MATHEMATICAL TREATMENT MODEL OF LASSA FEVER

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Abstract

We present and explore a novel mathematical treatment model of the epidemiology of Lassa Fever (LF). The model is a system of nonlinear ordinary differential equation model for rodent and human population. We analyzed the model to find the stability of the disease-free equilibrium and test which model parameters affect this stability most significantly. The purpose of this paper is to investigate the impact of treatment on the control of LF. The analysis revealed that treatment rate of humans will have a positive impact in reducing the burden of LF in the population. Our model predicts that treatment control can reduce the population level transmission by up to 12% alone without existing interventions. Therefore, treatment has significant effect on LF transmission, but it may not be able to eliminate the disease unless a multiple control strategy is adopted. Finally, some numerical simulations were carried out to support our theoretical results.

Keywords: *Lassa fever; Modelling; Treatment; Stability*

INTRODUCTION

Lassa fever (LF) is a deadly epidemic disease which threaten public health security and was discovered in Nigeria in 1969. LF is a viral hemorrhagic fever caused by the arenavirus and transmitted primarily from rodents (multimammate rats) to humans, human to human and aerosol transmission [7]. The Arenaviruses are a family of viruses whose members are generally associated with rodent-transmitted diseases in humans. The incubation period is 2-21 days in a susceptible host and treatment is done using ribavirin drug which is effective when started within the first 6 days of illness. An estimated 300,000-500,000 infections per year with 5000 deaths have been reported [7]. The spread of infection diseases has always been of concerns and a threat to public health epidemiologists [3]. Among the control strategies of control of LF, treatment is of interest in this paper. Treatment is essentially supportive. Antiviral, ribavirin is most effective when started within the first 6 days of illness [7, 10].

The prevention and control of LF abound such as village-based programs for rodent control and avoidance, hospital training programs to prevent the nosocomial spread, including barrier nursing, diagnostic technology transfer, and specific antiviral chemotherapy (ribavirin) [10]. The antiviral drug called ribavirin has been suggested to be an effective treatment for LF if given early on in the course of clinical illness. According to clinical literature, there is lack of

evidence to support the role of ribavirin as post-exposure prophylactic treatment for LF. Since vaccine against LF is not available, ribavirin has been recommended as standard treatment but the evidence base for this recommendation has been questioned recently. It has been noted that the efficacy of ribavirin for treating LF is uncertain but data from a prospective trial suggest a beneficial effect in patients with severe forms of LF. It has also been noted that re-assessment of the effectiveness of ribavirin in the treatment of LF is necessary and seems urgently required [11]. An important question asked by public health epidemiologists is: to what extent does treatment control reduce the population level transmission of LF alone without existing interventions? This is the motivation for this mathematical modelling study.

TREATMENT MODEL OF LASSA FEVER

It has been noted that no vaccine available against Lassa fever disease in humans, and the sole treatment relying on ribavirin is only effective if administered early in infection [5]. According to [1], the modeled viral kinetics suggests that the main mode of action of ribavirin is to protect infected cells from dying, possibly reducing the inflammatory response, while having no effect on viral production or transmission. Few modeling studies have been carried on the spread of LF [9, 8, & 6] with little understanding of treatment impact. The goal of this paper is to investigate, using mathematical modelling approach, the impact of treatment on the control of LF. To determine the effect of treatment as a control strategy on the transmission of Lassa fever disease, we incorporate early and late stage treatment compartments into the basic Lassa fever transmission model developed by Obasi and Mbah [6]. The resulting system is given in the following equations:

