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OPTIMAL CONTROL AND COST-EFFECTIVENESS ANALYSIS FOR THE DYNAMIC MODELING OF LASSA FEVER

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Abstract. In this work, we analyze the effective control of Lassa fever in a given population by formulating and analyzing a nonlinear optimal control problem. We extend an existing deterministic mathematical model to include four control variables namely educational campaign, condom usage, treatment care, and reduction of rodents. Using Pontryagin's maximal principle, we established the necessary conditions for the existence of optimal control. We use the fourth-order Runge Kutta forward-backward sweep approach to simulate the optimality system in order to demonstrate the impact of various combinations of controls on the spread of Lassa fever. A cost-effectiveness study is carried out to inform the public about the best cost-effective technique among several control combinations. The results suggest that, of all the combinations considered in this study, the combination of preventative tactics through educational campaigns and rodent reduction in the environment is the most cost-effective.

Keywords: Lassa fever; optimal control; cost-effectiveness; educational campaign; forward-backward sweep method.

2010 AMS Subject Classification: 93A30, 65P40, 92B10, 37C60.

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1. INTRODUCTION

Lassa fever (LF) is an acute and viral hemorrhagic fever. It is a zoonotic disease that is caused by the Lassa virus (LASV), a single-stranded RNA virus [1] that is borne by a mouse species called Mastomys natalensis. This rodent species serves as a primary vector for the transmission of the LASV [2] to humans. LASV is transmitted majorly via direct contact with infected rodents. Direct contact with the Mastomys rodent represents about 90 -95 percent of the modes of transmission of the LASV in the endemic regions. Secondary infection can be transmitted through contact with the blood, body fluids, contaminated medical equipment, skin breaks, mucous membranes, and aerosols of the infected rodents and humans [3] of all age groups [4]. Studies also reveal a seasonal drift of the infection patterns of LASV. The highest peak of infection is recorded during the dry seasons of the sub-Saharan West African countries (between December and April annually) and gradual steep during the wet seasons (between May and June annually). This is as a result of the reproductive seasons of the Mastomys rodents being in the wet season [5]. LF is known to be a major endemic disease in the sub-Saharan region of West Africa [6]. In this region, it has risen to become a major serious public health challenge. In recent times, there has been a rise in the number of emergencies involving LF and a 70 percent increase in fatality cases when not diagnosed and treated early in this region [5]. There has also been an increase in the spread of the virus across the non-endemic regions and countries of the world due to international travel. This points out an urgent need to seek better approaches to detect, diagnose, report and the treatment of Lassa fever illness and as well as train healthcare providers on how to control the spread and clinical manifestations of LASV [7]. The control of LF in the endemic region is a major problem as its clinical symptoms are similar to the symptoms of malaria. It is misdiagnosed as malaria, typhoid fever, and other febrile diseases that are common in the tropical region of Africa. Ribavirin is the only accepted antiviral treatment that is effective and employed in the treatment of Lassa Fever at the early stage of the viral infection [8]. This treatment is not 100 percent effective and efficient for the treatment of LASV and from review studies conducted, results prove that there is currently no vaccine for the prevention control of Lassa fever [9]. Alternatively, other methods of control are evaluated to curtail and reduce the spread of the disease most especially in the endemic region.

The other measures of control include maintenance of environmental hygiene and healthy living practices to control rodents and human contact around dwelling places [7], avoidance of rat consumption, timely detection and diagnosis of LF at primary health facilities [10]. The early symptoms of LF are initially treated as malaria signs and symptoms of other febrile diseases.

