

# An optimal control model for the transmission dynamics of Lassa fever

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## Research Article

**Keywords:** Lassa fever, Periodic, Optimal control, Sensitivity analysis, Control measures

**Posted Date:** April 7th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1513399/v1>

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## RESEARCH

# An optimal control model for the transmission dynamics of Lassa fever

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## Abstract

In this paper, a mathematical model for Lassa fever transmission dynamics with rodent logistic growth is developed and analysed. The stability analysis of the autonomous system of the model is presented. The sensitivity analysis of the parameters is performed using the Partial Rank Correlation Coefficient (PRCC) technique. The non-autonomous model is further analysed for stability of disease-free periodic equilibrium (DFPE) in terms of reproduction number ratio,  $R_{0t}$ . It is shown that DFPE is locally asymptotically stable when  $R_{0t} < 1$  and unstable if  $R_{0t} > 1$ . Additionally, the optimal control model is formulated with five control measures namely; personal protective equipment and avoiding hunting of rodents, proper handling of food, treatment and isolation, cleaning and disinfecting the environment, and rodent control. Simulations of the optimal control model show that the combined implementation of the five control measures reduce Lassa fever spread in the population. However, when there is limited resources to implement the five control measures, three or four combined control measures can be implemented provided that proper handling of food is among the combined control measures.

**Keywords:** Lassa fever; Periodic; Optimal control; Sensitivity analysis; Control measures.

## Introduction

Lassa fever is an acute illness that is caused by contact with infected *Mastomys* rodents [1]. These rodents are known to breed frequently and produce large numbers of offspring during the latter part of the rainy season [2]. *Mastomys* rodents are known to normally populate among human households and also in food storehouses, making it easy for transmission of the viruses like Lassa virus. Lassa fever is endemic in some Africa countries where the *Mastomys* rodents are prevalent, countries such as Sierra Leone, Liberia, Guinea and Nigeria. Transmission of the Lassa virus from the rodents to humans occurs through contact with infected rodents or ingesting foodstuffs that have been in contact with infected rodents or through air inhalation. Viral shedding of the infected rodents to the environment occurs through the passing of urine and droppings by the rodents.

Transmission of Lassa fever is not only through contact with the *Mastomys* rodent or viral shedding in the environment but it can also be transmitted from person to person. This occurs due to exposure to the virus via the blood, tissue, or secretions from an infected individual [1]. As a result of this, there is a need for proper handling of infected individuals by medical personnel through proper use of

personal protective equipment (PPE) [1]. It takes approximately 1 – 3 weeks for an infected individual to manifest signs and symptoms of Lassa fever infection from the time they come into contact with the Lassa virus. Mild symptoms of the Lassa fever include mild fever, weakness, and headaches, while serious symptoms include haemorrhaging in either the gums, nose or eyes, serious repeated vomiting, swelling of the face, chest, back and abdominal pains [1].

Several mathematical models have been developed to understand the dynamics of Lassa fever within a population. Ibrahim *et al.* [3] and Bakare *et al.* [4] presented a periodic model for Lassa fever transmission dynamics. Their results suggest interventions should be employed for the elimination of the Lassa virus within the community. However, their models did not include optimal control analysis of intervention measures [3]. Bakare *et al.* [4] further pointed out that a combination of intervention measures such as treatment of Lassa fever with Ribavirin, educating the community on how to practice environmental hygiene, isolation of infected Lassa fever patients and the probable culling any rodents found, could marginally reduce the prevalence of Lassa fever and its mortality rate [4]. Okolo *et al.* [5] developed a model for the dynamics of Lassa fever in the presence of isolation and treatment. The results of the study indicated that effective treatment strategies provide good control against Lassa fever spread. Other publications on the subject matter to take note of are [6, 7, 8, 9, 10] just to name a few. These models presented have one thing in common as they modelled the effect of certain control measures on the dynamics of Lassa fever. However, none of these above-mentioned authors studied the effect of Lassa virus concentration in the environment and optimal control model. Although, Peter *et al.* [11], Onah *et al.* [12] and Ibrahim *et al.* [3] presented an optimal control model of Lassa fever but the virus concentration compartment and periodic rodent population are not considered in their works which is the novelty of this paper. Virus concentration in the environment is considered in this paper due to the faecal droppings and urine discharge by the rodents. The rodents' droppings and urine may have contact with foodstuffs that are not properly handled or stored in rodent-proof containers. Furthermore, a periodic rodent population is important in this study as rodents breed more when grass and other seeds are ripening during the latter part of the rainy season [2].

Applying optimal control to infectious disease such as Lassa fever provides important information to public health specialists on how the implementation of control measures minimizes the spread of Lassa fever in the population. Reference literature on infectious diseases that have used the optimal control theory include [13, 14, 11, 12, 15, 16, 17, 18]. Based on the suggestions by Bakare *et al.* and the WHO guidelines, this work presents an optimal control theory model for the transmission dynamics of Lassa fever in the presence of control measures such as avoiding hunting of rodents, early treatment and isolation, proper handling of food, rodent control, the wearing of protective clothing when caring for the sick and avoiding contacts with rodents. This is different from other works on Lassa fever as it incorporates a virus concentration compartment, a periodic rodent population, [4, 3] and proper handling of food as an additional control measure to the controls investigated by Peter *et al.* [11], Onah *et al.* [12] and Ibrahim *et al.* [3].

68 The rest of this paper is arranged as follows: in Section 2 we present the model  
 69 formulation, Section 3, presents the basic properties of the autonomous model,  
 70 Section 4, presents the mathematical analysis of the autonomous model, Section 5,  
 71 presents the endemic equilibrium for the autonomous model, Section 6, presents the  
 72 sensitivity analysis, Section 7, presents the analysis of the non-autonomous model,  
 73 Section 8, presents the optimal control analysis, Section 9, presents the results  
 74 and discussions of the numerical simulations and finally Section 10, presents the  
 75 conclusions of the study. We have also attached an appendix for proofs.

## 76 Methods

### 77 Model Formulation

The model considers the human population,  $N_H(t)$ , rodent population,  $N_R(t)$  and Lassa virus concentration in the environment,  $V(t)$  at any time,  $t$ . The human population is subdivided into Susceptible individuals,  $S_H(t)$ , Exposed individuals,  $E_H(t)$ , Infected individuals,  $I_H(t)$ , and Recovered individuals,  $R_H(t)$ , such that

$$N_H(t) = S_H(t) + E_H(t) + I_H(t) + R_H(t).$$

The total rodent population at time,  $t$ , is denoted by  $N_R(t)$ . It is subdivided into susceptible rodents,  $S_R(t)$  and Infected rodents,  $I_R(t)$ , so that

$$N_R(t) = S_R(t) + I_R(t).$$

78 Susceptible humans are recruited into the population at a rate,  $\Lambda_H$ . They acquire  
 79 Lassa virus infection through effective contact with the infected humans,  $I_H(t)$ ,  
 80 or infected rodents,  $I_R(t)$ , or via eating food or touching surfaces that are virus-  
 81 contaminated at a force of infection is given by

$$\lambda_H = \frac{\beta_1 I_H + \beta_2 I_R}{N_H} + \frac{\beta_3 V}{K_1 + V}$$

where,  $\beta_1, \beta_2, \beta_3$ , represent the effective contact rates between susceptible humans and infected humans, infected rodents, and the virus concentration within the environment respectively.  $K_1$  is the half-saturation constant for the Lassa virus concentration. Humans exposed to the Lassa virus progress to the infected class,  $I_H(t)$ , at a rate,  $\sigma$ . Natural death rate,  $\mu_H$ , is assumed for all human classes. The infected humans recover from Lassa fever after treatment at a rate,  $\gamma$ , or they may die of the fever at a rate,  $\delta_H$ . Those that recovered from the fever are assumed to have partial immunity and become susceptible again at a rate,  $\psi$ .

For the rodent population, a logistic growth rate is assumed for the susceptible rodents which is given by  $\Lambda_R(t) \left(1 - \frac{N_R(t)}{K(t)}\right)$ , where  $\Lambda_R(t)$  and  $K(t)$  are the recruitment rate and carrying capacity of the rodent population. They are assumed continuous, positive and  $\omega$ -periodic functions as rodents breed more towards the end of the rainy season due to availability of food within that period [2]. The susceptible rodent population is reduced through effective contact with infected rodents

or via eating food that is contaminated with the Lassa virus and hence the force of infection is given as,

$$\lambda_R = \frac{\beta_4 I_R}{N_R} + \frac{\beta_5 V}{K_1 + V}$$

where  $\beta_4$  and  $\beta_5$  are the effective contact rates between the susceptible rodents and the infected rodents and virus concentration in the environment respectively.

The rodent population is assumed to die due to predation by other animals at a rate,  $d$ , or via natural death at a rate,  $\mu_R$ . Viral shedding among infected humans and infected rodents occurs at rates,  $\alpha_1$  and  $\alpha_2$  respectively and viral decay within the environment occurs at a rate,  $\mu_V$ . This work does not consider vertical transmission through breastfeeding for both human and rodent populations. The systematic diagram for model description is presented in Figure 1.

Hence, the model equation is given by

$$\begin{aligned} \frac{dS}{dt} &= \Lambda_H + \psi R_H - \lambda_H S_H - \mu_H S_H, \\ \frac{dE_H}{dt} &= \lambda_H S_H - \mu_H E_H - \sigma E_H, \\ \frac{dI_H}{dt} &= \sigma E_H - \mu_H I_H - \delta_H I_H - \gamma I_H, \\ \frac{dR_H}{dt} &= \gamma I_H - \mu_H R_H - \psi R_H, \\ \frac{dS_R}{dt} &= \Lambda_R(t) \left(1 - \frac{N_R}{K(t)}\right) N_R - \lambda_R S_R - \mu_R S_R - d S_R, \\ \frac{dI_R}{dt} &= \lambda_R S_R - \mu_R I_R - d I_R, \\ \frac{dV}{dt} &= \alpha_1 I_R + \alpha_2 I_H - \mu_V V \end{aligned} \tag{1}$$

with the initial conditions  $S_H(0) > 0$ ,  $E_H(0) \geq 0$ ,  $I_H(0) \geq 0$ ,  $R_H(0) \geq 0$ ,  $S_R(0) > 0$ ,  $I_R(0) \geq 0$ ,  $V(0) \geq 0$  and all the parameters of the model are positive.