$$
\begin{cases}
\frac{dS_h}{dt} = \Lambda_h + \phi(1-\nu)I_h + \psi R_h - \beta_1\sigma I_r S_h - \beta_2\varepsilon I_h S_h - \eta(1-e^{-rt})S_h - \mu_h S_h \\
\frac{dE_h}{dt} = \beta_1\sigma I_r S_h + \beta_2\varepsilon I_h S_h + \eta(1-e^{-rt})S_h - (\kappa+\mu_h)E_h \\
\frac{dI_h}{dt} = \kappa E_h - (\phi+\theta+\delta+\mu_h)I_h \\
\frac{dT_{h1}}{dt} = \alpha\theta I_h - \mu_h T_{h1} \\
\frac{dT_{h2}}{dt} = (1-\alpha)\theta I_h - (\delta+\mu_h)T_{h2} \\
\frac{dR_h}{dt} = \phi\nu I_h + \varpi T_{h1} - (\psi+\mu_h)R_h \\
\frac{dS_r}{dt} = \Lambda_r - \beta_3\vartheta I_r S_r + \varphi R_r - \mu_r S_r \\
\frac{dI_r}{dt} = \beta_3\vartheta I_r S_r - (\omega+\mu_r)I_r \\
\frac{dR_r}{dt} = \omega I_r - (\varphi+\mu_r)R_r
\end{cases}
\tag{1}
$$

The definitions of above model variables and parameters are listed in Table 1 and 2.

Table 1: Description of the state variables of the model

Variable	Description
S_h	Number of Susceptible humans
E_h	Number of Exposed humans
I_h	Number of Infectious humans
T_{h1}	Early stage treatment group
T_{h2}	Late stage treatment group
R_h	Number of Recovered humans
S_r	Number of Susceptible rodents
I_r	Number of Exposed rodents
R_r	Number of Infectious rodents

Table 2: Description of the parameters of the Lassa fever model

Parameters	Description	Values	Source
Λ_h	Recruitment level of humans	20	[6]
Λ_r	Recruitment level of rodents	200	[6]
δ	Per capita Lassa-induced death rate	0.2	[8]
ψ	Recovered human loss of immunity	0.9	[8]
ϕ	Spontaneous individual recovery	0.001	[9]
β_1	Transmission rate per contact by an infectious rodent	0.00002	[9]
β_2	Transmission rate per contact by an infective through sexual activity	0.2	[12]
β_3	Transmission rate per contact by an infected human	0.08	[6]
η	Relative infectiousness of individuals with aerosol	0.03	[6]
μ_h	Natural mortality rate for humans	0.02041	[8]

μ_r	Natural mortality rate for rodents	0.06	[8]
κ	Progression rate of human from exposed to infected	0.05	[6]
α	Progression rate of rodents from exposed to infected	0.42	Estimated
σ	Contact rate of rodent per human per unit time	0.005	[12]
ϑ	Relative human-to-rodent transmissibility of infected humans	0.6	[8]
ε	Relative human-to-human transmissibility of infected humans	0.4	[8]
r	Rate of exposure to aerosol	0.005	[6]
ω	Recovery rate of rodents	0.00001	[12]
φ	Recovered rodent loss of immunity	0.001	Estimated
ϖ	Rate of early stage treated group who recovers	0.2	Estimated
α	Fraction of early stage treatment group	(0,1)	Assumed
θ	Treatment rate of humans	0.8	Estimated

BASIC PROPERTIES OF THE MODEL

Since the model (1) monitors human population, all its associated parameters and state variables are assumed to be non-negative for all $t \geq 0$. Before analysing the model, it is instructive to show that the state variables of the model remain non-negative for all non-negative initial conditions. Thus, we claim the following result.

Theorem 1: Let the initial data $S_h(0), E_h(0), I_h(0), T_{h1}(0), T_{h2}(0), R_h(0), S_r(0), I_r(0), R_r(0)$ be non-negative. Then, the solutions $(S_h, E_h, I_h, T_{h1}, T_{h2}, R_h, S_r, I_r, R_r)$ of model (1) are positive and bounded for all $t > 0$, whenever they exists.

