEIR-type models and focusing on three key groups: humans, animal reservoirs, and vectors [27, 30, 31]. Extensive research has generated theoretical and simulation-based insights into VL dynamics from diverse perspectives. Studies have shown that under certain circumstances, integrating human therapy with vector control can effectively eradicate the disease [11, 17]. Additionally, research has explored the interaction between malaria and VL co-infection [23]. Optimal control theory has been employed to analyze dynamical models for VL transmission, determining the most effective approaches for disease management [2, 24].

In a recent study [29], we developed a comprehensive SEIR-type model to analyze the transmission dynamics of VL, incorporating the effectiveness of interventions, and published a Caputo fractional-order derivative version of it along with rigorous mathematical analysis. In the current study we focus on the deterministic version of that model, using it to estimate the efficacy of interventions made to combat VL in eastern Sudan from 2000 to 2021. We analyse the impact of interventions using percentages and consider that the number of reported human VL cases is only a portion of the total community infections. The article is organized as follows. In Section 2, we revisit the model published in [29]. Section 4 provides an overview of the parameter estimation procedure, while Section 6 deals with a comprehensive overview and analysis of the findings.

2. The Model

As mentioned above, the model is described in detail in [29]. However, for the sake of readability, we rewrite it here. Briefly, the model considers the dynamics of VL in three populations: humans, reservoirs, and vectors. Each population is divided into a number of distinct compartments, described in Table 1, and the transmission channels between these compartments are captured by system (1) of ordinary differential equations, governed by parameters described in Table 2.

Table 1: Description of the model's compartments

Compartment	**Description**
N_h	Total human population
S_h	Susceptible human population
E_h	Exposed human population
I_u	Undetected VL-infected human population
I_d	Detected VL-infected human population
P_h	PKDL VL-infected human population
R_h	Human population who are immune to VL disease
N_r	Total reservoir population
I_r	Susceptible reservoir population
I_r	VL-infected reservoir population
N_v	Total vector population
I_v	Susceptible vector population
I_v	VL-infected vector population

Table 2: Description of the model's parameters

Par.	Description
ϵ	Average detecting rate
α_h	Effectiveness of therapies for human population
α_r	Effectiveness of the interventions for reservoir population
α_v	Effectiveness of interventions for the control of population
β_1	Likelihood of a virus being transmitted from an infected vector to a host that is susceptible to the virus
β_2	Likelihood of transmission of VL from an infected human that has been identified to a vector that is susceptible to the virus
β_3	Likelihood of transmission of from undetected VL-infected person to a susceptible vector
β_4	Likelihood of transmission from a PKDL individual to susceptible vectors
β_5	Likelihood of transmitted from an infected reservoir to a susceptible vector
$\frac{1}{\omega}$	Average incubation period for VL in human
δ_1	Average mortality rate in detected VL-infected human population
δ_2	Average mortality rate in undetected VL-infected human population
δ_3	VL-induced death rate for individuals in P_h class
σ_1	Treatment rate for individuals in I_d class
σ_2	Treatment rate for individuals in P_h class
γ_1	Natural recovery rate for individuals in I_u class
γ_2	Natural recovery for individuals in P_h class
ρ_1	Rate of progression from I_d class to P_h class
ρ_2	Rate of progression from I_u class to P_h class
η	Rate of progression from R_h class to S_h class
λ_h	Constant growth rate of human population
λ_r	Constant growth rate of reservoir population
λ_v	Constant growth rate of vector population
μ_h	Constant death rate of human population
μ_r	Constant death rate of human reservoir
μ_v	Death rate of the vector population that remains constant