## The basic properties of the autonomous model

Positivity and boundedness of solutions

**Theorem 1** *Let  $S_H(0) > 0$ ,  $E_H(0) \geq 0$ ,  $I_H(0) \geq 0$ ,  $R_H(0) \geq 0$ ,  $S_R(0) > 0$ ,  $I_R(0) \geq 0$ ,  $V(0) \geq 0$  be the initial data for model(1). The solution set  $\{S_H(t), E_H(t), I_H(t), R_H(t), S_R(t), I_R(t), V(t)\}$  of model (1) will remain positive for all time  $t > 0$ .*

**Proof** Let  $t_1 = \sup\{t > 0 : S_H(0) > 0, E_H(0) \geq 0, I_H(0) \geq 0, R_H(0) \geq 0, S_R(0) > 0, I_R(0) \geq 0, V(0) \geq 0\} \in [0, t]$ . With  $t_1 > 0$ , it follows from the first equation of model (1) that

$$\frac{dS_H}{dt} \geq \Lambda_H - \lambda_H S_H - \mu_H S_H. \quad (2)$$

Using the integrating factor method, this yields

$$S_H(t) \geq \exp\left(-\int_0^t (\mu_H + \lambda_H(s))ds\right) \left[ S_H(0) + \Lambda_H \int_0^t \exp\left(\int_0^s (\mu_H + \lambda_H(m))dm\right) ds \right] > 0. \quad (3)$$

In a similar way,  $E_H(t) \geq 0, I_H(t) \geq 0, R_H(t) \geq 0, S_R(t) > 0, I_R(t) \geq 0, V(t) \geq 0$  for all time,  $t > 0$ . Hence, all the solutions of the model (1) are positive for all initial data. To prove boundedness, we add the first four equations of the model (1) to obtain

$$\frac{dN_H}{dt} = \Lambda_H - \mu_H N_H - dI_R \quad (4)$$

such that  $\frac{dN_H}{dt} \leq \Lambda_H - \mu_H N_H$ . With application of Comparison theorem, we have

$$N_H(t) \leq N_H(0)e^{-\mu_H t} + \frac{\Lambda_H}{\mu_H}(1 - e^{-\mu_H t}). \quad (5)$$

This means that  $N_H(t) \leq \frac{\Lambda_H}{\mu_H}$  is bounded if  $N_H(0) \leq \frac{\Lambda_H}{\mu_H}$ . For the rodent population, we add the fifth and sixth equations of model (1) to yield

$$\frac{dN_R}{dt} = \Lambda_R(t) \left(1 - \frac{N_R}{K(t)}\right) N_R - (\mu_R + d)N_R \quad (6)$$

which can be written as

$$\frac{dN_R}{dt} - m(t)N_R = -n(t)N_R^2 \quad (7)$$

with  $m(t) = \Lambda_R(t) - \mu_R + d$  and  $n(t) = \frac{\Lambda_R(t)}{K(t)}$ . Using the method of variation of constants by Xin *et al.* [19], we have

$$N_R(t) = C(t)A(t) \quad (8)$$

with  $A(t) = e^{\int_0^t m(r)dr}$ . Differentiating (8) and substituting into (7) yields

$$C'(t) = -n(t)C^2(t)A(t). \quad (9)$$

Upon integration of (9) from  $[0, t]$  when  $t \in [0, \omega]$ , we have

$$C(t) = \frac{C(0)}{1 + C(0)U(t)} \quad (10)$$

such that

$$C(\omega) = \frac{C(0)}{1 + C(0)U(\omega)} \quad (11)$$

with  $U(t) = \int_0^t n(s)A(s)ds$ . Since  $N_R(t)$  is periodic, it implies that  $C(0) = C(\omega)A(\omega)$ . This gives

$$C(\omega) = C(0)A^{-1}(\omega)$$

with  $A^{-1}(\omega) = e^{-\int_0^t m(r)dr}$ . Now  $C(0) = \frac{A(\omega) - 1}{U(\omega)}$  by simplification. So, equation (10) becomes

$$C(t) = \frac{1}{U(t) + \frac{U(\omega)}{A(\omega) - 1}} \quad (12)$$

With the definition of  $C(t), A(t), U(t), m(t)$  and  $n(t)$ , we have from (8) that the rodent population is given by

$$N_R(t) = \frac{e^{\int_0^t (\Lambda_R(t) - \mu_R - d)dr}}{\int_0^t \frac{\Lambda_R(s)}{K(s)} e^{\int_0^s (\Lambda_R(k) - \mu_R - d)dk} + \frac{\int_0^\omega \frac{\Lambda_R(s)}{K(s)} e^{\int_0^s (\Lambda_R(k) - \mu_R - d)dk}}{e^{\int_0^\omega (\Lambda_R(r) - \mu_R - d)dr} - 1}}. \quad (13)$$

This population,  $N_R(t)$  has a globally asymptotically stable periodic solution

$$N_R^*(t) = K(t) \left( 1 - \frac{\mu_R + d}{\Lambda_R(t)} \right)$$

that is positive whenever  $\Lambda_R(t) > (\mu_R + d)$ .

Let  $\Lambda_R(t)$  and  $K(t)$  be continuous, positive and  $\omega$ -periodic functions, then, there exists a positive number  $N_R^*(t)$  such that  $\Lambda_R(t) - (\mu_R + d) \leq \frac{\Lambda_R(t)}{K(t)} N_R(t)$  provided  $N_R(t) \geq N_R^*(t)$ . For the virus concentration, it is true that  $I_H(t) \leq N_H(t)$  and  $I_R(t) \leq N_R(t)$ .

So from the seventh equation of model (1), we have

$$\frac{dV}{dt} \leq \alpha_1 N_R + \alpha_2 N_H - \mu_V V. \quad (14)$$

Using Growall's inequality, we have

$$V(t) \leq \frac{1}{\mu_V} \left( \alpha_1 N_R(t) + \frac{\alpha_2 \Lambda_H}{\mu_H} \right) + e^{-\mu_V t} \left( V(0) - \frac{1}{\mu_V} \left( \alpha_1 N_R(t) + \frac{\alpha_2 \Lambda_H}{\mu_H} \right) \right) \quad (15)$$

which implies that  $V(t) \leq \frac{1}{\mu_V} (\alpha_1 N_R(t) + \frac{\alpha_2 \Lambda_H}{\mu_H})$  as  $t \rightarrow \infty$ . We state the following

Lemma;

**Lemma 1** *There exist a positive number  $N_R^*(t) = \lim_{t \rightarrow \infty} \text{Sup } K(t) \left(1 - \frac{(\mu_R + d)}{\Lambda_R(t)}\right) > 0$  provided that  $\Lambda_R(t) > (\mu_R + d)$  so that any solutions of the model (1) enters*

$$\begin{aligned} \Omega &= \left\{ (S_H, E_H, I_H, R_H, S_R, I_R, V) \in R_+^7 : N_H \leq \frac{\Lambda_H}{\mu_H}, N_R(t) \leq N_R^*(t), V(t) \right. \\ &\leq \left. \frac{1}{\mu_V} \left( \alpha_1 N_R(t) + \frac{\alpha_2 \Lambda_H}{\mu_H} \right) \right\} \end{aligned} \quad (16)$$

and for each  $N_R(t) \geq N_R^*(t)$ ,  $\Omega$  is a positive invariant set of model (1).

## The mathematical analysis of the autonomous model

The disease-free equilibrium points

We assume that  $\Lambda_R(t) = \Lambda_R$  and  $K(t) = K$  for autonomous system. At the equilibrium point, the rodent population will be  $N_R^* = 0$  and  $N_R^* = K \left(1 - \frac{(\mu_R + d)}{\Lambda_R}\right)$ .  $N_R^* = 0$  is a trivial solution of the rodent population that gives an unstable disease-free equilibrium,  $E_0 = \left(\frac{\Lambda_H}{\mu_H}, 0, 0, 0, 0, 0, 0\right)$  while  $N_R^* = K \left(1 - \frac{(\mu_R + d)}{\Lambda_R}\right)$  will give another disease-free equilibrium state,

$$E_1 = (S_H^0, 0, 0, 0, S_R^0, 0, 0) = \left(\frac{\Lambda_H}{\mu_H}, 0, 0, 0, N_R^*, 0, 0\right), \quad (17)$$

that exists when  $\Lambda_R > (\mu_R + d)$ .

The basic reproduction number,  $\mathcal{R}_0$

The basic reproduction number,  $\mathcal{R}_0$ , is a threshold quantity that determines how the disease spreads within the population. When  $\mathcal{R}_0 < 1$ , it means that the disease will be eliminated within the population while  $\mathcal{R}_0 > 1$  implies that there is a continuation in the spread of disease within the population. Let

$$f = \sigma + \mu_H, g = \gamma + \mu_H + \sigma + \delta_H, h = \mu_H + \psi, q = \mu_R + d. \quad (18)$$

Using the approach of the next-generation matrix method by van den Driessche and Watmough [20], the Jacobian matrices at the DFE for new infection matrix,  $\mathcal{F}$ , and transition matrix,  $\mathcal{V}$ , are given by

$$\mathcal{F} = \begin{bmatrix} 0 & \beta_1 & \beta_2 & \frac{\beta_3 S_H^0}{K_1} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_4 & \frac{\beta_5 S_R^0}{K_1} \\ 0 & 0 & 0 & 0 \end{bmatrix}, \mathcal{V} = \begin{bmatrix} f & 0 & 0 & 0 \\ -\sigma & g & 0 & 0 \\ 0 & 0 & q & 0 \\ 0 & -\alpha_2 & -\alpha_1 & \mu_V \end{bmatrix}. \quad (19)$$

The basic reproduction number,  $\mathcal{R}_0$ , is the spectral radius of the matrix,  $\mathcal{F}\mathcal{V}^{-1}$ .

This is the maximum positive solution of the polynomial

$$\kappa^2 (\kappa^2 - (R_{rv} + R_{rr} + R_{hv} + R_{hh})\kappa + R_{rr}R_{hh} + R_{rv}R_{hh} + R_{hv}R_{rr} - R_{hr}R_{rv}) = 0 \quad (20)$$

where  $R_{hv} = \frac{\sigma\beta_3\alpha_2 S_H^0}{fgK_1\mu_V}$ ,  $R_{rv} = \frac{\beta_5\alpha_1 S_R^0}{qK_1\mu_V}$ ,  $R_{rr} = \frac{\beta_4}{q}$ ,  $R_{hh} = \frac{\sigma\beta_1}{fg}$ ,  $R_{hr} = \frac{\sigma\beta_2\alpha_2}{fg\alpha_1}$ .  
Therefore,

$$\mathcal{R}_0 = \frac{(\mathcal{Q}_1 + \sqrt{(\mathcal{Q}_1^2 - 4\mathcal{Q}_2)})}{2} \quad (21)$$

where  $\mathcal{Q}_1 = R_{rv} + R_{rr} + R_{hv} + R_{hh}$  and  $\mathcal{Q}_2 = R_{rr}R_{hh} + R_{rv}R_{hh} + R_{hv}R_{rr} - R_{hr}R_{rv}$ .  
This is equivalent to

$$\mathcal{R}_0 = \frac{(\mathcal{Q}_1 + \sqrt{((R_{rv} + R_{rr} - R_{hv} - R_{hh})^2 + 4R_{rv}(R_{hr} + R_{hv}))})}{2}. \quad (22)$$

Here,  $R_{rv}$ ,  $R_{hv}$ ,  $R_{rr}$ ,  $R_{hh}$  and  $R_{hr}$  are the reproduction numbers for rodent and virus concentration, human and virus concentration, rodent and rodent, human and human, and human and rodent interactions respectively. Based on the approach of the next-generation matrix method, we state the following lemma.

**Lemma 2** *The disease-free equilibrium,  $E_0$ , is locally asymptotically stable if  $\mathcal{R}_0 < 1$  and unstable if  $\mathcal{R}_0 > 1$ .*

## Endemic equilibrium state of the autonomous model

The endemic equilibrium state of the model (1) is solved when  $\lambda_H \neq 0$  and  $\lambda_R \neq 0$ . It is given by  $E^* = (S_H^*, E_H^*, I_H^*, R_H^*, S_R^*, I_R^*, V^*)$  where

$$\begin{aligned} S_H^* &= \frac{\Lambda_H \sigma h f}{(f \sigma h \mu_H + D \lambda_H^*)}, E_H^* = \frac{\Lambda_H g h \lambda_H^*}{(f \sigma h \mu_H + D \lambda_H^*)}, I_H^* = \frac{\Lambda_H \sigma h \lambda_H^*}{(f \sigma h \mu_H + D \lambda_H^*)}, \\ R_H^* &= \frac{\Lambda_H \sigma \gamma \lambda_H^*}{(f \sigma h \mu_H + D \lambda_H^*)}, S_R^* = \frac{q N_R^*}{(q + \lambda_R^*)}, I_R^* = \frac{N_R^* \lambda_R^*}{(q + \lambda_R^*)}, \\ V^* &= \frac{\alpha_1 N_R^* f \mu_H \sigma h \lambda_R^* + \lambda_R^* \lambda_H^* (\alpha_1 N_R^* D + \alpha_2 \sigma h \Lambda_H)}{(\mu_V (q + \lambda_R^*) (f \sigma h \mu_H + D \lambda_H^*))} \end{aligned} \quad (23)$$

$$\begin{aligned} \text{with } \lambda_H^* &= \frac{\beta_1 I_H^*}{N_H^*} + \frac{\beta_2 I_R^*}{N_H^*} + \frac{\beta_1 V^*}{(K_1 + V^*)}, \lambda_R^* = \frac{\beta_4 I_R^*}{N_R^*} + \frac{\beta_5 V^*}{(K_1 + V^*)}, \\ N_R^* &= K \left( 1 - \frac{(\mu_R + d)}{\Lambda_R} \right), N_H^* = S_H^* + E_H^* + I_H^* + R_H^*, D = fgh - \sigma \gamma \psi > 0. \end{aligned}$$

### Local stability of endemic equilibrium

The local stability of the endemic equilibrium state of model (1) is established using the Centre manifold theory by Castillo *et al.* [21]. The theory is used to establish the existence of a forward bifurcation of a system at  $\mathcal{R}_0 = 1$ . With a forward bifurcation, it means that the endemic equilibrium is locally asymptotically stable when  $\mathcal{R}_0 > 1$  but near unity.