Proof:

Suppose $S_h(0) \geq 0$. The first equation (1) of the system can be written as:

$$\frac{dS_h}{dt} + [\lambda(S_h) + \mu_h] S_h = \Lambda_h + \phi(1-\nu) I_h + \psi R_h$$

$$\frac{d}{dt}[S_h(t)\eta(t)] = (\Lambda_h + \phi(1-\nu) I_h + \psi R_h)\eta(t),$$

where $\eta(t) = \exp\left(\int_0^t [\lambda(S_h) + \mu_h] t dt\right) > 0$ is the integrating factor. Hence, integrating this last relation from 0 to t_1, we have

$$\left[S_h(t_1)\eta(t_1)\right]-S_h(0)\eta(0)=\int_0^{t_1}\left(\Lambda_h+\phi(1-\nu)I_h+\psi R_h\right)\exp\left[\left(\lambda(S_h)+\mu_h\right)p\right]dp,$$
$$\eta(0)=1,$$
$$\left[S_h(t_1)\eta(t_1)\right]-S_h(0)=\int_0^{t_1}\left(\Lambda_h+\phi(1-\nu)I_h+\psi R_h\right)\exp\left[\left(\lambda(S_h)+\mu_h\right)p\right]dp$$
$$S_h(t_1)\eta(t_1)=S_h(0)+\int_0^{t_1}\left(\Lambda_h+\phi(1-\nu)I_h+\psi R_h\right)\exp\left[\left(\lambda(S_h)+\mu_h\right)p\right]dp$$

so that the division of both side by $\eta(t)$ yields

$$S_h(t_1)=\left[S_h(0)+\int_0^{t_1}\left(\Lambda_h+\phi(1-\nu)I_h+\psi R_h\right)\exp\left[\left(\lambda(S_h)+\mu_h\right)p\right]dp\right]\times\eta^{-1}(t_1)>0.$$

The same arguments can be used to prove that $E_h(t),I_h(t),R_h(t),S_r(t),I_r(t),R_r(t)\geq 0$ for all $t>0$.

Furthermore, let $N=S_h+E_h+I_h+T_{h1}+T_{h2}+R_h$. Then,

$$\dot{N}(t)=\dot{S}_h+\dot{E}_h+\dot{I}_h+\dot{T}_{h1}+\dot{T}_{h2}+\dot{R}_h$$
$$=\Lambda_h+\phi(1-\nu)I_h+\psi R_h-\lambda_h S_h-\mu_h S_h+\lambda_h S_h-(\kappa+\mu_h)E_h+\kappa E_h-(\phi+\theta+\delta+\mu_h)I_h$$
$$+\alpha\theta I_h-\mu_h T_{h1}+(1-\alpha)\theta I_h-(\delta+\mu_h)T_{h2}+\phi\nu I_h+\varpi T_{h1}-(\psi+\mu_h)R_h$$
$$\leq\ \Lambda_h-\mu_h N_h-\delta I_h,\ \delta=0$$

This implies that as $t\to\infty,\sup N_h\leq\frac{\Lambda_h}{\mu_h}$. Also from (1), we have that as: $t\to\infty,\sup S_r(t)\leq\frac{\Lambda_r}{\mu_r}$.

This completes the proof.

Combining Theorem 1 with the trivial existence and uniqueness of a local solution for the model (1), we have established the following theorem which ensures the mathematical and biological well-posedness of system (1).

Theorem 2: The dynamics of model (1) is a dynamical system in the biological feasible compact set

$$\Gamma:=\left\{\left(S_h,E_h,I_h,T_{h1},T_{h2},R_h,S_r,I_r,R_r\right)\in\mathbb{R}_+^9:0\leq S_h\leq\frac{\Lambda_h}{\eta\left(1-e^{-rt}\right)+\mu_h};N_h\leq\frac{\Lambda_h}{\eta\left(1-e^{-rt}\right)+\mu_h},N_r\leq\frac{\Lambda_r}{\mu_r}\right\}\qquad(2)$$