Many studies have been carried out to broaden the knowledge about the spread and control of many diseases (see [11, 12, 13, 14, 15, 16, 17, 18, 19, 20] for examples), particularly some studies on the effect of control strategies on the spread of Lassa fever have been presented. A few of these studies are discussed as follows. In [21], the authors considered the dynamics of Lassa fever in Nigeria by developing a mathematical model formulation solved numerically by using the fifth-order Runge-Kutta method. The findings suggest that reduction in rodent sizes and transmission between rodent-to-human will greatly improve the population control action of Lassa fever. There have been several approaches to finding an optimal control for the dynamics of Lassa fever in Sub-Saharan Africa. In [22], the authors considered four different controls: pesticide fumigation, condom use to prevent human-to-human transmission during sexual activities, early treatment, and the use of indoor residual sprays. It was observed in their results that the fumigation of the environment does not have any effect on the exposed and infected humans but the exposed and infected rodents. The use of condoms helped reduce secondary transmission from humans to humans but does not affect the infected rodents. Early treatment control strategies have a greater impact on reducing the population of infected humans. Indoor sprays have no side effects on humans but control the number of infected rodents. The authors of [23] conducted a four-year field experiment in rural Upper Guinea and constructed a model to investigate the region's varied control techniques. Rodent immunization, annual density control, and continuous density control were all investigated. They conclude that the annual density control might not be effective in reducing the Lassa virus spillover to humans as the rodent recovered quickly after rodenticides application. However, continuous density and rodent vaccination could lead to Lassa virus elimination. The authors of [24] considered the dynamical system analysis and optimal control strategies of the Lassa virus disease. They explored controls like external protection, isolation, treatment, and rodent control. A different model was developed based on these control parameters to understand the influence of each

control strategy. Their model revealed that the most effective control measure is to combine all control techniques for the reduction of Lassa fever spread. Nevertheless, despite all these control measures, the spread of Lassa fever has not diminished in any form, and because of the lack of a potent vaccine. We continue to battle this disease and seek other best optimal strategies to reduce this Lassa fever infection. Because present control methods are limited, we will investigate the following control strategies: disease education and information, sanitation, safe food storage and preparation, clean water availability, and treatment for Lassa fever patients. This study is arranged as follows: in section 2, we offer the mathematical formulation of the non-optimal control model. The optimal control problem and its analysis are discussed in detail in section 3, where we go through all of the necessary factors and criteria for optimality. In section 4, numerical simulations and discussion of optimal control mechanisms with cost-effectiveness analysis are presented, while section 5 presents the conclusion and recommendations.

2. Lassa Fever Model Without Optimal Control

Lassa fever model without optimal control is provided in this section. We note that in [21], the authors developed and critically analyzed a six compartmental model to study the effect of control variables on the control of Lassa fever in Nigeria. The population is stratified into the human population of susceptible, exposed, infectious, and recovered individuals, and also the rodent population of susceptible and infectious rodents. Consequently, the non-optimal control model as described in [21] is given below

$$
\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h + \tau_h R_h - \beta_1 S_h - \mu_h S_h \\
\frac{dE_h}{dt} &= \beta_1 S_h - (\sigma_h + \mu_h) E_h \\
\frac{dI_h}{dt} &= \sigma_h E_h - (\phi_h + \mu_h + \delta_h) I_h \\
\frac{dR_h}{dt} &= \phi_h I_h - (\mu_h + \tau_h) R_h \\
\frac{dS_r}{dt} &= \Lambda_r - \beta_2 S_r - \mu_r S_r \\
\frac{dI_r}{dt} &= \beta_2 S_r - \mu_r I_r
\end{aligned} \tag{1}
$$

with the following initial conditions: $S_h(0) > 0$, $E_h(0) \geq 0$, $I_h(0) \geq 0$, $R_h \geq 0$, $S_r(0) > 0$, $I_r(0) \geq 0$. The description of model variables and parameters are given in Table 1 of [21]. In addition, the parameter values are tabulated in Table 2 of [21]. It is imperative to mention that the non-optimal control model (1) analysis is presented in [21], thus we extend this model to include the optimal control problem in the next section.

3. Optimal Control Model

In this section, we employ the Pontryagin's Maximum Principle to determine the necessary conditions for the optimal control of Lassa fever in the population. To achieve this, we modify the model (1) by incorporating the time-dependent control functions u_1, u_2, u_3, and u_4. The control function u_1 represents the preventive strategies towards the prevention of transmission of infection from rodents to humans. These strategies include personal hygiene, environmental fumigation, and are achieved through an educational campaign. The control function u_2 represents condom usage which is aimed at reducing the secondary transmission of the infection from human to human. We assume the treatment rate ϕ_h presented in model (1) to be time-dependent represented as u_3, while u_4 denotes the control function targeted at reducing the rodent population, such as the use of rodents trap. Consequently, the optimal control Lassa fever model with the four time-dependent functions is given below