**Theorem 2** *The endemic equilibrium of the model (1) is locally asymptotically stable if  $\mathcal{R}_0 > 1$  and  $\psi = 0$  but near unity.*

**Proof** See Appendix I.

## Sensitivity analysis

There is uncertainty in the selection of parameters of the model. Hence, we use the Latin Hypercube Sampling and the Partial Rank Correlation Coefficients (PRCC) technique to investigate sensitive parameters that affect the basic reproduction number,  $\mathcal{R}_0$ . Following the approach in [22], the scatter plots and tornado plot display parameters that affect  $\mathcal{R}_0$  in Figures 2 and 3. The tornado plot in Figure 2 presents the PRCCs for the 17 parameters in  $\mathcal{R}_0$ . It can be seen from Table 1 and Figure 2 that parameters of interest with positive PRCCs and significant P-values are  $\beta_3$ ,  $\alpha_2$ ,  $\alpha_1$ . Increasing these parameters will marginally increase  $\mathcal{R}_0$ . The parameters with relatively high negative PRCCs and significant P-values are  $\mu_R$ ,  $\mu_V$  and increasing them will consequently decrease  $\mathcal{R}_0$ . Table 1 and Figure 2 are generated using R-studio. For the scatter plots presented in Figure 3, Monte Carlo simulations for the six parameters that have the greatest PRCC values are simulated. In each simulation, we run a 1000 simulations that are randomly drawn for each parameter. Figure 3 shows that an increase in the parameters,  $\mu_V$  and  $\mu_R$  and a decrease in the parameters,  $\beta_3, \beta_5$ ,  $\alpha_1$  and  $\alpha_2$  will result in a decrease in  $\mathcal{R}_0$  which supports the PRCCs in Table 1 and Figure 2.

## Analysis of the non-autonomous model

### The disease-free periodic equilibrium

Considering the non-autonomous system when  $\Lambda_R(t)$  and  $K(t)$  are  $\omega$ -periodic function, the disease-free periodic equilibrium, (DFPE), is given by

$$E_{0t} = [S_{Ht}^0, E_{Ht}^0, I_{Ht}^0, R_{Ht}^0, S_{Rt}^0, I_{Rt}^0, V_t^0] = \left[ \frac{\Lambda_H}{\mu_H}, 0, 0, 0, N_{Rt}^*, 0, 0 \right]$$

where  $N_{Rt}^* = K(t) \left[ 1 - \frac{(\mu_R + d)}{\Lambda_R(t)} \right]$  is a positive  $\omega$ -periodic rodent population that exists whenever  $\Lambda_R(t) > (\mu_R + d)$ .

### Local stability of disease-free periodic equilibrium

The local stability of disease-free periodic equilibrium,  $E_{0t}$ , is established in terms of basic reproduction ratio,  $R_{0t}$ , of the non-autonomous system using the approach described in Wang and Zhao [23]. This is done by linearizing the non-autonomous system at DFPE,  $E_{0t}$ .

Consider the infected compartments of the model given by

$$\left. \begin{aligned} \frac{dE_H}{dt} &= \frac{\beta_1 S_H I_H + \beta_2 S_H I_R}{N_H} + \frac{\beta_3 S_H V}{K_1 + V} - \sigma E_H - \mu_H E_H, \\ \frac{dI_H}{dt} &= \sigma E_H - \gamma I_H - \mu_H I_H - \delta_H I_H, \\ \frac{dI_R}{dt} &= \frac{\beta_4 S_R I_R}{N_R} + \frac{\beta_5 S_R V}{K_1 + V} - d I_H - \mu_R I_R, \\ \frac{dV}{dt} &= \alpha_1 I_R + \alpha_2 I_H - \mu_V V. \end{aligned} \right\} \quad (24)$$

The Jacobian matrices at DFPE for the new infection and transition by other means,  $\mathcal{F}(t)$  and  $\mathcal{V}(t)$  are given by

$$\mathcal{F}(t) = \begin{bmatrix} 0 & \frac{\beta_1 S_{Ht}^0}{N_{Ht}^0} & \frac{\beta_2 S_{Ht}^0}{N_{Ht}^0} & \frac{\beta_3 S_{Ht}^0}{K_1} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_4 S_{Rt}^0}{N_{Rt}^0} & v \frac{\beta_5 S_{Rt}^0}{K_1} \\ 0 & 0 & 0 & 0 \end{bmatrix}, \mathcal{V}(t) = \begin{bmatrix} f & 0 & 0 & 0 \\ -\sigma & g & 0 & 0 \\ 0 & 0 & q & 0 \\ 0 & -\alpha_1 & -\alpha_2 & \mu_V \end{bmatrix}, \quad (25)$$

where  $\mathcal{F}(t)$  is non-negative while  $-\mathcal{V}(t)$  is cooperative.

**Theorem 3** *The disease-free periodic equilibrium,  $E_{0t}$  of system (1) is locally asymptotically stable if  $R_{0t} < 1$  otherwise unstable if  $R_{0t} > 1$  provided that  $\Lambda_t(t) > (\mu_R + d)$ .*

**Proof.** The Jacobian matrix at DFPE,  $E_{0t}$  of the system (1) is given by

$$J(E_{0t}) = \begin{bmatrix} \mathcal{F}(t) - \mathcal{V}(t) & 0 \\ H(t) & M(t) \end{bmatrix}, \quad (26)$$

where

$$H(t) = \begin{bmatrix} 0 & -\frac{\beta_1 S_{Ht}^0}{N_{Ht}^0} & -\frac{\beta_2 S_{Ht}^0}{N_{Ht}^0} & -\frac{\beta_3 S_{Ht}^0}{K_1} \\ 0 & \gamma & 0 & 0 \\ 0 & 0 & -\frac{\beta_4 S_{Rt}^0}{N_{Rt}^0} & -\frac{\beta_5 S_{Rt}^0}{K_1} \end{bmatrix}, M(t) = \begin{bmatrix} -\mu_H & \psi & 0 \\ 0 & -h & 0 \\ 0 & 0 & -(\mu_R + d) \end{bmatrix}. \quad (27)$$

The local stability of  $E_{0t}$  depends on the eigenvalues of  $\mathcal{F}(t) - \mathcal{V}(t)$  and  $M(t)$ . The matrix  $M(t)$  has negative eigenvalues,  $-\mu_H, -h, -q$  which implies that  $\rho(\Phi_M(\omega)) < 1$ . For the matrix  $\mathcal{F}(t) - \mathcal{V}(t)$ , we apply Theorems 2.1 and 2.2 of Wang and Zhao [23] which state that  $R_{0t} < 1$  if  $\rho(\Phi_{\mathcal{F}-\mathcal{V}}(\omega)) < 1$  and  $R_{0t} > 1$  if  $\rho(\Phi_{\mathcal{F}-\mathcal{V}}(\omega)) > 1$ . With the approach of Garba *et al.* [24] and Ibrahim *et al.* [3], the DFPE,  $E_{0t}$ , is locally asymptotically stable whenever  $\rho(\Phi_{\mathcal{F}-\mathcal{V}}(\omega)) < 1$  and unstable if  $\rho(\Phi_{\mathcal{F}-\mathcal{V}}(\omega)) > 1$ . Here,  $\rho(\Phi_{\mathcal{F}-\mathcal{V}}(\omega))$  is the spectral radius of  $\Phi_{\mathcal{F}-\mathcal{V}}(\omega)$  while  $\Phi_{\mathcal{F}-\mathcal{V}}(\omega)$  is the fundamental matrix of a periodic system. The computation of  $\rho(\Phi_{\mathcal{F}-\mathcal{V}}(\omega))$  is described in Theorem 2.1 of Wang and Zhao [23].

## Optimal control analysis

Based on the most sensitivity parameters that fuel the spread of Lassa, the following are considered as control measures to reduce the transmission of the Lassa virus:

- $u_1(t)$ : personal protective equipment in caring for the sick and avoiding contact with rodents,
- $u_2(t)$ : proper handling of food through; storing foodstuffs in rodent-proof containers, cooking foods thoroughly and refraining from drying food in the open,
- $u_3(t)$ : early treatment and isolation of infected persons,

- $u_4(t)$ : rodent control through trapping and fumigation,
- $u_5(t)$ : cleaning and disinfecting the environment.

The optimal control model is given by

$$\begin{aligned}
 \frac{dS_H}{dt} &= \Lambda_H + \psi R_H - \lambda_H^* S_H - \mu_H S_H \\
 \frac{dE_H}{dt} &= \lambda_H^* S_H - \sigma E_H - \mu_H E_H \\
 \frac{dI_H}{dt} &= \sigma E_H - \gamma(1 + u_3(t))I_H - \mu_H I_H - \delta_H I_H \\
 \frac{dR_H}{dt} &= \gamma(1 + u_3(t))I_H - \psi R_H - \mu_H R_H \\
 \frac{dS_R}{dt} &= \Lambda_R(t)(1 - u_4(t))(1 - \frac{N_R}{K(t)}) - \lambda_R S_R - (\mu_R + d)(1 + u_4(t))S_R \\
 \frac{dI_R}{dt} &= \lambda_R S_R - (\mu_R + d)(1 + u_4(t))I_R \\
 \frac{dV}{dt} &= \alpha_1 I_R + \alpha_2 I_H - \mu_V(1 + u_5(t))V
 \end{aligned} \tag{28}$$

where

$$\lambda_H^* = \frac{(1 - u_1(t))(\beta_1 I_H + \beta_2 I_R)}{N_H} + \frac{(1 - u_2(t))\beta_3 V}{K_1 + V}.$$

The objective functional,  $\mathcal{J}$ , is given as

$$\mathcal{J}(u_1, u_2, u_3, u_4, u_5) = \int_0^{t_f} (\rho_1 E_H + \rho_2 I_H + \rho_3 N_R + \rho_4 V + \frac{1}{2} \sum_{i=1}^5 c_i u_i^2(t)) dt \tag{29}$$

and it is subject to the optimal control model (28) with the initial conditions of system (1), where  $\rho_i > 0$  ( $i = 1, 2, 3, 4$ ) are the balancing weight constants for the exposed humans, infected humans, rodents population and the Lassa virus concentration in the environment. The parameters  $c_i > 0$ , ( $i = 1, 2, 3, 4, 5$ ) are the relative cost measures that are associated with the control functions,  $u_i > 0$ , ( $i = 1, 2, 3, 4, 5$ ) respectively,  $t_f$  is the final time for the implementation of the controls.