$$
\begin{aligned}
S_h'(t) &= \lambda_h - \beta_1 I_v(t)\tfrac{S_h(t)(1-\alpha_h(t))}{N_h(t)} + \eta R_h(t) - \mu_h S_h(t), \\
E_h'(t) &= \beta_1 I_v(t)\tfrac{S_h(t)(1-\alpha_h(t))}{N_h(t)} - (\omega+\mu_h)E_h(t), \\
I_d'(t) &= \epsilon(t)\omega E_h(t) - (\sigma_1+\rho_1+\delta_1+\mu_h)\, I_d(t), \\
I_u'(t) &= [1-\epsilon(t)]\,\omega E_h(t) - (\gamma_1+\rho_2+\delta_2+\mu_h)\, I_u(t), \\
P_h'(t) &= \rho_1 I_d(t) + \rho_2 I_u(t) - (\sigma_2+\gamma_2+\mu_h)P_h(t), \\
R_h'(t) &= \sigma_1 I_d(t) + \gamma_1 I_u(t) + (\sigma_2+\gamma_2)P_h(t) - (\eta+\mu_h)R_h(t), \\
S_r'(t) &= \lambda_r - \beta_1 I_v(t)\tfrac{S_r(t)}{N_r(t)} - (\alpha_r(t)+\mu_r)S_r(t), \\
I_r'(t) &= \beta_1 I_v(t)\tfrac{S_r(t)}{N_r(t)} - (\alpha_r(t)+\mu_r)I_r(t), \\
S_v'(t) &= -\left(\left(\beta_2\tfrac{I_d(t)}{N_h(t)} + \beta_3\tfrac{I_u(t)}{N_h(t)} + \beta_4\tfrac{P_h(t)}{N_h(t)}\right)(1-\alpha_h(t)) + \beta_5\tfrac{I_r(t)}{N_r(t)}\right) S_v(t) \\
&\quad +\lambda_v - (\alpha_v(t)+\mu_v)S_v(t), \\
I_v'(t) &= \left(\left(\beta_2\tfrac{I_d(t)}{N_h(t)} + \beta_3\tfrac{I_u(t)}{N_h(t)} + \beta_4\tfrac{P_h(t)}{N_h(t)}\right)(1-\alpha_h(t)) + \beta_5\tfrac{I_r(t)}{N_r(t)}\right) S_v(t) \\
&\quad -(\alpha_v(t)+\mu_v)I_v(t).
\end{aligned} \tag{1}
$$

In addition, the following three equations are also implicit in model (1) construction:

$$\begin{aligned} N_h^{'}(t) &= \lambda_h - \mu_h N_h(t) - \delta_1 I_d(t) - \delta_2 I_u(t), \\ N_r^{'}(t) &= \lambda_r - (\alpha_r(t) + \mu_r) N_r(t), \\ N_v^{'}(t) &= \lambda_v - (\alpha_v(t) + \mu_v) N_v(t). \end{aligned} \tag{2}$$

All parameters of the model are non-negative, and since the model tracks the number of living things, all compartments within the model are also non-negative. A detailed mathematical treatment of model (1) was conducted in [29], including positivity, invariant region, stability and sensitivity analysis, and a formula for calculating the basic reproduction number.

3. Numerical Simulations

The data from the regional Ministry of Health's VL control campaign is used to represent the annual VL confirmed cases in Eastern Sudan from 2000 to 2021 in Figure 1. Each point on the line chart, which represents a different year, shows the annual variations in VL cases in the plot. To further show the average yearly VL cases over the whole time, a blue horizontal line is superimposed. This persistent presence emphasizes how difficult it is to eradicate VL in Sudan.