$$
\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h + \tau_h R_h - (1-u_1)\frac{\beta_r S_h I_r}{N_h} - (1-u_2)\frac{\beta_h S_h I_h}{N_h} - \mu_h S_h \\
\frac{dE_h}{dt} &= (1-u_1)\frac{\beta_r S_h I_r}{N_h} + (1-u_2)\frac{\beta_h S_h I_h}{N_h} - (\sigma_h + \mu_h)E_h \\
\frac{dI_h}{dt} &= \sigma_h E_h - (u_3 + \mu_h + \delta_h)I_h \\
\frac{dR_h}{dt} &= u_3 I_h - (\mu_h + \tau_h)R_h \\
\frac{dS_r}{dt} &= \Lambda_r - \frac{\beta_r S_r I_r}{N_r} - (\mu_r + u_4)S_r \\
\frac{dI_r}{dt} &= \frac{\beta_r S_r I_r}{N_r} - (\mu_r + u_4)I_r
\end{aligned} \tag{2}
$$

The purpose of implementing optimal control functions is to decrease the spread of Lassa fever in the community by reducing the number of exposed humans, infected humans, and rodent

populations while keeping costs down. To accomplish this, we define the objective functional (also known as the cost functional) as

$$J(u_i) = \int_0^T \left(m_1 E_h + m_2 I_h + m_3 N_r + \frac{1}{2}\sum_{i=1}^{4} k_i u_i^2(t) \right) dt \tag{3}$$

where T is the final time for control implementation, in the sense that $t \in [0,T]$. The balancing positive weight constants are represented by m_1, m_2, m_3, and k_i for $(i = 1,\ldots,4)$, while $\frac{k_i u_i^2}{2}$ represents the total cost associated with the controls u_i for $i = 1,\ldots,4$. The cost control functions take a quadratic form, such that $\frac{k_1 u_1^2}{2}$ represents the cost control function for preventive strategies by educational campaign, and $\frac{k_2 u_2^2}{2}$ represents the cost control function for condom usage. Also, the cost control functions associated with treatment and rodents reduction are given as $\frac{k_3 u_3^2}{2}$, and $\frac{k_4 u_4^2}{2}$ respectively. Thus, the quadruplet optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ is sought such that

$$J(u^*) = min\{J(u_1,u_2,u_3,u_4) : u_1,u_2,u_3,u_4 \in \mathscr{U}\} \tag{4}$$

where $\mathscr{U}$ is the non-empty control set given as $\mathscr{U} = \{(u_1,u_2,u_3,u_4) : 0 \le u_1,u_2,u_3,u_4 \le 1, t \in [0,T]\}$. Following the existence results by [25], the quadruplet optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ exists.

3.1. Control characterization. The Pontryagin's Maximum Principle [26] gives the necessary conditions for which the quadruple optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ exists. The Pontryagin's Maximum Principle transforms the control minimization problem (4) subject to the optimal control system (2) into a problem of minimizing point-wise Hamiltonian. As a result, the Hamiltonian equation denoted by $\mathscr{H}$ is given by

$$\mathscr{H}(t,y,u,\lambda) = m_1 E_h + m_2 I_h + m_3 N_r + \frac{1}{2}\sum_{i=1}^{4} k_i u_i^2(t) + \sum_{i=1}^{6} \lambda_i A_i \tag{5}$$

where λ_i for $i = 1,\ldots,6$ are the adjoint functions associated with the state variables of the optimal control model in (2), while A_i for $i = 1,...,6$ is the right-hand side of the differential equations of the state variables in system (2). The expanded form of the Hamiltonian function

is given by

$$
\begin{aligned}
\mathscr{H}(t,y,u,\lambda) &= m_1E_h + m_2I_h + m_3N_r + \frac{1}{2}\left(k_1u_1^2 + k_2u_2^2 + k_3u_3^2 + k_4u_4^2\right) \\
&+ \lambda_1\left[\Lambda_h + \tau_hR_h - (1-u_1)\frac{\beta_rS_hI_r}{N_h} - (1-u_2)\frac{\beta_hS_hI_h}{N_h} - \mu_hS_h\right] \\
&+ \lambda_2\left[(1-u_1)\frac{\beta_rS_hI_r}{N_h} + (1-u_2)\frac{\beta_hS_hI_h}{N_h} - (\sigma_h+\mu_h)E_h\right] \\
&+ \lambda_3\left[\sigma_hE_h - (u_3+\mu_h+\delta_h)I_h\right] \\
&+ \lambda_4\left[u_3I_h - (\mu_h+\tau_h)R_h\right] \\
&+ \lambda_5\left[\Lambda_r - \frac{\beta_rS_rI_r}{N_r} - (\mu_r+u_4)S_r\right] \\
&+ \lambda_6\left[\frac{\beta_rS_rI_r}{N_r} - (\mu_r+u_4)I_r\right]
\end{aligned} \tag{6}
$$

Following the method in [25, 27], we claim the characterization result in the following theorem.