Let  $U = \{(u_1, u_2, u_3, u_4, u_5) : u_i, \text{ Lebesgue measurable, } 0 \leq u_i(t) \leq 1, \text{ for } t \in [0, t_f], (i = 1, 2, 3, 4, 5)\}$  be a non-empty control set. With the objective functional,  $\mathcal{J}$ , defined on the non-empty control set,  $U$ , and subject to the optimal control model with non-negative initial conditions, there exists an optimal control  $u^* = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$  such that

$$\mathcal{J}(u^*) = \min_U \mathcal{J}(u_1, u_2, u_3, u_4, u_5). \tag{30}$$

The optimal control model and the objective functional,  $\mathcal{J}$ , is converted to a problem of minimizing a point-wise Hamiltonian,  $\mathcal{H}$ , using the necessary conditions of the Pontryagin's maximum principle with regards to the control quintuple,  $u_1, u_2, u_3, u_4,$

277  $u_5$ . This is given by

278

$$\begin{aligned}
 \mathcal{H} &= \rho_1 E_H + \rho_2 I_H + \rho_3 N_R + \rho_4 V + \frac{1}{2} \sum_{i=1}^5 c_i u_i^2(t) + \Omega_1 (\Lambda_H + \psi R_H - \lambda_H^* S_H - \mu_H S_H) \\
 &+ \Omega_2 (\lambda_H^* S_H - \sigma E_H - \mu_H E_H) + \Omega_3 (\sigma E_H - \gamma(1 + u_3) I_H - \mu_H I_H - \delta_H I_H) \\
 &+ \Omega_4 (\gamma(1 + u_3) I_H - \psi R_H - \mu_H R_H) + \Omega_5 (\Lambda_R(t)(1 - u_4) \left(1 - \frac{N_R}{K(t)}\right) - \lambda_R S_R) \\
 &- (\mu_R + d)(1 + u_4) S_R + \Omega_6 (\lambda_R S_R - (\mu_R + d)(1 + u_4) I_R) I_R \\
 &+ \Omega_7 (\alpha_1 I_R + \alpha_2 I_H - \mu_V (1 + u_5))
 \end{aligned} \tag{31}$$

280 where  $\Omega_i$ , ( $i = 1, 2, \dots, 7$ ) are the respective adjoint variables to the state variables,  
 281  $S_H$ ,  $E_H$ ,  $I_H$ ,  $R_H$ ,  $S_R$ ,  $I_R$  and  $V$ . If  $u^* = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$  is an optimal control  
 282 quintuple and  $S_H^*$ ,  $E_H^*$ ,  $I_H^*$ ,  $R_H^*$ ,  $S_R^*$ ,  $I_R^*$ ,  $V^*$ , are the optimal state solutions that  
 283 minimize,  $\mathcal{J}(U)$ , over the control set,  $U$ . Therefore, there exists adjoint variables  
 284 through the application of Pontryagin's maximum principle that satisfy

$$\begin{aligned}
 \frac{d\Omega_1}{dt} &= -\frac{\partial \mathcal{H}}{\partial S_H}, \quad \frac{d\Omega_2}{dt} = -\frac{\partial \mathcal{H}}{\partial E_H}, \quad \frac{d\Omega_3}{dt} = -\frac{\partial \mathcal{H}}{\partial I_H}, \quad \frac{d\Omega_4}{dt} = -\frac{\partial \mathcal{H}}{\partial R_H}, \quad \frac{d\Omega_5}{dt} = -\frac{\partial \mathcal{H}}{\partial S_R}, \\
 \frac{d\Omega_6}{dt} &= -\frac{\partial \mathcal{H}}{\partial I_R}, \quad \frac{d\Omega_7}{dt} = -\frac{\partial \mathcal{H}}{\partial V},
 \end{aligned} \tag{32}$$

286 such that

$$\begin{aligned}
 \frac{d\Omega_1}{dt} &= (\Omega_1 - \Omega_2)(\lambda_{H1}^* (1 - \frac{S_H}{N_H}) + \lambda_{H2}^*) + \Omega_1 \mu_H, \\
 \frac{d\Omega_2}{dt} &= -\rho_1 + (\Omega_2 - \Omega_3)\sigma + (\Omega_2 - \Omega_1) \frac{\lambda_{H1}^*}{N_H} + \Omega_2 \mu_H, \\
 \frac{d\Omega_3}{dt} &= -\rho_2 - \Omega_7 \alpha_2 + (\Omega_1 - \Omega_2)((1 - u_1(t))\beta_1 - \lambda_{H1}^*) \frac{S_H}{N_H} + (\Omega_3 - \Omega_4)\gamma(1 + u_3(t)) \\
 &+ \Omega_3(\mu_H + \delta_H), \\
 \frac{d\Omega_4}{dt} &= (\Omega_4 - \Omega_1)\psi + \Omega_4 \mu_H + (\Omega_2 - \Omega_1) \frac{\lambda_{H1}^*}{N_H}, \\
 \frac{d\Omega_5}{dt} &= -\rho_3 - \Omega_5 \Lambda_R(t)(1 - u_4(t)) \left(1 - \frac{2S_R}{K(t)}\right) + (\Omega_5 - \Omega_6)(\lambda_{R1}^* (1 - \frac{S_R}{N_R}) + \lambda_{R2}^*) \\
 &+ \Omega_5(1 + u_4(t))(\mu_R + d), \\
 \frac{d\Omega_6}{dt} &= -\rho_3 - \Omega_7 \alpha_1 - \Omega_5 \Lambda_R(t)(1 - u_4(t)) \left(1 - \frac{2I_R}{K(t)}\right) \\
 &+ (\Omega_5 - \Omega_6) \frac{(N_R - I_R)\lambda_{R1}^* S_H}{N_R I_R} (\Omega_1 - \Omega_2) \frac{((1 - u_1(t))\beta_2 S_H}{N_H} + \Omega_6(1 + u_4(t))(\mu_R + d), \\
 \frac{d\Omega_7}{dt} &= -\rho_4 + (1 - u_2(t)) \frac{K_1}{(K_1 + V)^2} (\beta_3 S_H (\Omega_1 - \Omega_2) + \beta_5 S_R (\Omega_5 - \Omega_6)) + \Omega_7(1 + u_5(t))\mu_V
 \end{aligned} \tag{33}$$

with

$$\lambda_{H1}^* = \frac{(1 - u_1(t))(\beta_1 I_H + \beta_2 I_R)}{N_H}, \lambda_{H2}^* = \frac{(1 - u_2(t))\beta_3 V}{K_1 + V}, \lambda_{R1}^* = \frac{\beta_4 I_R}{N_R}, \lambda_{R2}^* = \frac{(1 - u_2(t))\beta_5 V}{K_1 + V}$$

and transversality conditions

$$\Omega_i(t_f) = 0, i = 1, 2, \dots, 7. \quad (34)$$

Furthermore, the optimal control quintuple,  $u^* = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)$  that minimizes,  $\mathcal{J}(U)$ , over the control set  $U$ , are the respective solutions of following equations

$$\frac{\partial \mathcal{H}}{\partial u_1} = 0, \quad \frac{\partial \mathcal{H}}{\partial u_2} = 0, \quad \frac{\partial \mathcal{H}}{\partial u_3} = 0, \quad \frac{\partial \mathcal{H}}{\partial u_4} = 0, \quad \frac{\partial \mathcal{H}}{\partial u_5} = 0, \quad (35)$$

and this is given as

$$\left. \begin{aligned} u_1^*(t) &= \frac{(\Omega_2^* - \Omega_1^*)(\beta_1 S_H^* I_H^* + \beta_2 S_H^* I_R^*)}{c_1 N_H}, \\ u_2^*(t) &= \frac{(\beta_2 S_H^* (\Omega_2^* - \Omega_1^*) + \beta_5 S_R^* (\Omega_6^* - \Omega_5^*)) V^*}{c_2 (K_1 + V)}, \\ u_3^*(t) &= \frac{(\Omega_3^* - \Omega_4^*) \gamma I_H}{c_3}, \\ u_4^*(t) &= \frac{1}{c_4} (\Omega_5^* \Lambda_R(t) (1 - \frac{N_R^*}{K(t)}) N_R^* + (\mu_R + d) (\Omega_5^* S_R^* + \Omega_6^* S_R^*)), \\ u_5^*(t) &= \frac{\Omega_7^* m u_V V^*}{c_5}. \end{aligned} \right\} \quad (36)$$

Considering the bounds of the control quintuple, we have

$$\left. \begin{aligned} u_1^*(t) &= \max \left\{ 0, \min \left( 1, \frac{(\Omega_2^* - \Omega_1^*)(\beta_1 S_H^* I_H^* + \beta_2 S_H^* I_R^*)}{c_1 N_H} \right) \right\}, \\ u_2^*(t) &= \max \left\{ 0, \min \left( 1, \frac{(\beta_2 S_H^* (\Omega_2^* - \Omega_1^*) + \beta_5 S_R^* (\Omega_6^* - \Omega_5^*)) V^*}{c_2 (K_1 + V)} \right) \right\}, \\ u_3^*(t) &= \max \left\{ 0, \min \left( 1, \frac{(\Omega_3^* - \Omega_4^*) \gamma I_H}{c_3} \right) \right\}, \\ u_4^*(t) &= \max \left\{ 0, \min \left( 1, \frac{1}{c_4} (\Omega_5^* \Lambda_R(t) (1 - \frac{N_R^*}{K(t)}) N_R^* + (\mu_R + d) (\Omega_5^* S_R^* + \Omega_6^* S_R^*)) \right) \right\}, \\ u_5^*(t) &= \max \left\{ 0, \min \left( 1, \frac{\Omega_7^* m u_V V^*}{c_5} \right) \right\}. \end{aligned} \right\} \quad (37)$$

The optimality system comprises of equations (28), the adjoint system (33), initial conditions at  $t = 0$ , boundary conditions (34) and the characterisation of the optimal control, (37). Thus, the optimal control can be computed using the optimality system. Hence, using the fact that the second derivatives of the Lagrangian with respect to  $u_1, u_2, u_3, u_4$  and  $u_5$  respectively are positive indicates that the optimal problem is minimum at control  $u_1^*, u_2^*, u_3^*, u_4^*$  and  $u_5^*$ .

## Results and discussions of numerical simulations

The numerical simulations are implemented for the non-autonomous model and optimal control model to study the dynamics of the Lassa virus with and without control measures. The periodic functions,  $\Lambda_R(t)$  and  $K(t)$  are defined as

$$\Lambda_R(t) = \Lambda_R \left[ 1 + a \sin \left( \frac{2\pi(t+b)}{p} \right) \right], \quad K(t) = K \left[ 1 - \gamma_1 \cos \left( \frac{2\pi(t+b)}{p} \right) \right] \quad (38)$$

where  $\gamma_1$  is the seasonality amplitude,  $b$  is the phase angle,  $p$  is the phase shift of the periodic functions,  $\Lambda_R$  is the constant recruitment value for  $\Lambda_R(t)$  and  $K$  is the constant carrying capacity value for  $K(t)$ . The initial conditions for the state variables are  $S_H(0) = 2 \times 10^8$  [3],  $E_H(0) = 40$  [3],  $I_H(0) = 49$  [3],  $R_H(0) = 0$ ,  $S_R(0) = 5 \times 10^3$ ,  $I_R(0) = 1 \times 10^3$  [3] and  $V(0) = 10$ . The parameter values for the simulations are presented in Table 2 except where they are stated otherwise in the simulations. The simulations in this work are performed using the results of the sensitivity analysis.

Figure 4 shows the dynamics of the Lassa virus when  $R_0 < 1$  and  $R_0 > 1$ . When  $R_0 > 1$ , the infected rodents increase and remain in the population at a periodic interval (see Figure 4(b)). This causes an increase in the virus concentration that peaks at about  $3 \times 10^6$  and becomes periodic after 1000 days with a minimum amplitude. It also increases the number of infected humans in the population. Whereas for  $R_0 < 1$ , the population of infected humans (see Figure 4(a)), infected rodents (see Figure 4(b)), and virus concentration reduces drastically within the community (see Figure 4(c)). Also, the periodic occurrence of infected rodents and virus concentration within the environment is stopped. This implies that the Lassa free population will be achieved when  $R_0 < 1$ .