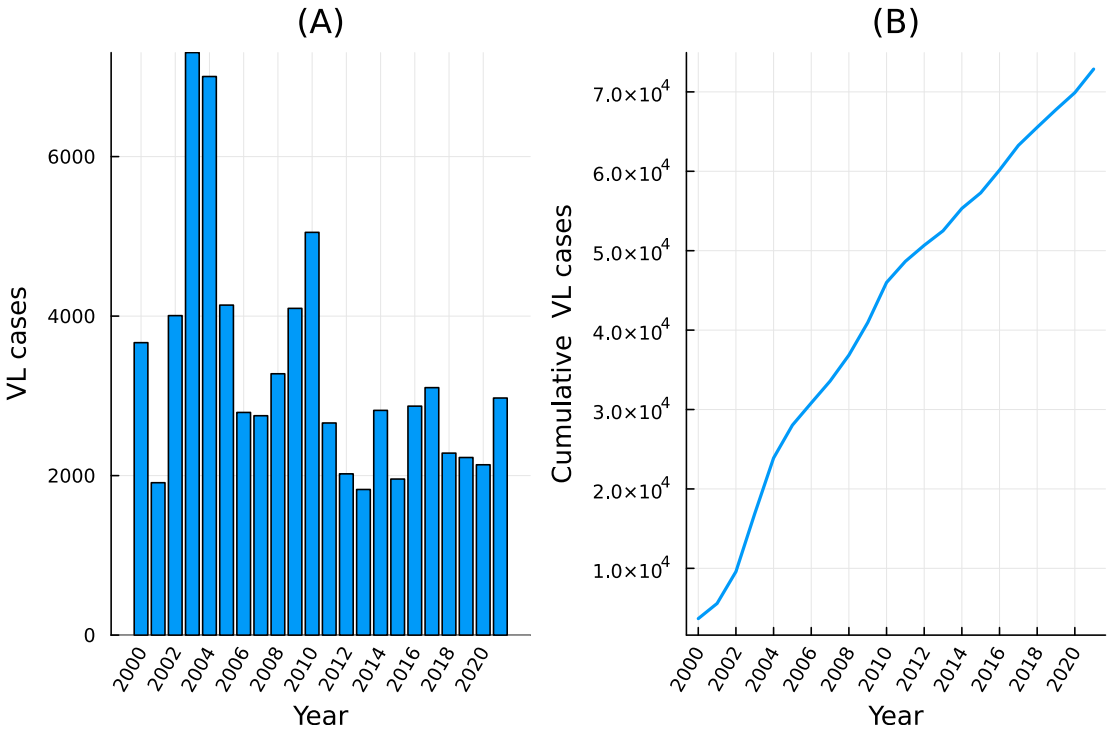

Figure 1: (A) Annual VL confirmed cases in Eastern Sudan from 2000 to 2021 and (B) cumulative VL cases.

To evaluate the consistency of model (1), we performed numerical simulations within a hypothetical ecosystem incorporating human, reservoir, and vector populations. Through systematic manipulation of control parameters, namely the average case detection rate ϵ, interventions to protect human population α_h, measures against the vector population, and measures to control reservoir population α_v and α_r. We investigated the impact of different values of the parameters on the cumulative number of human VL cases, as elaborated in Section 4. For our simulations, we initialized the human population at 1 million individuals, denoted as $N_h = 10^6$ to closely resemble the population of eastern Sudan [22, 33], with the reservoir population set at half of the human population, $N_r = 0.5 \times N_h$, and the vector population at double the human population, $N_v = 2 \times N_h$. Additionally, we assumed that 1% of each population was infected at the onset of the simulations.

The impact of various values of ϵ on the annual cumulative VL cases is illustrated in Figure 2. The figure highlights how enhancing the average case detection rate, attainable through heightened surveillance and diagnostic capabilities, health education, capacity building, and ensuring affordable and accessible healthcare, correlates with a rise in cumulative VL cases. However, this increase is accompanied by a positive outcome: detected cases can be effectively managed and their spread contained, thereby contributing to the overall control of the disease within the community.