TREATMENT REPRODUCTION NUMBER AND LOCAL STABILITY OF DFE

The model (1) has a disease-free equilibrium (DFE), obtained by setting the right hand sides of the equations in the model to zero, given by

$$\xi_0=\left(S_h^0,E_h^0,I_h^0,T_{h1}^0,T_{h2}^0,R_h^0,S_r^0,I_r^0,R_r^0\right)=\left(\frac{\Lambda_h}{\eta\left(1-e^{-rt}\right)+\mu_h},0,0,0,0,0,\frac{\Lambda_r}{\mu_r},0,0\right)\qquad(3)$$

The stability of ξ_0 can be established using the next generation operator method on the system (1). Using the notations in van den Driessche and Watmough [6], the matrices F *and* V, for the new infection terms and the remaining transfer terms respectively, are given by

$$F=\begin{pmatrix} 0 & \beta_2\varepsilon S_h^0 & 0 & 0 & \beta_1\sigma S_h^0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_3\vartheta S_r^0 \end{pmatrix}; \quad V=\begin{pmatrix} (\mu_h+\kappa) & 0 & 0 & 0 & 0 \\ -\kappa & (\phi+\mu_h+\delta+\theta) & 0 & 0 & 0 \\ 0 & \alpha\theta & \mu_h & 0 & 0 \\ 0 & -\alpha(1-\theta) & 0 & (\delta+\mu_h) & 0 \\ 0 & 0 & 0 & 0 & (\omega+\mu_r) \end{pmatrix}$$

In the calculation of matrices F *and* V, we took the infection variables to be E_h, I_h, T_{h1}, T_{h2} and I_r as explained in [6]. Thus

$$R_T = R_h + R_r = \frac{\beta_2\kappa\varepsilon\Lambda_h}{(\kappa+\mu_h)(\phi+\mu_h+\delta+\theta)\left(\eta\left(1-e^{-rt}\right)+\mu_h\right)} + \frac{\beta_3\vartheta\Lambda_r}{\mu_r(\omega+\mu_r)} \tag{3}$$

where R_T is obtained from $\rho\left(FV^{-1}\right)$ with ρ being the spectral radius of the matrix FV^{-1}. Computing the partial derivatives of R_T with respect to the parameters under investigation (θ, ϖ) further reveals the effect of these parameters on Lassa fever control in the community. This gives

$$\frac{\partial R_T}{\partial\theta} = -\frac{\beta_2\varepsilon\kappa}{(\mu_h+\kappa)(\phi+\mu_h+\delta+\theta)^2}\left[\frac{\Lambda_h}{\eta\left(1-e^{-rt}\right)+\mu_h}\right] < 0 \tag{4}$$

Clearly, it follows from (4) that the partial derivative is less than zero, unconditionally. Hence, treatment rate of humans will have a positive impact in reducing the burden of LF in the population, irrespective of the values of the other parameters in the expressions on the right-hand sides of (4). Furthermore, if the combined effect of preventive measures reduces R_0 by a factor q, then effective reproduction number $R_T = (1-q)R_0$ [6]. This implies that no outbreak if $R_T \le 1, ie, \; if \; q \ge 1-\frac{1}{R_0}$. Assuming treatment control can reduce the basic reproduction number R_0 by a factor q, i.e. $R_T = (1-q)R_0$, we obtain that

$$\frac{R_T}{R_0} = \frac{\phi+\mu_h+\delta}{\phi+\mu_h+\delta+\theta} = 0.88 \Rightarrow R_T = (1-q)R_0$$
$$\therefore 1-q = 0.88 \Rightarrow q = 0.12$$

Thus, introduction of treatment control significantly reduces the transmission of LF required for successful eradication of the disease (requirement of at least 12% effectiveness). This means that the treatment reproduction number R_T is 12% smaller than the basic reproduction number R_0, indicating that the use of treatment as a control strategy is 12% effective on reducing LF transmission. This implies that early detection is of paramount importance in the control of Lassa fever in a population. However, this is an indication that the early stage group treatment program alone at this rate is not enough to eliminate the disease. So, multiple control strategy requires urgent assessment.