The impact of the virus decay rate is examined in Figure 5. It is observed that as the virus decay rate increases, there is a reduction in the virus concentration within the environment which therefore reduces infected human and rodent populations. However, it does not stop the periodic occurrence of the infected rodent and virus concentration and the reduction in the number of infected humans is not minimum as the case of  $R_0 < 1$  in Figure 4. This means that implementing intervention strategies that increase virus decay rate is not enough to achieve a Lassa virus-free population. It will be good to complement such efforts with other interventions that also reduce direct contact with virus concentration by humans and rodents, and eliminates the rodent population if it is possible. With the results of Figures 4 and 5, we consider the simulations of optimal control model by solving the optimality system using forward and backward sweep of the Runge-Kutta

method described in Lenhart *et al.* [25] and implement using Matlab. The weight constants and the relative cost constants for the optimality system are assumed to be  $\rho_1 = 0.7$ ,  $(\rho_2, \rho_3, \rho_4) = 0.001$ ,  $(c_1, c_2) = 1 \times 10^5$ ,  $c_3 = 200$ ,  $c_4 = 100$  and  $c_5 = 10$ . Three scenarios are investigate in the presence of optimal use of personal protective equipment (PPE),  $u_1$  and early treatment,  $u_3$ .

#### A. Optimal use of three controls

*Case 1.* Personal protective equipment in caring for the sick and avoiding contact with rodents + early treatment and isolation of infected persons + rodent control through trapping and fumigation,  $(u_1 \neq 0, u_2 = 0, u_3 \neq 0, u_4 \neq 0, u_5 = 0)$ ,

*Case 2.* Personal protective equipment in caring for the sick and avoiding contact with rodents + early treatment and isolation of infected persons + cleaning and disinfecting the environment,  $(u_1 \neq 0, u_2 = 0, u_3 \neq 0, u_4 = 0, u_5 \neq 0)$

*Case 3.* Personal protective equipment in caring for the sick and avoiding contact with rodents + early treatment and isolation of infected persons + proper handling of food items/stuffs  $(u_1 \neq 0, u_2 \neq 0, u_3 \neq 0, u_4 = 0, u_5 = 0)$ .

#### B. Optimal use of four controls

*Case 4.* Personal protective equipment in caring for the sick and avoiding contact with rodents + early treatment and isolation of infected persons + proper handling of food items/stuffs + rodent control through trapping and fumigation,  $(u_1 \neq 0, u_2 \neq 0, u_3 \neq 0, u_4 \neq 0, u_5 = 0)$ ,

*Case 5.* Personal protective equipment in caring for the sick and avoiding contact with rodents + early treatment and isolation of infected persons + proper handling of food items/stuffs + cleaning and disinfecting the environment,  $(u_1 \neq 0, u_2 \neq 0, u_3 \neq 0, u_4 = 0, u_5 \neq 0)$ ,

*Case 6.* Personal protective equipment in caring for the sick and avoiding contact with rodents + Early treatment and isolation of infected persons + rodent control through trapping and fumigation + cleaning and disinfecting the environment,  $(u_1 \neq 0, u_2 = 0, u_3 \neq 0, u_4 \neq 0, u_5 \neq 0)$ .

#### C. Optimal use of all the controls

*Case 7.* Personal protective equipment in caring for the sick and avoiding contact with rodents + Early treatment and isolation of infected persons + proper handling of food items/stuffs + rodent control through trapping and fumigation + cleaning and disinfecting the environment,  $(u_1 \neq 0, u_2 \neq 0, u_3 \neq 0, u_4 \neq 0, u_5 \neq 0)$ .

#### Scenario A. Optimal use of three controls

In Figure 6, the implementation of Case 3 gives a better result when compared with Cases 1 and 2. It reduces the number of infected humans (Figure 6(a)) and the virus concentration in the environment (Figure 6(c)) drastically than Cases 1 and 2. But for the infected rodent population, Case 1 has a lower number of infected rodents which is similar to with Cases 2 and 3 (see Figure 6(b)). The implementation of Case 2 initially increases the number of infected humans and virus concentration before declining and remaining in the population while the number of infected rodents rises and becomes stable within the population.

### Scenario B. Optimal use of four controls

This is displayed in Figure 7. Application of Case 4 gives a preferable result when compared to Cases 5 and 6 as it lowers the number of infected humans (Figure 6(a)) and the virus concentration in the environment (Figure 6(c)) than other Cases 5 and 6. But for infected rodents, it is a different situation. Case 6 has a higher number of infected rodents when compared to Cases 4 and 5. It (Case 6) increases initially before a decline to a minimum after 500 days. For Cases 4 and 5, the number of infected rodents reduce but Case 4 achieves a minimum after 2000 days while Case 5 remains in the community after the duration of implementing the controls.

### Scenario C. Optimal use of all controls

Figure 8 shows the application of the five controls and without the control. Without control results, a periodic population for the infected rodent (Figure 8(b)) causes a periodic virus concentration after 1000 days (Figure 8(b)). It also increases the number of infected humans in the population (Figure 8(c)). Whereas with the implementation of Case 7, the number of infected humans, infected rodents and virus concentration within the environment reduces to a minimum, that is the best when compared to Cases 1 to 6. This is achieved when the proper handling of food items/stuffs ( $u_1$ ) is maintained at 100% throughout the period of implementation of the control while early treatment and isolation of infected human control ( $u_3$ ) are kept at 30% for about 2000 days before increasing to 100% where it is maintained for next 1000 days and then decline to the lower bound. The controls,  $u_4$  and  $u_5$ , gradually increase to 100% after 2000 days and are maintained for the next 1000 days before a decline to their lower bound. Similar interpretation goes for the control,  $u_1$ . Based on the results of the seven cases, the implementation of Case 7 which included all the five controls is the best strategy as it reduces the burden of the Lassa virus in the population. When the only available resources are the four controls, Case 4 should be implemented. For three control resources, Case 3 should be carried out. Apart from the presence of optimal PPE and avoiding hunting of rodents ( $u_1$ ), and early treatment and isolation of infected humans ( $u_3$ ), we notice that optimal proper handling of food items/stuffs,  $u_3$ , is common in these combined controls (cases 3, 4 and 7). This highlights how the improper handling of food contributes to the spread of the Lassa virus in the community. Hence, if the food items/stuffs are handled well by storing food in rodent-proof containers, stoppage of drying food along the roadside and cooking food thoroughly before eating, the spread of the Lassa virus within the population will be minimized. These combined controls in this work are among the combined controls contained in the WHO prevention and control guidelines [26] which is novel and different from other works on Lassa virus [11, 3] as it focuses on virus concentration in the community and how it affects the Lassa virus dynamics.

### Conclusion

A mathematical model with periodic logistic growth rate is formulated for Lassa fever transmission dynamics. The model has a periodic solution at equilibrium for rodent population which exists when  $\Lambda_R > (\mu_R + d)$ . The autonomous system of the model is analysed for stability analysis of equilibrium in terms of basic reproduction number,  $\mathcal{R}_0$ . The model has three equilibria; unstable disease-free equilibrium

when there is no rodent in the population, stable disease-free equilibrium when  $\mathcal{R}_0 < 1$  and  $\Lambda_R > (\mu_R + d)$  and the endemic equilibrium that is stable when  $\mathcal{R}_0 > 1$  and  $\psi = 0$ . The model also exhibits a forward bifurcation when  $\psi = 0$ . Through the implementation of Partial Rank Correlation Coefficient (PRCC) for  $\mathcal{R}_0$ , it is observed that reducing the parameters,  $\alpha_1, \alpha_2, \beta_3, \beta_5$ , and increasing  $\mu_v, \mu_R$  reduces Lassa fever transmission within the population. The non-autonomous system (1) is further analysed for the stability of disease-free periodic equilibrium if the reproduction ratio,  $R_{0t}$  is less than unity otherwise it is unstable. The optimal control model of system (1) is developed by considering the use of PPE and avoiding hunting of rodents,  $u_1$ , food handling,  $u_2$ , early treatment and isolation of infected humans,  $u_3$ , rodent control,  $u_4$  and cleaning and disinfecting the environment,  $u_5$  as control measures. The simulations of the non-autonomous indicate that when  $R_{0t} < 1$ , Lassa fever will be eliminated within the population and the periodicity of the rodent population will be stopped. Furthermore, increasing the decay rate of virus concentration reduces the burden of Lassa fever. For the optimal control model, implementation of five control measures reduces the Lassa virus. However, when there are limited resources to implement the five control measures, combined control measures,  $u_1, u_2, u_3, u_4$  or  $u_1, u_2, u_3$  can be implemented for four or three available control resources respectively. In all the combined control measures, it is observed that proper handling of food items is beneficial in the reduction of the spread of the Lassa virus within the population.

#### Declarations

#### Availability of data and materials

The data used and analysed during the current study is available in the list of references and can also be obtained from the authors upon request.

#### Competing interests

The authors declare that they have no competing interests.

#### Funding

The authors received no funding for the current study.

#### Author's contributions

C.E. M performed the preliminary model formulation, analysis and numerical simulations and was the major contributor to the work. Z.C performed the sensitivity analysis and general write-up of the work. All authors read and approved the final manuscript.

#### Acknowledgements

C.E. Madubueze was supported by TWAS-DFG Cooperation Visits Programme with ID no KO 3409/8 – 1. The authors greatly appreciate the assistance by Dr Sunday C. Madubueze in editing the paper.

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## Appendix A.

Using Centre manifold theory by Castillo [21], let  $\hat{\beta} = \min(\beta_1, \beta_2, \beta_3, \beta_4, \beta_5)$  be a bifurcation parameter at  $\mathcal{R}_0 = 1$ . The Jacobian matrix,  $J(E_0)$  of the model (1) at DFE,  $E_0$ , is given as

$$J(E_0) = \begin{bmatrix} -\mu_H & 0 & -\beta_1 & \psi & 0 & -\beta_2 & -\frac{\beta_3 S_H^0}{K_1} \\ 0 & -f & \beta_1 & 0 & 0 & \beta_2 & \frac{\beta_3 S_H^0}{K_1} \\ 0 & \sigma & -g & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -h & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \Lambda_R + q & -\Lambda_R + 2q - \beta_4 & -\frac{\beta_5 S_R^0}{K_1} \\ 0 & 0 & 0 & 0 & 0 & \beta_4 - q & \frac{\beta_5 S_R^0}{K_1} \\ 0 & 0 & \alpha_2 & 0 & 0 & \alpha_1 & -\mu_V \end{bmatrix}. \quad (39)$$