Theorem 1. *Given a quadruplet optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ that minimizes the objective functional* (3) *over the non-empty control set $\mathscr{U}$ subject to the state system* (2)*, then there exist an adjoint functions $\lambda_1(t), \lambda_2(t), ..., \lambda_6(t)$ which satisfy the adjoint system*

$$
\begin{aligned}
\frac{d\lambda_1}{dt} &= \lambda_1\mu_h + (\lambda_1-\lambda_2)\left(1-\frac{S_h}{N_h}\right)\left[\frac{(1-u_1)\beta_rI_r}{N_h} + \frac{(1-u_2)\beta_hI_h}{N_h}\right] \\
\frac{d\lambda_2}{dt} &= -m_1 - \lambda_3\sigma_h + \lambda_2(\sigma_h+\mu_h) + (\lambda_2-\lambda_1)\left[(1-u_1)\beta_rI_r + (1-u_2)\beta_hI_h\right]\frac{S_h}{N_h^2} \\
\frac{d\lambda_3}{dt} &= -m_2 - \lambda_4u_3 + \lambda_3(\delta_h+\mu_h+u_3) + (\lambda_2-\lambda_1)\left[(1-u_1)\beta_rI_r + (1-u_2)\beta_hI_h\right]\frac{S_h}{N_h^2} \\
&- (\lambda_2-\lambda_1)(1-u_2)\frac{S_h\beta_h}{N_h} \\
\frac{d\lambda_4}{dt} &= -\lambda_1\tau_h + \lambda_4(\mu_h+\tau_h) + (\lambda_2-\lambda_1)\left[(1-u_1)\beta_rI_r + (1-u_2)\beta_hI_h\right]\frac{S_h}{N_h^2} \\
\frac{d\lambda_5}{dt} &= -m_3 + \lambda_5(\mu_r+u_4) + (\lambda_5-\lambda_6)\frac{\beta_rI_r}{N_r}\left(1-\frac{S_r}{N_r}\right) \\
\frac{d\lambda_6}{dt} &= -m_3 + \lambda_6(\mu_r+u_4) + (\lambda_1-\lambda_2)(1-u_1)\frac{\beta_rS_h}{N_h} + (\lambda_5-\lambda_6)\frac{\beta_rS_r}{N_r}\left(1-\frac{I_r}{N_r}\right)
\end{aligned} \tag{7}
$$

with transversality conditions $\lambda_i(T) = 0$*, for all* $i = 1,2,...,6$*. Furthermore, the optimal control quadruple* $\left(u_1^*, u_2^*, u_3^*, u_4^*\right)$ *is characterized by*

$$
\begin{aligned}
u_1^* &= min\left\{1, max\left\{0, \quad \frac{\beta_r S_h I_r(\lambda_2 - \lambda_1)}{k_1 N_h}\right\}\right\} \\
u_2^* &= min\left\{1, max\left\{0, \quad \frac{\beta_h S_h I_h(\lambda_2 - \lambda_1)}{k_2 N_h}\right\}\right\} \\
u_3^* &= min\left\{1, max\left\{0, \quad \frac{I_h(\lambda_3 - \lambda_4)}{k_3}\right\}\right\} \qquad (8) \\
u_4^* &= min\left\{1, max\left\{0, \quad \frac{S_r\lambda_5 + I_r\lambda_6}{k_4}\right\}\right\}
\end{aligned}
$$