Lemma 1: The DFE of the model (1), ξ_0, is locally asymptotically stable if $R_T < 1$ and unstable if $R_T > 1$. The threshold quantity R_T is the effective reproduction number under treatment control for the Lassa fever model. Biologically speaking, Lemma (1) implies that Lassa fever can be eliminated from the community (when $R_T < 1$) if the initial sizes of the subpopulation of the model are in the basin of attraction of ξ_0 in the presence of treatment.

GLOBAL ASYMPTOTIC STABILITY: SPECIAL CASE $\sigma = \eta = 0$.

Consider the model (1) with $\sigma = \eta = 0$. We claim the following:

Theorem 2: The DFE of the model (1) with $\sigma = \eta = 0$ is globally-asymptotically stable (GAS) whenever $R_T < 1$.

Proof

Consider the model (1) with $\sigma = \eta = 0$. Further, consider the following linear Lyapunov function

$$F = \kappa E_h + (\kappa + \mu_h) I_h$$

with Lyapunov derivative (where a dot represents differentiation with respect to *t*)

$$\begin{aligned}
\dot{F} &= \kappa \dot{E}_h(t) + (\kappa + \mu_h)\dot{I}_h(t) \\
&= \kappa\left(\lambda_h S_h - (\kappa + \mu_h) E_h\right) + (\kappa + \mu_h)\left(\kappa E_h - (\phi + \theta + \delta + \mu_h) I_h\right) \\
&= (\kappa + \mu_h)(\phi + \theta + \delta + \mu)\left[\frac{\beta_2 \varepsilon \kappa S_h}{(\kappa + \mu_h)(\phi + \theta + \delta + \mu)} - 1\right] I_h \\
\dot{F} &\le (\kappa + \mu_h)(\phi + \theta + \delta + \mu_h)[R_T - 1] I_h
\end{aligned}$$

Hence, $\dot{F} \le 0$ if $R_T \le 1$ with $\dot{F} = 0$ if and only $I_h = 0$. Therefore F is a Lyapunov function in Γ and it follows Salle's Invariance Principle [6], that every solution to the equations in (1) (with $\sigma = \eta = 0$) with initial conditions in Γ converges to ξ_0 as $t \to \infty$. i.e.,

Theorem 3: If $R_T > 1$, then endemic equilibrium point of the model (1) is globally asymptotically stable if $S_h = S_h^*, E_h = E_h^*, I_h = I_h^*, T_{h1} = T_{h1}^*, T_{h2} = T_{h2}^*$ and unstable if $R_T < 1$.

Proof

Consider the following Lyaponuv function,

$$Q(S_h, E_h, I_h, T_{h1}, T_{h2}) = \frac{1}{2}\left(S_h - S_h^*\right)^2 + \frac{1}{2}\left(E_h - E_h^*\right)^2 + \frac{1}{2}\left(I_h - I_h^*\right)^2$$

Differentiating wrt t,

$$\frac{dQ}{dt} = \left(S_h - S_h^* + E_h - E_h^* + I_h - I_h^*\right)\left(S_h'(t) + E_h'(t) + I_h'(t)\right)$$

$$= \left(S_h - S_h^* + E_h - E_h^* + I_h - I_h^*\right)\left(\Lambda_h - \mu_h S_h + \lambda S_h - (\kappa + \mu_h)E_h + \kappa E_h - (\phi + \theta + \delta + \mu_h)I_h\right)$$