The eigenvalues of  $J(E_0)$  are  $-\mu_H, -h, -\Lambda_R + q$  and the roots of the polynomial

$$\lambda^4 + C_1 \lambda^3 + C_2 \lambda^2 + C_3 \lambda + C_4 = 0, \quad (40)$$

where

$$C_1 = f + g + \mu_V + q(1 - R_{rr}),$$

$$\begin{aligned}
C_2 &= q\mu_V(1 - R_{rr} - R_{rv}) + (f + g)(\mu_V + q(1 - R_{rr})) + fg(1 - R_{hh}), \\
C_3 &= q\mu_V(1 - R_{rr} - R_{rv}) + fg\mu_V(1 - R_{hh} - R_{hv}) + fgq(1 - R_{rr} - R_{hh}) \\
&\quad + \sigma\beta_1\beta_4, \\
C_4 &= fgq\mu_V(1 - D_1 + D_2).
\end{aligned} \tag{41}$$

with  $D_1 = R_{rv} + R_{rr} + R_{hv} + R_{hh}$ ,  $D_2 = R_{rr}R_{hh} + R_{rv}R_{hh} + R_{hv}R_{rr} - R_{hr}R_{rv}$ . According to Heffernan [27], the polynomial (40) has negative real part roots if  $C_i > 0$  for  $i = 1, 2, 3, 4$ .  $C_i > 0$  when  $R_0 < 1$ . To show this, we express  $\mathcal{R}_0$  of (22) as

$$\mathcal{R}_0 = \frac{(D_1 + \sqrt{(D_1^2 - 4D_2)})}{2}. \tag{42}$$

If  $\mathcal{R}_0 < 1$ , it implies that  $D_1 + \sqrt{(D_1^2 - 4D_2)} < 2$  which simplifies to  $D_2 > D_1 - 1$ . With the definition of  $\mathcal{R}_0$ , we have  $C_i > 0$ ,  $i = 1, 2, 3, 4$  if  $\mathcal{R}_0 < 1$ . Hence, the Jacobean matrix,  $J(E_0)$ , has a simple zero eigenvalues and negative real part eigenvalues at  $D_2 = D_1 - 1$  which occurs when  $\mathcal{R}_0 = 1$ . Let  $\mathbf{w} = (w_1, w_2, w_3, w_4, w_5, w_6, w_7)$  and  $\mathbf{v} = (v_1, v_2, v_3, v_4, v_5, v_6, v_7)$  be the left and right eigenvectors of the  $J(E_0)$  at  $\mathcal{R}_0 = 1$  such that  $\mathbf{v} \cdot \mathbf{w} = 1$ . To get  $\mathbf{w}$ , we multiply  $J(E_0)$  with  $\mathbf{w}$  and equate to zero to yield

$$\begin{aligned}
w_1 &= -\frac{1}{\mu_H \sigma}(\beta_1 b_2 g + \beta_2 \sigma + \beta_3 b_1 \sigma)w_6 + \frac{\psi \gamma b_2}{h \mu_H}, \quad w_2 = \frac{g b_2}{\sigma} w_6, \quad w_3 = b_2 w_6, \\
w_4 &= \frac{\gamma b_2}{h} w_6, \quad w_5 = -w_6, \quad w_7 = b_1 w_6
\end{aligned} \tag{43}$$

with  $b_1 = \frac{q}{\beta_5}(1 - R_{rr})$  and  $b_2 = \frac{q\mu_V}{\alpha_2 \beta_2}(1 - R_{rr} - R_{rv})$ . For the right eigenvector, we multiply the transpose of  $J(E_0)$  with  $\mathbf{v}$  and equate to zero and this gives

$$v_1 = 0, v_2 = \frac{\sigma}{f} v_3, v_4 = 0, v_5 = 0, v_6 = b_4 v_3, v_7 = b_3 v_3, \tag{44}$$

where  $b_3 = \frac{g}{\alpha_2}(1 - R_{hh})$ ,  $b_2 = \frac{g\mu_V}{\alpha_2 \beta_5}(1 - R_{hh} - R_{hv})$  with  $b_i > 0$ , ( $i = 1, 2, 3, 4$ ) at  $\mathcal{R}_0 = 1$ . Let  $S_H = x_1, E_H = x_2, I_H = x_3, R_H = x_4, S_R = x_5, I_R = x_6, V = x_7$  so that  $N_H = x_1 + x_2 + x_3 + x_4$  and  $N_R = x_5 + x_6$ . The functions

$$f_2 = \frac{(\beta_1 x_3 + \beta_2 x_3)x_1}{N_H} + \frac{\beta_3 x_1 x_7}{K_1 + x_7} - f x_2, f_6 = \frac{\beta_4 x_5 x_6}{N_R} + \frac{\beta_5 x_5 x_7}{K_1 + x_7} - q x_6$$

are considered for the second partial derivatives at DFE,  $E_0$ , since  $v_1 = v_4 = v_5 = 0$ . The non-zero second partial derivatives of  $f_2$  and  $f_6$  at DFE,  $E_0$ , are given as

$$\begin{aligned}
\frac{\partial^2 f_2(E_0)}{\partial x_2^2} &= -\frac{2\beta_3 S_H^0}{K_1^2}, \quad \frac{\partial^2 f_2(E_0)}{\partial x_1 x_7} = \frac{\beta_3}{K_1}, \quad \frac{\partial^2 f_6(E_0)}{\partial x_7^2} = -\frac{2\beta_5 S_R^0}{K_1^2}, \\
\frac{\partial^2 f_6(E_0)}{\partial x_5 x_7} &= \frac{\beta_5}{K_1}, \quad \frac{\partial^2 f_2(E_0)}{\partial \beta_1 x_3} = 1, \quad \frac{\partial^2 f_2(E_0)}{\partial \beta_2 x_6} = 1, \quad \frac{\partial^2 f_2(E_0)}{\partial \beta_3 x_7} = \frac{S_H^0}{K_1}, \\
\frac{\partial^2 f_2(E_0)}{\partial \beta_4 x_6} &= 1, \quad \frac{\partial^2 f_2(E_0)}{\partial \beta_5 x_7} = \frac{S_R^0}{K_1}.
\end{aligned} \tag{45}$$

The bifurcation coefficients,  $\mathbf{a}$  and  $\mathbf{b}$ , that determine the bifurcation direction are given as

$$\begin{aligned}
\mathbf{a} &= \sum_{i,j,k=1}^n v_i w_j w_k \frac{\partial^2 f_i(0,0)}{\partial x_j \partial x_k} = -(Q - \psi R) v_3 w_6^2, \\
\mathbf{b} &= \sum_{i,j=1}^n v_i w_j \frac{\partial^2 f_i(0,0)}{\partial \beta x_j} = T v_3 w_6
\end{aligned} \tag{46}$$

556 where

$$Q = \frac{b_1}{K_1} \left[ \frac{2b_1}{K_1 f} (\sigma \beta_3 S_H^0 + f b_4 \beta_5 S_R^0) + \frac{\beta_3}{\mu_H} \left( \frac{g \beta_1 b_2}{\sigma} + \beta_2 + \beta_3 b_1 + \beta_5 b_4 \right) \right],$$

$$R = \frac{\sigma \gamma \beta_3 b_1 b_2}{f K_1}, T = \frac{b_1}{K_1} \left( \frac{\sigma S_H^0}{f} + b_4 S_R^0 \right) + \frac{1}{f} (f b_4 + \sigma (1 + b_2)).$$

557 (47)

558 A forward bifurcation exists if  $\mathbf{a} < 0$  and  $\mathbf{b} > 0$ . So,  $\mathbf{a} < 0$  if  $\psi = 0$ . Therefore, the endemic equilibrium is locally  
 559 asymptotically stable if  $\mathcal{R}_0 > 1$  and  $\psi = 0$ .

560 **Figures**

FIG1

**Figure 1** A systematic diagram for the dynamics of Lassa fever.

FIG2

**Figure 2** The Tornado plot for the 17 parameters of  $\mathcal{R}_0$ .

FIG3

**Figure 3** Monte Carlo simulations for the four parameters with the greatest significant PRCC values, generated using the parameter values in Table 3. In each simulations run, 1000 simulations of the randomly selected parameters were used.

FIG4

**Figure 4** Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $R_0 < 1$  and  $R_0 > 1$ . For  $R_0 < 1$ ,  $\mu_V = 0.429$ ,  $\beta_3 = 0.0005$ ,  $\beta_5 = 0.00145$ ,  $\alpha_1 = 0.009$ ,  $\alpha_2 = 0.001$  while for  $R_0 > 1$ , the all parameter values of Table 3 are used.

FIG5

**Figure 5** Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $\mu_V$  is increasing. All parameter values of Table 3 are used.

FIG6

**Figure 6** Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $R_0 < 1$  and  $R_0 > 1$ . For  $R_0 < 1$ ,  $\mu_V = 0.429$ ,  $\beta_3 = 0.0005$ ,  $\beta_5 = 0.00145$ ,  $\alpha_1 = 0.009$ ,  $\alpha_2 = 0.001$  while for  $R_0 > 1$ , the all parameter values of Table 3 are used.

561

FIG7

**Figure 7** Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $R_0 < 1$  and  $R_0 > 1$ . For  $R_0 < 1$ ,  $\mu_V = 0.429$ ,  $\beta_3 = 0.0005$ ,  $\beta_5 = 0.00145$ ,  $\alpha_1 = 0.009$ ,  $\alpha_2 = 0.001$  while for  $R_0 > 1$ , the all parameter values of Table 3 are used.

[FIG8]

**Figure 8** Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $R_0 < 1$  and  $R_0 > 1$ . For  $R_0 < 1$ ,  $\mu_V = 0.429$ ,  $\beta_3 = 0.0005$ ,  $\beta_5 = 0.00145$ ,  $\alpha_1 = 0.009$ ,  $\alpha_2 = 0.001$  while for  $R_0 > 1$ , the all parameter values of Table 3 are used.

## 562 Tables

**Table 1** Sensitivity analysis of the optimal control model.

| Variable    | PRCC value  | P-value   | Significant? |
|-------------|-------------|-----------|--------------|
| $\mu_H$     | -0.59129915 | 0.000     | TRUE         |
| $\beta_1$   | 0.02597055  | 4.419e-01 | FALSE        |
| $\beta_2$   | 0.03220826  | 3.546e-01 | FALSE        |
| $\gamma$    | -0.10088111 | 1.990e-03 | TRUE         |
| $\beta_3$   | 0.74302562  | 0.000     | TRUE         |
| $\delta_H$  | -0.71416985 | 0.000     | TRUE         |
| $\beta_4$   | 0.16845065  | 1.545e-07 | TRUE         |
| $\sigma$    | 0.07584152  | 2.102e-02 | TRUE         |
| $\psi$      | 0.02188902  | 4.929e-01 | FALSE        |
| $\beta_5$   | 0.26126815  | 0.000     | TRUE         |
| $\mu_R$     | -0.23671852 | 7.759e-14 | TRUE         |
| $\alpha_2$  | 0.90583527  | 0.000     | TRUE         |
| $\alpha_1$  | 0.37832219  | 0.000     | TRUE         |
| $d_2$       | -0.15512149 | 1.371e-06 | TRUE         |
| $\Lambda_H$ | 0.36875616  | 0.000     | TRUE         |
| $\mu_V$     | -0.75207063 | 0.000     | TRUE         |
| $K_1$       | -0.22100090 | 3.314e-12 | TRUE         |

**Table 2** Parameter estimates of the optimal control model.

| Parameter   | Baseline(Range)         | Units                     | Sources |
|-------------|-------------------------|---------------------------|---------|
| $\Lambda_H$ | 10000                   | Persons day <sup>-1</sup> | [32]    |
| $\Lambda_R$ | 0.2                     | -                         | [3]     |
| $\sigma$    | 0.299 (0.1 - 0.5)       | Day <sup>-1</sup>         | [8,29]  |
| $\delta_H$  | 0.269 (0.1 - 0.4)       | Day <sup>-1</sup>         | [8]     |
| $d$         | 0.002 (0.0017 - 0.0172) | Day <sup>-1</sup>         | Assumed |
| $\psi$      | 0.00578 (0.0035 - 0.03) | Day <sup>-1</sup>         | [8]     |
| $\mu_H$     | 0.00005                 | Day <sup>-1</sup>         | [32]    |
| $\mu_R$     | 0.005 (0.00003 - 0.08)  | Day <sup>-1</sup>         | [8,29]  |
| $\mu_V$     | 0.00429 (0.0172 - 0.05) | Day <sup>-1</sup>         | Assumed |
| $K_1$       | 20000 (18000 - 22000)   | -                         | Assumed |
| $K$         | 20000                   | -                         | [3]     |
| $\beta_1$   | 0.275 (0.2 - 0.5)       | Day <sup>-1</sup>         | [8,33]  |
| $\beta_2$   | 0.0296 (0.01 - 0.09)    | Day <sup>-1</sup>         | [8]     |
| $\beta_3$   | 0.005 (0.002 - 0.007)   | Day <sup>-1</sup>         | Assumed |
| $\beta_4$   | 0.007 (0.005 - 0.4)     | Day <sup>-1</sup>         | [8,29]  |
| $\beta_5$   | 0.0145 (0.01 - 0.1)     | Day <sup>-1</sup>         | Assumed |
| $\gamma$    | 0.123 (0.1 - 0.5)       | Day <sup>-1</sup>         | [28].   |
| $\alpha_1$  | 0.09 (0.01 - 0.6)       | Day <sup>-1</sup>         | Assumed |
| $\alpha_2$  | 0.01 (0.001 - 0.05)     | Day <sup>-1</sup>         | Assumed |