Proof. The result from [25] is used in showing the necessary conditions for the existence of the optimal control problem. Consequently, there exist the adjoint system (7) obtained by computing the partial derivatives of system (6) with its state variables, satisfying

$$
\begin{aligned}
&\frac{d\lambda_1}{dt} = -\frac{\partial \mathscr{H}}{\partial S_h}, \quad \frac{d\lambda_2}{dt} = -\frac{\partial \mathscr{H}}{\partial E_h}, \quad \frac{d\lambda_3}{dt} = -\frac{\partial \mathscr{H}}{\partial I_h}, \\
&\frac{d\lambda_4}{dt} = -\frac{\partial \mathscr{H}}{\partial R_h}, \quad \frac{d\lambda_5}{dt} = -\frac{\partial \mathscr{H}}{\partial S_r}, \quad \frac{d\lambda_6}{dt} = -\frac{\partial \mathscr{H}}{\partial I_r}
\end{aligned}
$$

with the terminal conditions $\lambda_i(T) = 0$, for all $i = 1,2,...,6$. Additionally, the optimal control characterization (8) are obtained by solving the equation

$$
\frac{\partial \mathscr{H}}{\partial u_i} = 0, \quad i = 1,2,...,4
$$

for the quadruplet optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$. Thus, the characterization u^* is obtained by using the standard argument involving control bounds as follows

$$
u_i^* = \begin{cases} 0 & if \quad \Delta_i^* \leq 0 \\ \Delta_i^* & if \quad 0 \leq \Delta_i^* \leq 1 \\ 1 & if \quad \Delta_i^* \geq 1 \end{cases} \qquad (9)
$$

for $i = 1,2,3,4$ and Δ_i are given below

$$\begin{aligned}
\Delta_1^* &= \frac{\beta_r S_h I_r(\lambda_2 - \lambda_1)}{k_1 N_h} \\
\Delta_2^* &= \frac{\beta_h S_h I_h(\lambda_2 - \lambda_1)}{k_2 N_h} \\
\Delta_3^* &= \frac{I_h(\lambda_3 - \lambda_4)}{k_3} \\
\Delta_4^* &= \frac{S_r\lambda_5 + I_r\lambda_6}{k_4}
\end{aligned}$$

This completes the proof. □

4. Numerical Simulations and Cost-Effectiveness Analysis

We numerically solve the optimal control problem to illustrate the effect of control strategies on the dynamics of Lassa fever in the population. We further investigate the most cost-effective strategy among all the alternative control strategies.

4.1. Numerical simulations of optimal control. Here we implement using Matlab, the Runge-Kutta forward-backward sweep method to simulate the effects of eight different optimal control strategies on the total infected human and rodent population. The eight different control strategies that are applied for the numerical simulations of the optimal control problem (2) are described as follows.

(i) Strategy A: the optimal use of educational campaign only ($u_1 \neq 0$, $u_2 = u_3 = u_4 = 0$)

(ii) Strategy B: optimal condom usage ($u_2 \neq 0$, $u_1 = u_3 = u_4 = 0$)

(iii) Strategy C: the optimal use of treatment only ($u_3 \neq 0$, $u_1 = u_2 = u_4 = 0$)

(iv) Strategy D: optimal use of rodents reduction only ($u_4 \neq 0$, $u_1 = u_2 = u_3 = 0$)

(v) Strategy E: the optimal use of educational campaign and rodents reduction only ($u_1 \neq 0, u_4 \neq 0$, $u_2 = u_3 = 0$)

(vi) Strategy F: optimal condom usage and rodents reduction only ($u_2 \neq 0, u_4 \neq 0$, $u_1 = u_3 = 0$)

(vii) Strategy G: the optimal use of treatment and rodents reduction only ($u_3 \neq 0, u_4 \neq 0$, $u_1 = u_2 = 0$)

(viii) Strategy H: the optimal use of all the control strategies ($u_1 \neq 0, u_2 \neq 0$, $u_3 \neq 0, u_4 \neq 0$)

We note that the initial conditions and parameter values used are adopted from [21]. For simulation purposes, we assume the weight constants in the objective functions to be equal such that $m_1 = m_2 = m_3 = 1$, while the weight constants associated with the total costs of control implementation are assumed to be unequal. Consequently, the weight constants are assumed to be $k_1 = k_2 = k_4 = 50$, while the weight constant $k_3 = 100$ based on the assumption that the weight constant for measuring the total cost to apply treatment is greater than other controls. Unless otherwise stated, the control intervention is simulated for 60 weeks.