$$= -\left(S_h - S_h^* + E_h - E_h^* + I_h - I_h^*\right)(H - W)$$

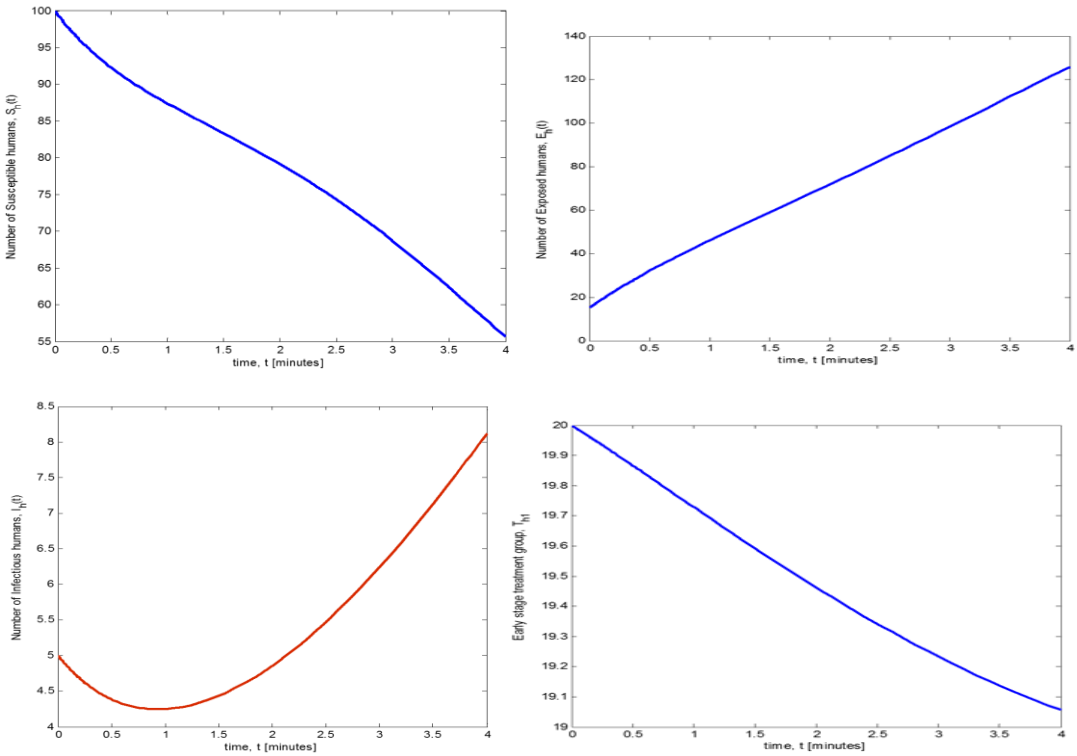
where

$$H = \mu_h S_h + (\kappa + \mu_h)E_h + (\phi + \theta + \delta + \mu_h)I_h; W = \Lambda_h + \kappa E_h$$

Hence we have $\frac{dQ}{dt} = 0$ if $S_h = S_h^*, E_h = E_h^*, I_h = I_h^*, T_{h1} = T_{h1}^*, T_{h2} = T_{h2}^*$, also $\frac{dQ}{dt} < 0$ if $H > W$. Thus, it is clear that the endemic equilibrium point of the model (1) is globally asymptotically stable. So the proof is completed.

NUMERICAL SIMULATIONS

In this section, we use a numerical example to support the theoretical analysis above in this paper. By extracting some values from [9]. The simulations are produced by MATLAB. See Table 2 above for the description of parameters and their based line or range value.