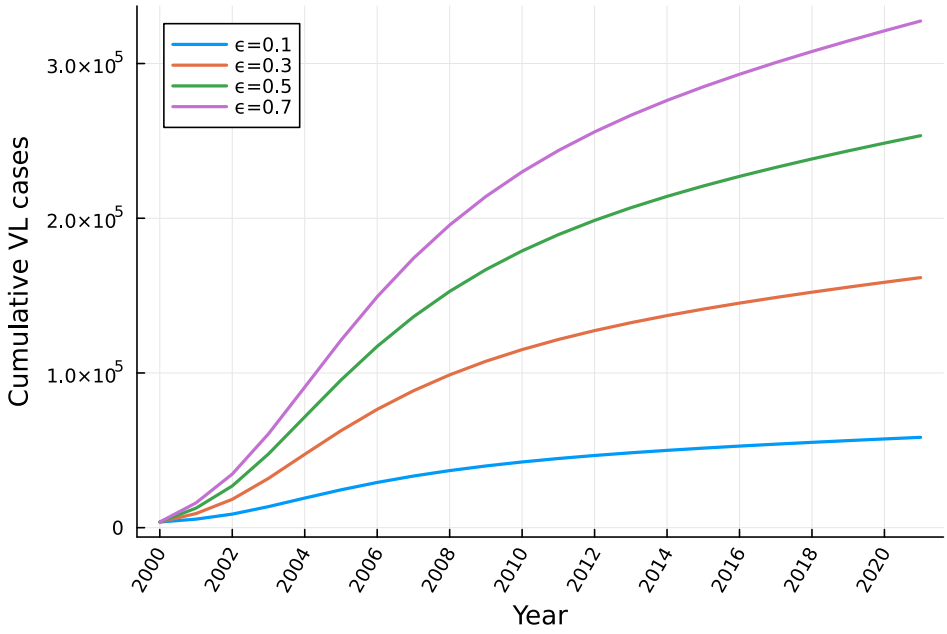

Figure 2: Simulations of model (1) for different values of ϵ and their impact on cumulative VL cases.

The primary intervention to protect the human population against VL often involves the widespread use of insecticide-treated nets (ITNs). These nets act as a physical bar-

rier against the sandflies that transmit the parasite causing VL, thereby reducing the risk of infection among individuals sleeping under them. Additionally, ITNs can also be impregnated with insecticides, which further enhance their effectiveness by repelling or killing the sandflies upon contact. Figure 3 illustrates the impact of different values of α_h, representing the cumulative efforts aimed at enhancing the efficacy of interventions to protect populations, on the cumulative VL cases. It suggests that higher values of α_h correspond to lower cumulative VL cases, which aligns with intuitive understanding. Implementing mass-scale distribution of ITNs and promoting their consistent and correct use can significantly reduce the incidence of the disease.

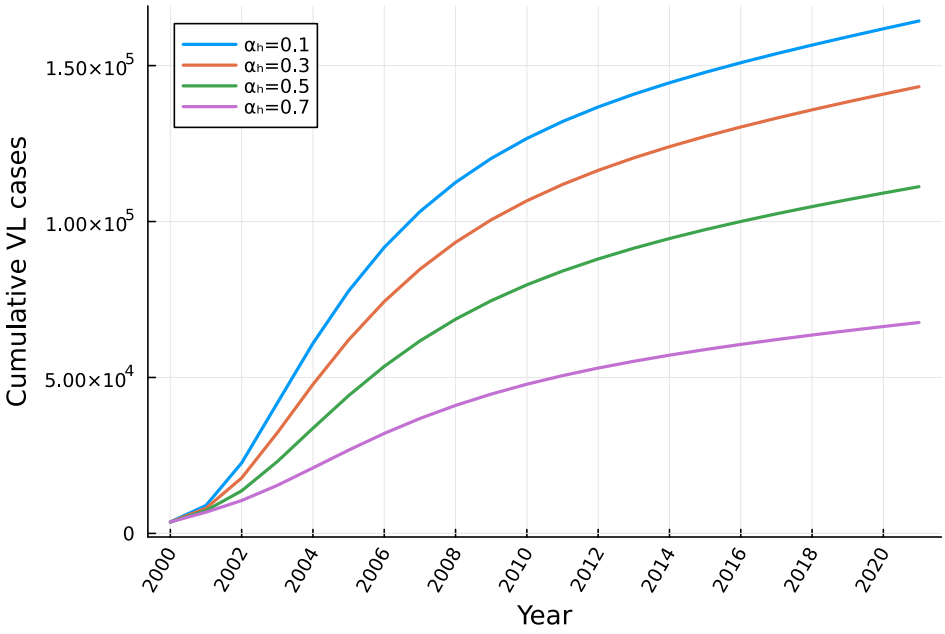

Figure 3: Simulations of model (1) for different values of α_h and their impact on cumulative VL cases.

The main intervention for controlling vector populations is the application of insecticide spray. Figure 4 illustrates the simulation results depicting the impact of varying intensities of α_v. It indicates that an increase in the efficacy of these interventions is correlated with a decrease in the cumulative cases of VL.