4.1.1. *Strategy A: the optimal use of educational campaign u_1 only.* In Figure 1, we present the effects of the optimal control of educational campaign u_1 only on the total infected human and rodent population. We see a drastic reduction in the size of the total infected human population in the presence of optimal control when compared to the case with no control in Figure 1(a). We expect to see this dynamic since the educational campaign is aimed at educating the populace on how to utilize preventive strategies such as personal hygiene, and environmental cleanliness among many other measures. These preventive strategies have been shown to reduce the transmission probabilities of the Lassa virus from infectious rodents to humans. However, as seen in Figure 1(b) the control Strategy A does not have any effect on the total rodent population since this strategy does not impact the reduction of rodents in the environment. The control profile of Strategy A is depicted in Figure 1(c). The result demonstrates that the ideal educational campaign use is kept at the upper bound 100% for 57 weeks of intervention before declining to the lower bounds.

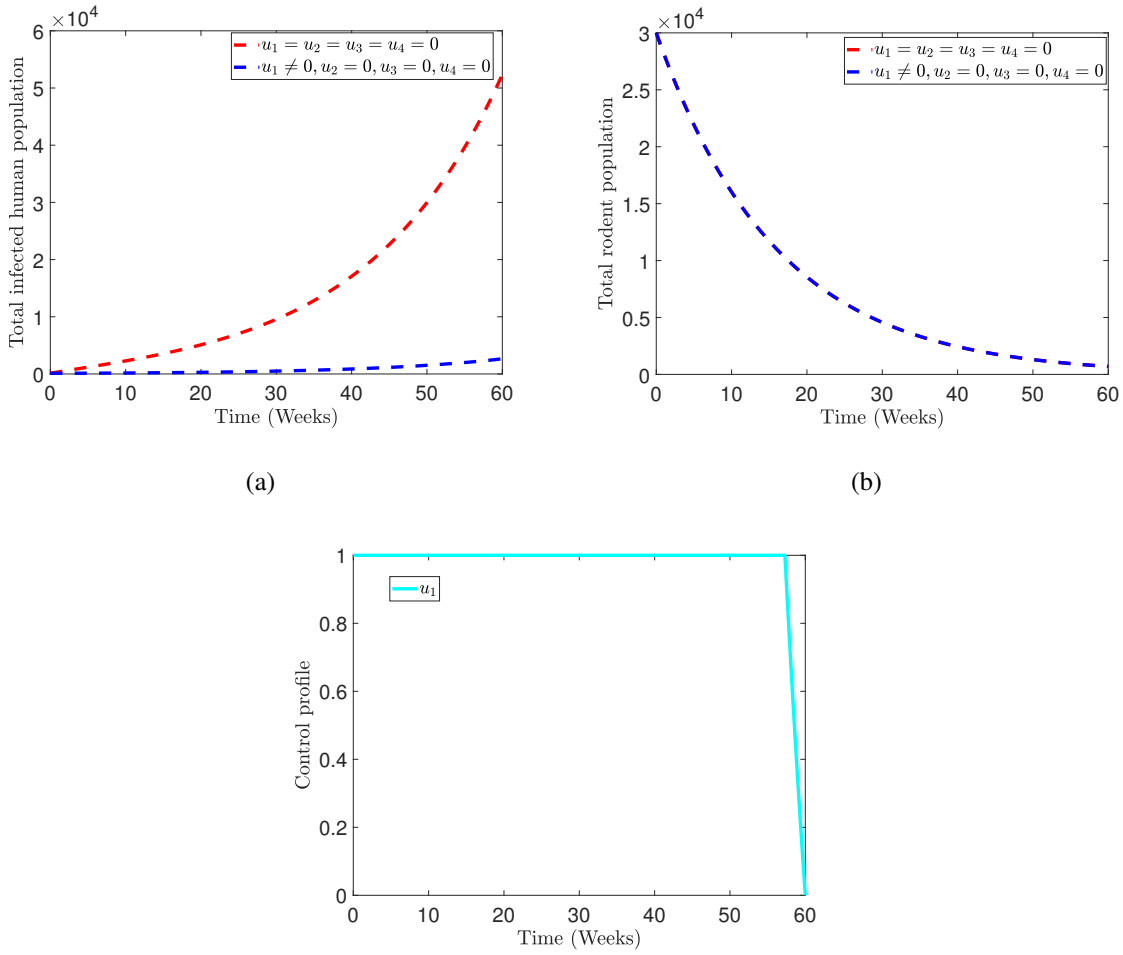


Figure 1: Simulations of the effects of Strategy A optimal control on (a) size of infected human $(E_h + I_h)$; (b) rodent population (N_r); and (c) control profile.