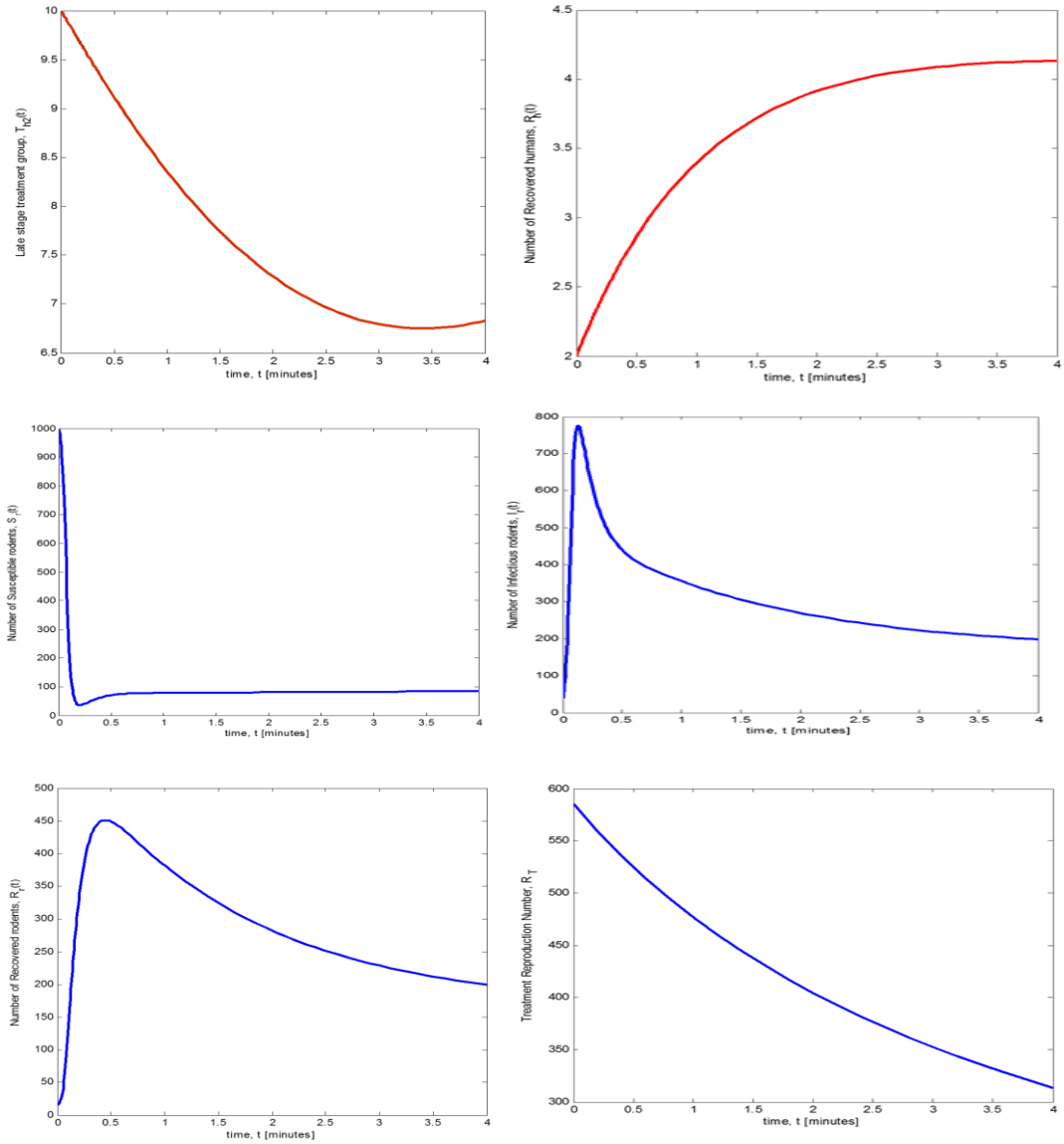


Figure 1. Simulation results showing the general dynamics of the model

EFFECT OF THE EFFECTIVE TREATMENT RATE

In order to investigate the impact of the effective treatment rate on the spread of LF, we carry out some numerical simulations to show the contribution of effective treatment rate during the whole infection. From Figure 2, we can observe that infected individuals reach a lower point level as θ increases. This Figure 2 illustrates the great influence of the effective treatment rate as shown in the threshold analysis.