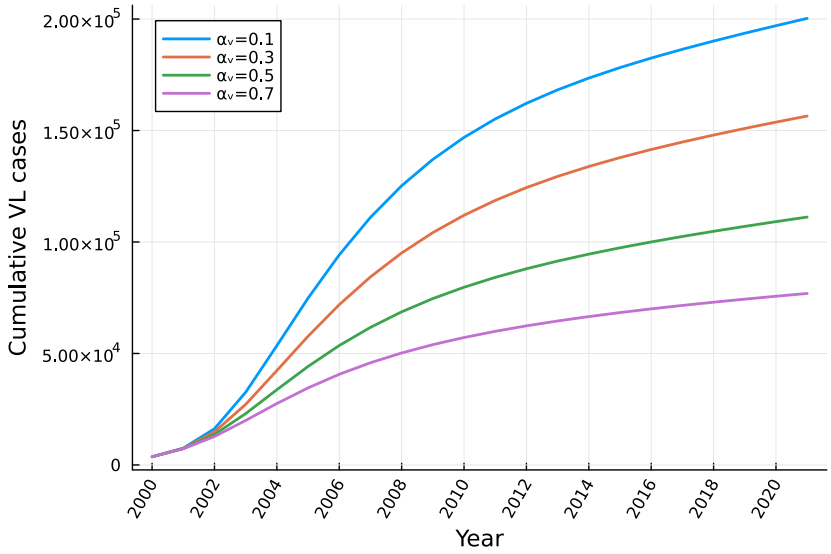

Figure 4: Simulations of model (1) for different values of α_v and their impact on cumulative VL cases.

The primary intervention for controlling VL in the reservoir population has traditionally been culling. However, this approach may have negative consequences, as detailed in Elmojtaba et al. [17], because eliminating animals creates a vacant niche for vectors, potentially increasing human exposure. Our simulation results align with this conclusion (see Figure 5), showing that different values of α_r have similar effects on cumulative VL cases

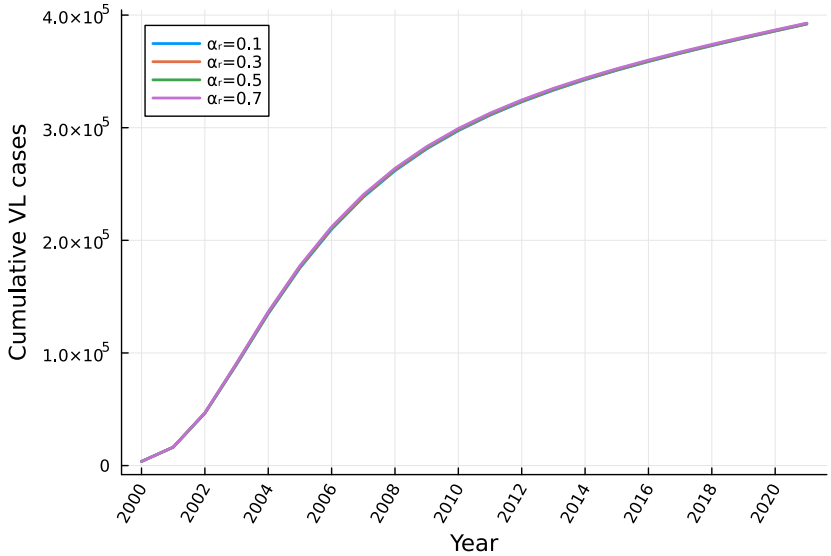

Figure 5: Simulations of model (1) for different values of α_r and their impact on cumulative VL cases.

4. Parameters Estimation

Many parameters related to VL disease features in model (1) have approximate values that can be gathered from relevant literature (see Table 4). However, parameters representing interaction rates ($\beta_1, \beta_2, \beta_3, \beta_4$, and β_5), intervention effectiveness ($\epsilon, \alpha_h, \alpha_r$, and α_v), and the initial values of $N_h, E_h, I_u, P_h, R_h, N_r, N_v, I_r$, and I_v are unknown. We denote these unknown parameters collectively by θ:

$$\begin{aligned}\theta = \{&\epsilon, \alpha_h, \alpha_r, \alpha_v, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, N_h(0), E_h(0), I_u(0), P_h(0), N_r(0),\\ &I_r(0), N_v(0), I_v(0)\}.\end{aligned} \tag{3}$$

Furthermore, as in [11], the initial number of the human population can be modeled as $N_h(0) = K_h \times 10^m$, for $m > 0$ and $K_h \in (a, b)$ for a and b non-negative numbers. Similarly, we set $S_h(0) = K_{sh} \times N_h(0)$, $E_h(0) = K_{eh} \times S_h(0)$, $N_r(0) = K_r \times N_h(0)$, and $N_v(0) = K_v \times N_h(0)$.