# Figures

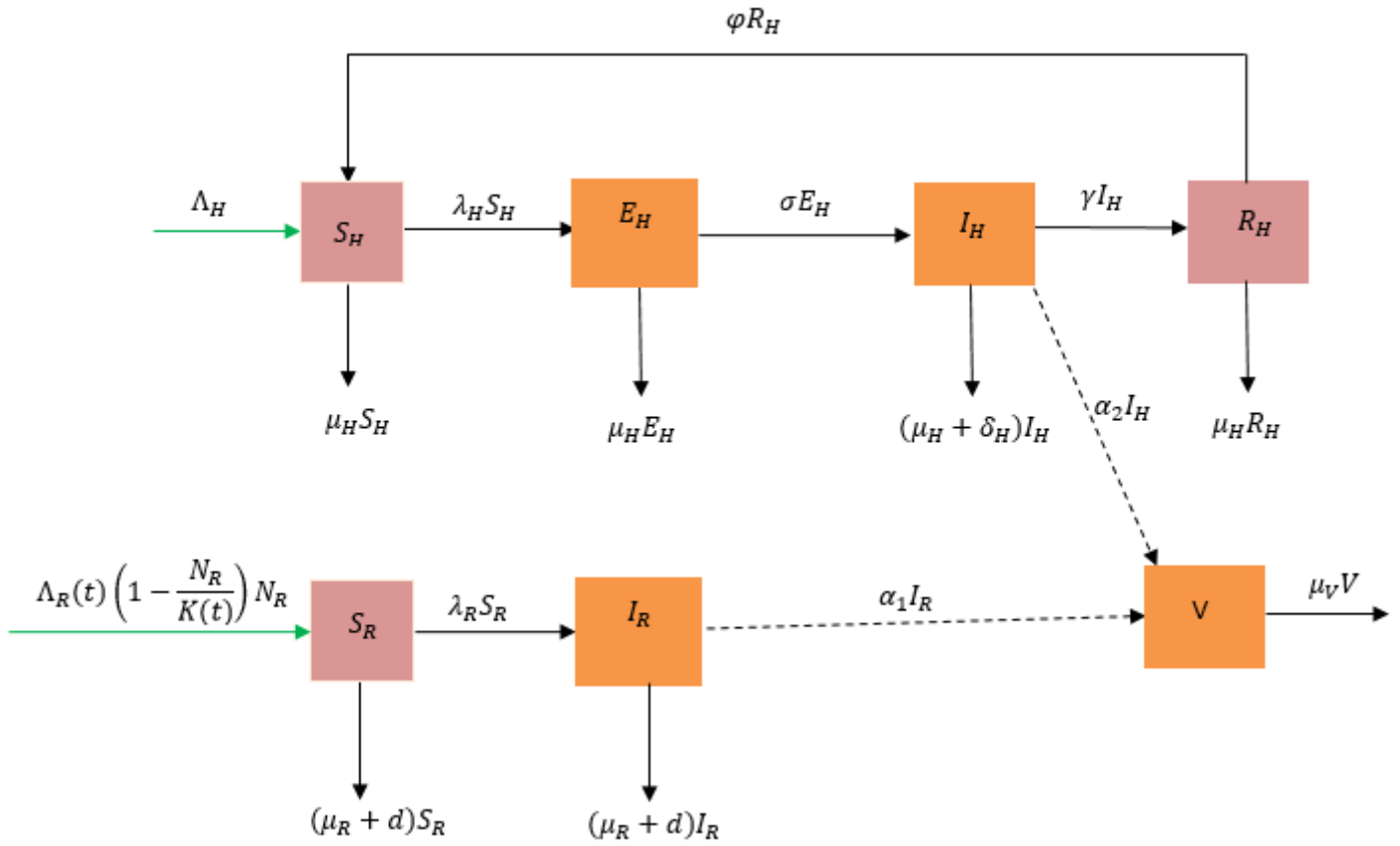


**Figure 1**

A systematic diagram for the dynamics of Lassa fever.

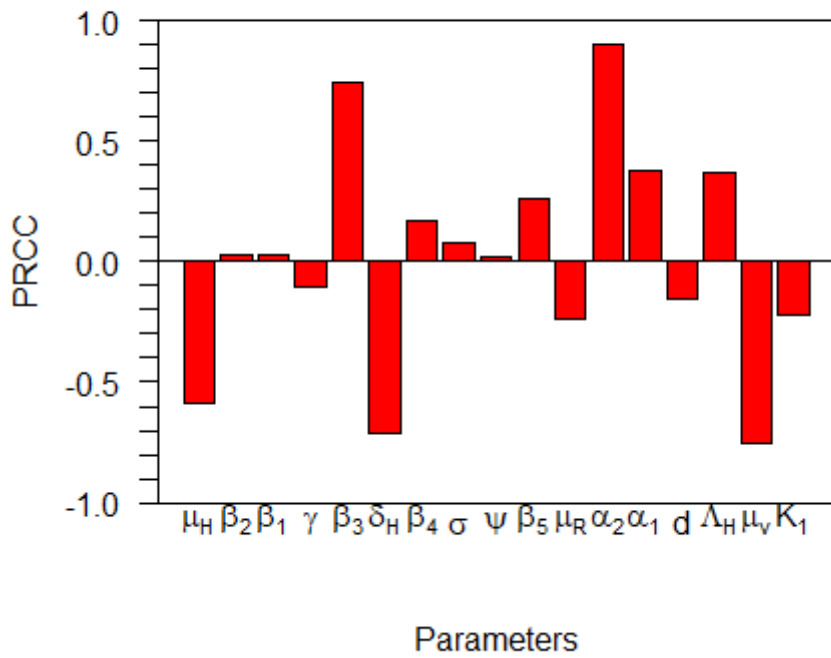


**Figure 2**

The Tornado plot for the 17 parameters of R0.

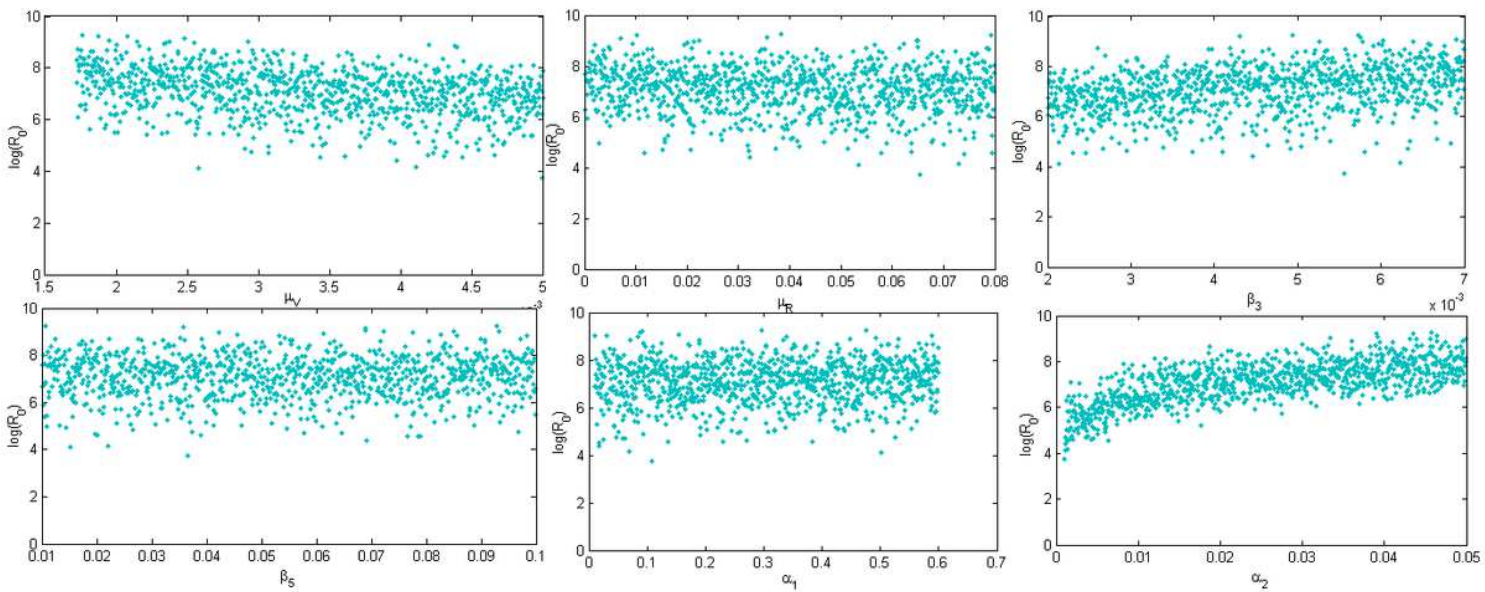


**Figure 3**

Monte Carlo simulations for the four parameters with the greatest significant PRCC

values, generated using the parameter values in Table 3. In each simulations run, 1000 simulations of the randomly selected parameters were used.

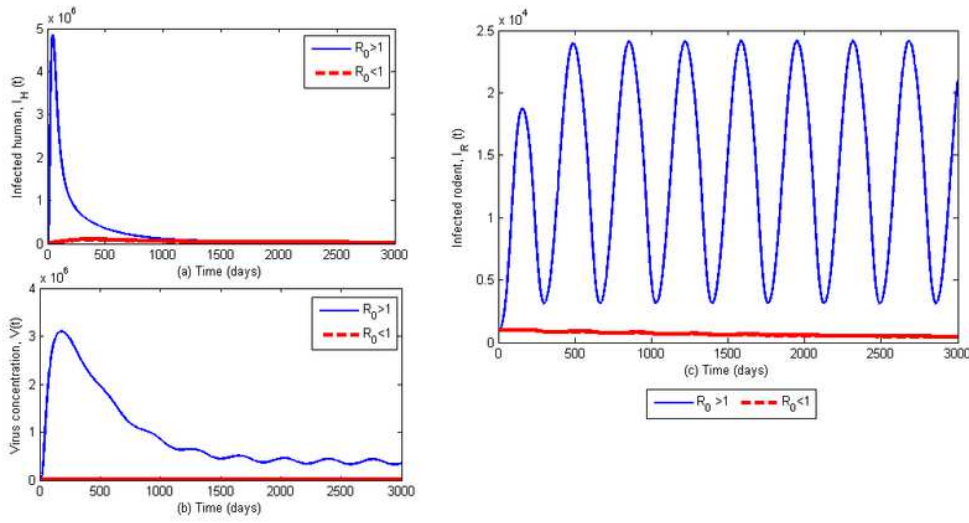


**Figure 4**

Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $R_0 < 1$  and

$R_0 > 1$ . For  $R_0 < 1$ ,  $\mu_V = 0.429$ ,  $\beta_3 = 0.0005$ ,  $\beta_5 = 0.00145$ ,  $\alpha_1 = 0.009$ ,  $\alpha_2 = 0.001$  while for  $R_0 > 1$ , the all parameter values of Table 3 are used.