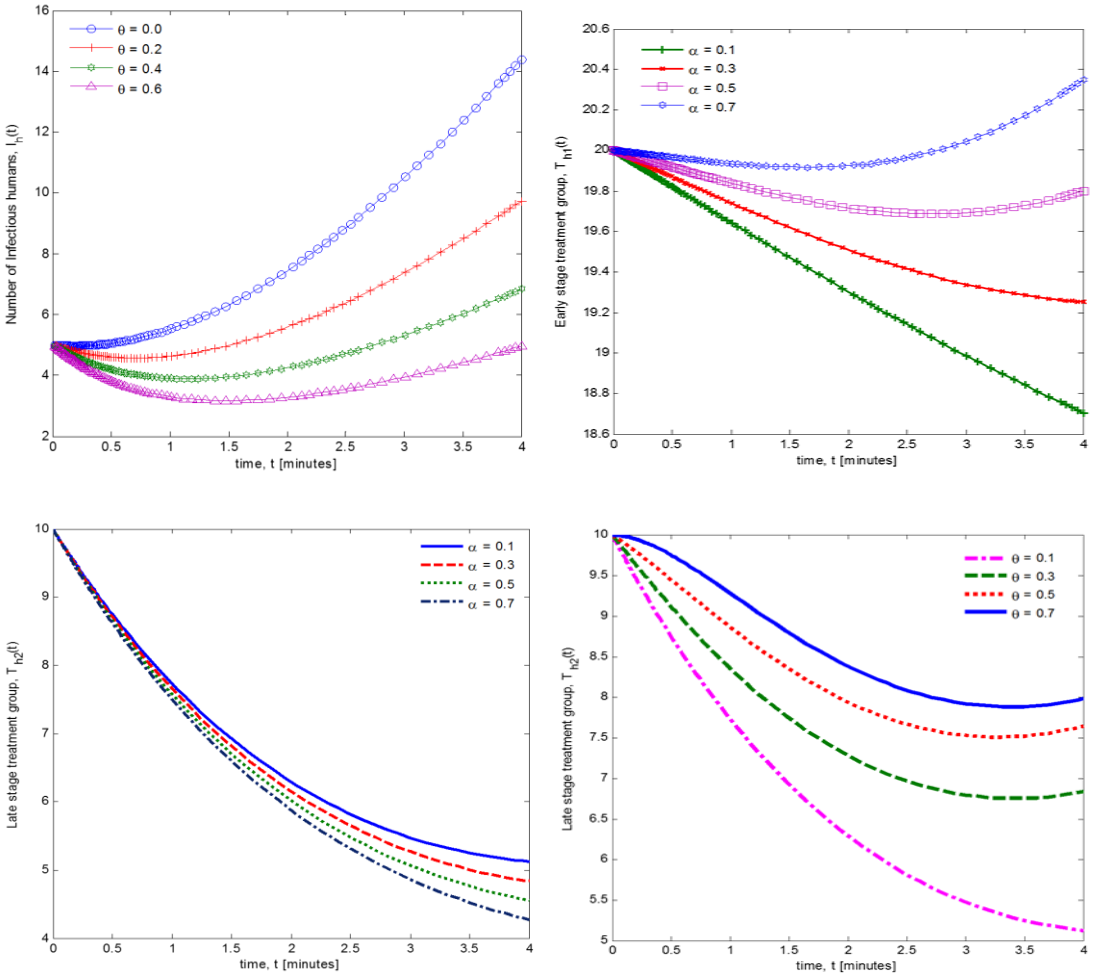


Figure 2. Impact of effective treatment rate on the spread of LF.

CONCLUDING REMARKS

This paper is concerned with an epidemiological treatment model of Lassa fever (LF). The effect of treatment rate of humans on the model is investigated and the main results are given in terms of local and global stability. It has been shown that that treatment rate of humans will have a positive impact in reducing the burden of LF in the population. Our model predicts that treatment control can reduce the population level transmission by up to 12% alone without existing interventions. Therefore, treatment has significant effect on LF transmission, but it may not be able to eliminate the disease unless a multiple control strategy is adopted. Accordingly, we should reduce the reproduction number periodically so as to keep the number of infected below the capacity for treatment. Finally, some numerical simulations are carried out to support our theoretical results. Based on this, we carry out some numerical simulations to show the contribution of effective treatment rate during the whole infection. From the simulation results, we observed that infected individuals reach a lower point level as θ increases. This figure illustrates the great influence of the effective treatment rate as shown in the threshold analysis. It is hoped that this study would motivate public health epidemiologists to collect relevant data for further and better understanding of the effect of treatment on the dynamics of LF.

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