Given annual cases of VL, we seek to estimate the values of these known parameters using a Bayesian approach. In particular, we are interested in the cumulative number of reported human VL cases at time t, denoted by y, which can be calculated from system (1) as follows:

$$\frac{dy(t)}{dt} = \epsilon\omega E(t). \tag{4}$$

Cumulative number of annual VL cases are count data, and thus can be modelled using negative binomial (NB) distribution as a random number of occurrences. Therefore, the joint posterior distribution of the parameters vector θ:

$$J(\theta, \phi|y_1, y_2, ...y_L) = \prod_{t=1}^{L} NB(y(t)|\theta, \phi)P(\theta)P(\phi), \tag{5}$$

where L is the number of years, $y(t)$ is derived is given by (4),$P(\theta)$ is the joint prior distribution of all parameters in vector θ, and $P(\phi)$ is the prior distribution for dispersion parameter ϕ. We assumed flat uninformative prior distributions $u(0, 1)$ or $\mathbb{N}(0, 1)$ (see Table 4) for the parameters in θ, and $\phi^{-1} \sim \text{Gamma}(0.1, 0.1)$.

5. Results

The cumulative number of reported cases of VL in eastern Sudan from 2000 to 2021 ($L = 22$) was modeled using (5), employing an MCMC algorithm. Specifically, we employed the No-U-Turn sampler, a sophisticated MCMC method integrated into the Turing framework for Bayesian computation in Julia [10]. This method offers rapid convergence to the target distribution, avoids random walks, and automatically adjusts the learning rate.

The program was executed for 15,000 iterations, with the initial 5,000 samples of θ discarded as burn-in. Subsequently, point estimates and 95% credible intervals for each parameter were computed from the remaining samples. It's worth noting that the

human population in Gadaref state in 2000 is estimated to be around one million [22, 33], Therefore, in our implementation, we set $m = 6, a = 0.8$, and $b = 1.4$, i.e., $K_h \sim U(0.8, 0.14)$.

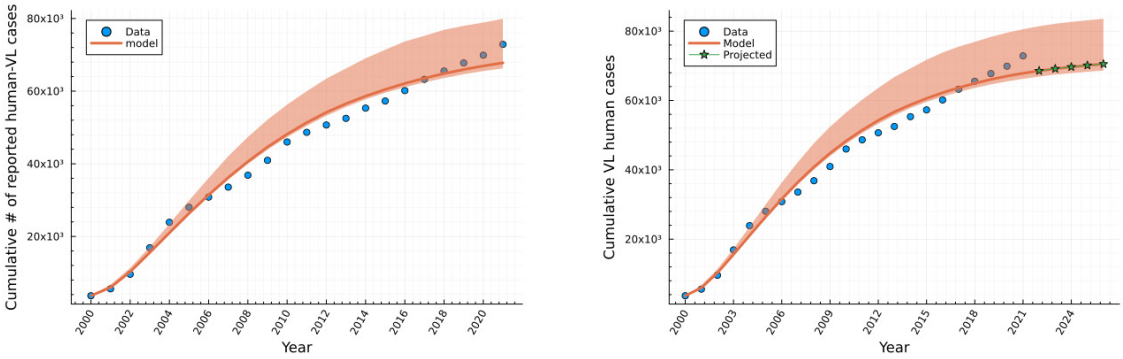

Figure 6: Comparison between actual and predicted annual Cumulative VL Cases in eastern Sudan from (2000 - 2021) and projection for (2022- 2026).

Figure 6a compares the simulation results of model (1) with the actual cumulative VL cases in Eastern Sudan. Despite missing a few data points, the model's findings closely match the real data. Furthermore, we utilized the estimated parameter values to project cumulative VL cases in the region for five year period, from 2022 to 2027. If existing measures remain unchanged, VL is expected to persist in the region for the foreseeable future, as projected in Figure 6b. Point estimates and 95% credible intervals for the initial values of system (1) compartments and parameters are provided in Tables 3 and 4, respectively.