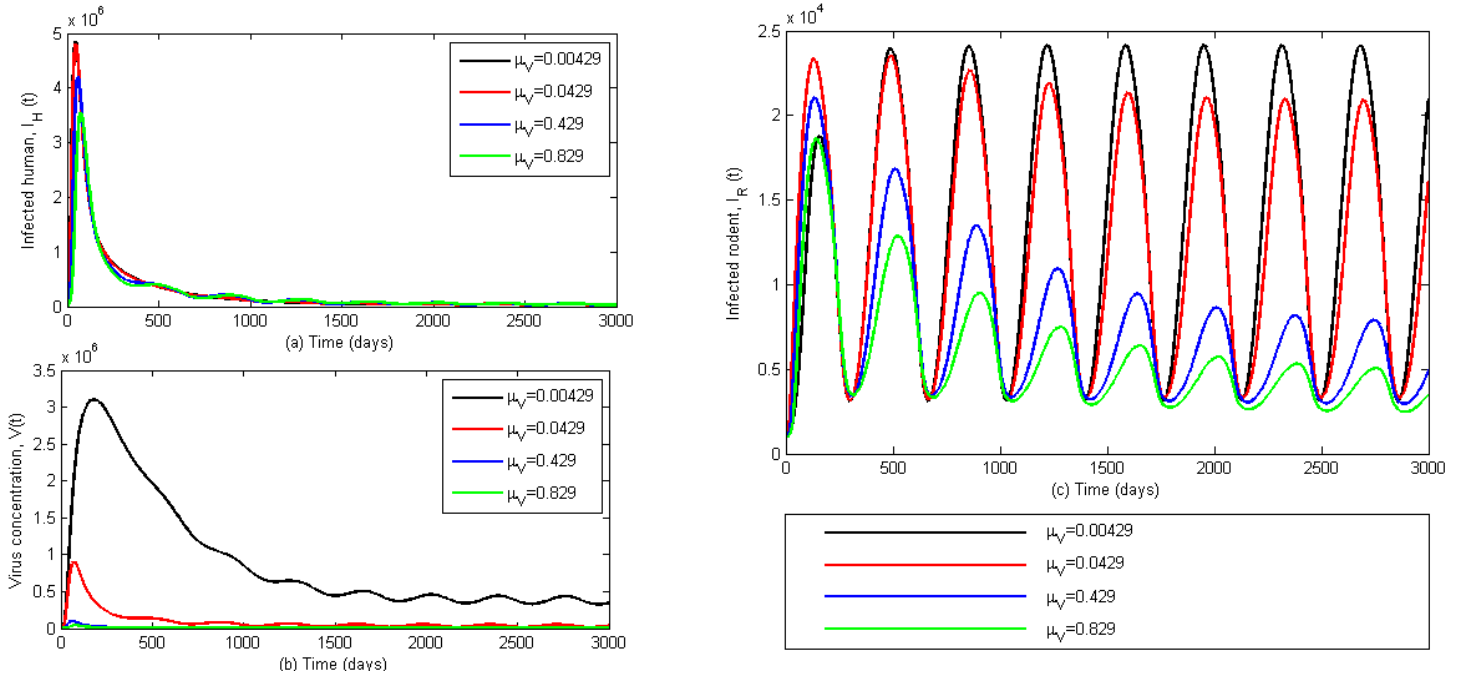


**Figure 5**

Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $\mu_V$  is increasing. All parameter values of Table 3 are used.

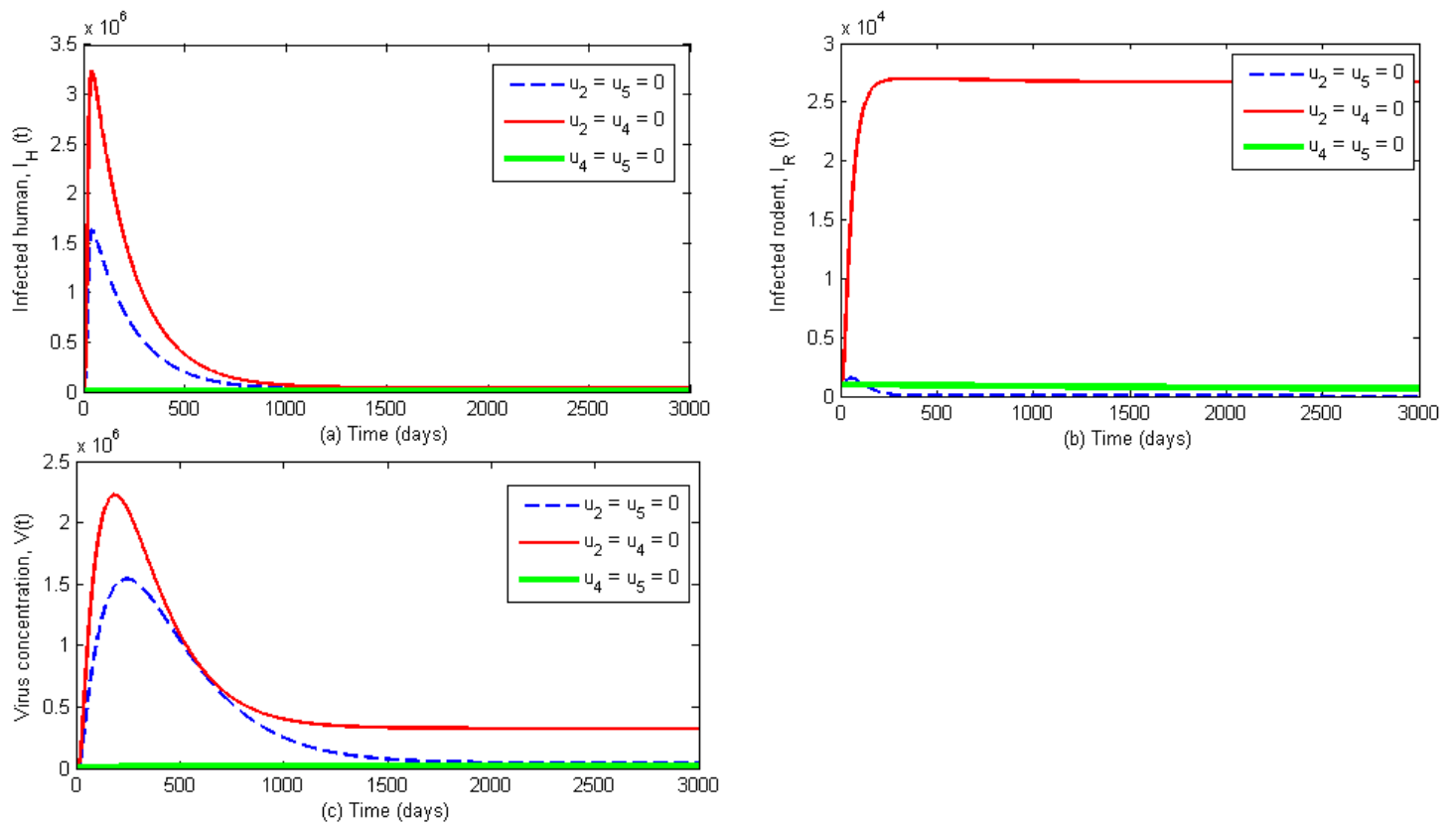


**Figure 6**

Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $R_0 < 1$  and

$R_0 > 1$ . For  $R_0 < 1$ ,  $\mu V = 0.429$ ,  $\beta_3 = 0.0005$ ,  $\beta_5 = 0.00145$ ,  $\alpha_1 = 0.009$ ,  $\alpha_2 = 0.001$  while for  $R_0 > 1$ , the all parameter values of Table 3 are used.

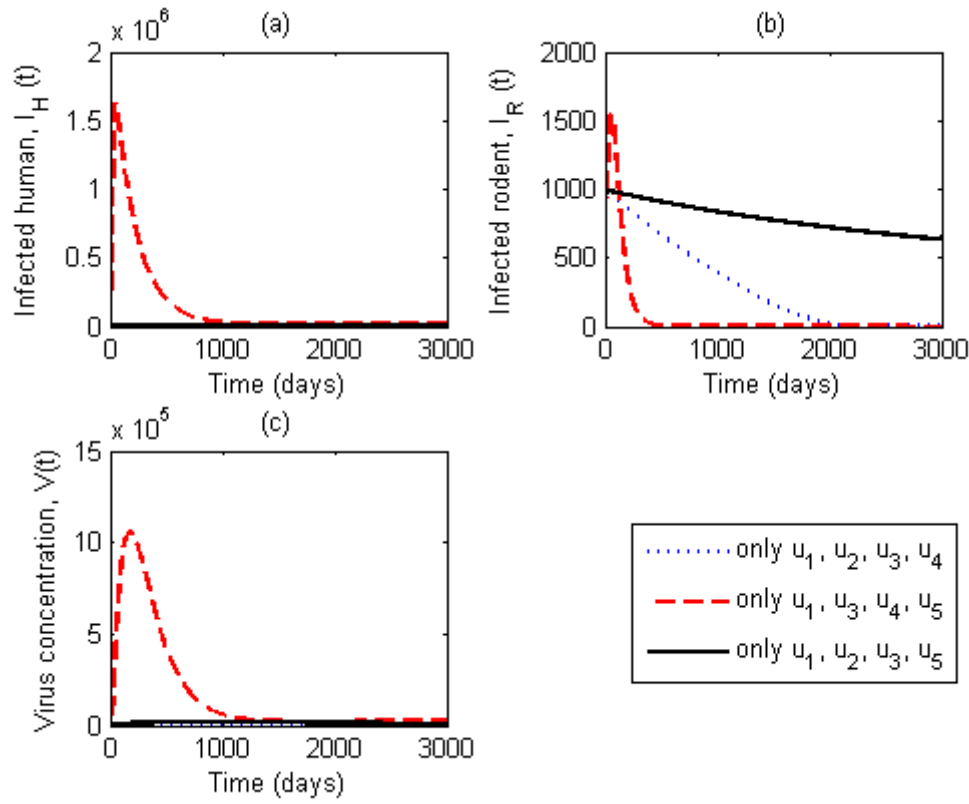


**Figure 7**

Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $R_0 < 1$  and

$R_0 > 1$ . For  $R_0 < 1$ ,  $\mu_V = 0.429$ ,  $\beta_3 = 0.0005$ ,  $\beta_5 = 0.00145$ ,  $\alpha_1 = 0.009$ ,  $\alpha_2 = 0.001$  while for  $R_0 > 1$ , the all parameter values of Table 3 are used.

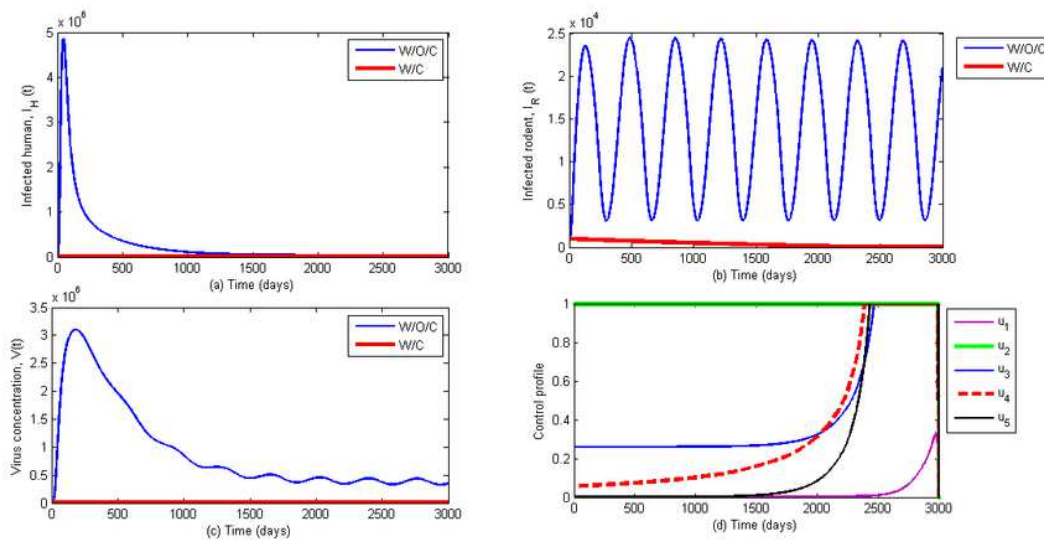


**Figure 8**

Simulation results for the infected classes,  $I_H(t)$ ,  $I_R(t)$  and  $V(t)$  when  $R_0 < 1$  and

$R_0 > 1$ . For  $R_0 < 1$ ,  $\mu_V = 0.429$ ,  $\beta_3 = 0.0005$ ,  $\beta_5 = 0.00145$ ,  $\alpha_1 = 0.009$ ,  $\alpha_2 = 0.001$  while for  $R_0 > 1$ , the all parameter values of Table 3 are used.