Table 3: Estimates for the initial value of the compartment.

Compartment	**Value**
$N_h(0)$	10859000
$S_h(0)$	$0.27 \times N_h(0)$
$E_h(0)$	$2.1 \times 10^{-1} \times S_h(0)$
$I_u(0)$	$3.659 \times 10^{-1} \times E_h(0)$
$P_h(0)$	$3.659 \times 10^{-1} \times [I_d(0) + I_u(0)]$
$R_h(0)$	
$N_r(0)$	$18 \times 10^{-2} \times N_h(0)$
$I_r(0)$	$7 \times 10^{-2} \times N_r(0)$
$N_v(0)$	$6.15 \times N_h(0)$
$I_v(0)$	$0.2 \times N_v(0)$

Table 4: Description of the model's parameters.

Parameter	Value	Range	Source
ϵ	0.18	[0.12,0.57]	Fitted
α_h	0.7	[0.3, 0.9]	Fitted
α_r	0.015	[0.01, 0.44]	Fitted
α_v	0.5	[0.13 , 1]	Fitted
β_1	0.6	[0.22 , 0.94]	Fitted
β_2	0.34	[0.004 , 0.92]	Fitted
β_3	0.46	[0.04, 0.93]	Fitted
β_4	0.37	[0.02.0, 0.94]	Fitted
β_5	0.74	[0.3, 1]	Fitted
$\frac{1}{\omega}$	60 days	$[30, 180]$	[31, 34]
δ_1	4.015	–	[31, 32]
δ_2	4.015	–	[31, 32]
δ_3	4.015	–	[31, 32]
σ_1	0.03 day^{-1}	-	[32]
σ_2	0.033 day^{-1}	-	[18]
γ_1	0.84	$[0.8, 0.9]$	[32]
γ_2	0.005 day^{-1}	$[0.001, 0.005]$	[32]
ρ_1	0.36	-	[18]
ρ_2	0.0001	[0.0001,0.0002]	[32]
η	0.002 day^{-1}	$[0.001, 0.006]$	[32]
λ_h	0.027	-	[8]
λ_r	$\mu_h \times N_r(0)$	-	[11, 32]
λ_v	$\mu_h \times N_v(0)$	-	[11, 32]
μ_h	0.0067	-	[8]
μ_r	0.0017	-	[15]
μ_v	0.067	-	[32]

6. Discussion and Conclusion

VL remains a severe health concern in eastern Sudan despite numerous control efforts. In this study, we employ a Bayesian inference method to fit a previously developed mathematical model for VL transmission dynamics, incorporating the effects of control measures. We analyzed 22 years of cumulative VL cases and evaluated intervention effectiveness over this period. The best-fit results (see Figure 6a and Table 4) suggest that VL is prevalent, with reported cases representing less than 20% of community infections, highlighting a significant gap in disease surveillance and diagnosis.

Our analysis indicates that the efficacy of interventions targeting vector population control is limited, with α estimated around 50% (see Table 4). Notably, there are no documented interventions aimed at controlling the disease reservoir in the region. Our model predicts a negligible effect for $\alpha_r > 2\%$. Furthermore, the model projects a potential increase in cumulative VL cases in the future (see Figure 6b), underscoring the necessity for adaptable multifaceted disease control initiatives.

To achieve its stated goal of eradicating VL as a public health concern by 2030, the Sudanese National Leishmaniasis Control Program must implement concerted efforts. Embracing innovative research methodologies and strengthening public health infrastructure are essential steps toward mitigating the impact of VL. We advocate for continuous mon-

itoring and evaluation of VL control programs, emphasizing the development of dynamic and responsive interventions tailored to the complex landscape of VL transmission. This study not only provides insights into the current state of VL management in eastern Sudan but also emphasizes the imperative for innovation in surveillance, treatment methodologies and disease control strategies.In future research, we aim to extend our focus beyond visceral leishmaniasis control measures to the exploration of new fractional models using alternative techniques [3, 6, 9, 16, 20, 21, 29] .

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