4.1.2. *Strategy B: optimal condom usage u_2 only.* In Figure 2, we illustrate the effects of Strategy B (optimal condom usage) only on the total infected human and rodent population. We see in Figure 2(a) that the size of the total infected human population decreases largely in the presence of the optimal use of a condom when compared to the scenario without a control measure. However, this control strategy does not have any impact on the reduction of the total rodent population as shown in Figure 2(b). In Figure 2(c), the control profile of the optimal condom usage u_2 only shows that the optimal control of the strategy must be maintained at the maximum bound till the control intervention period reaches its end.

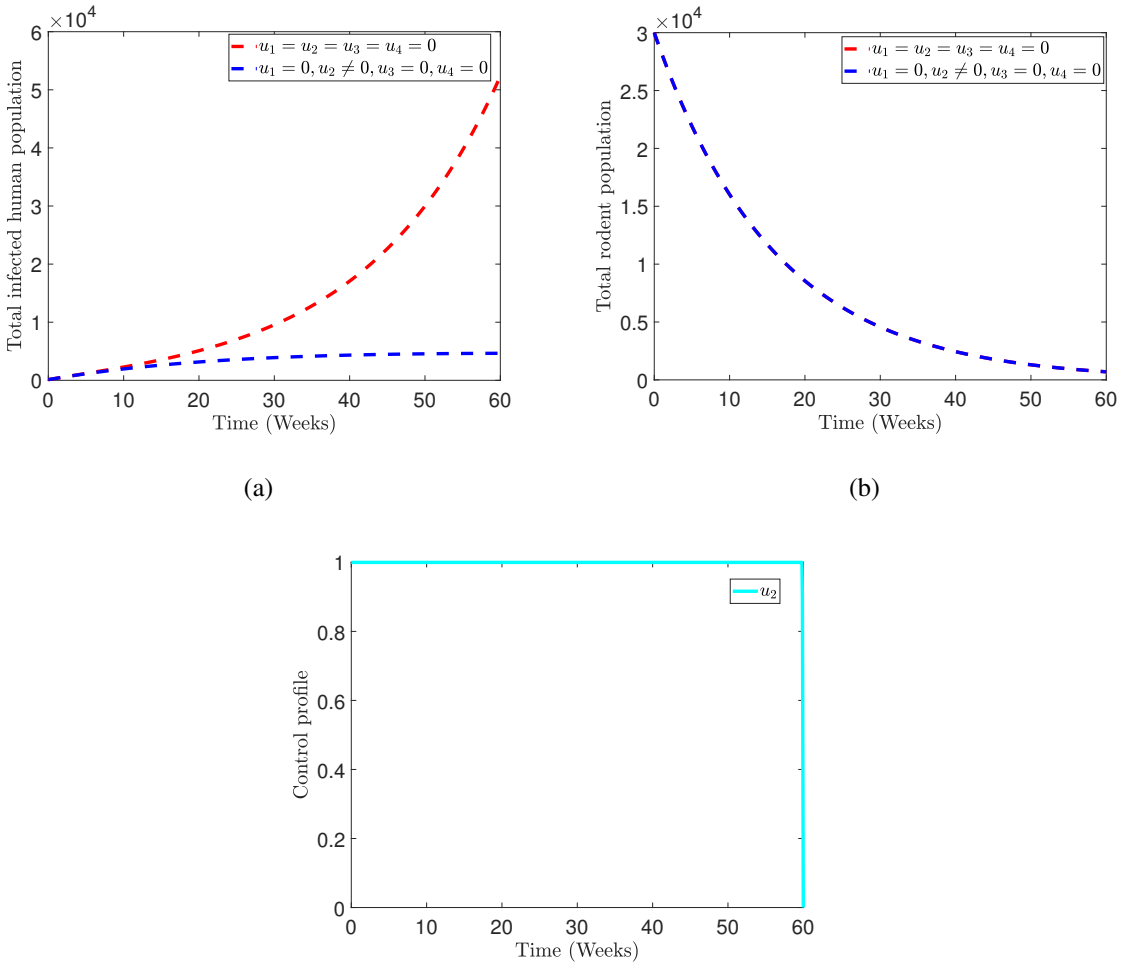
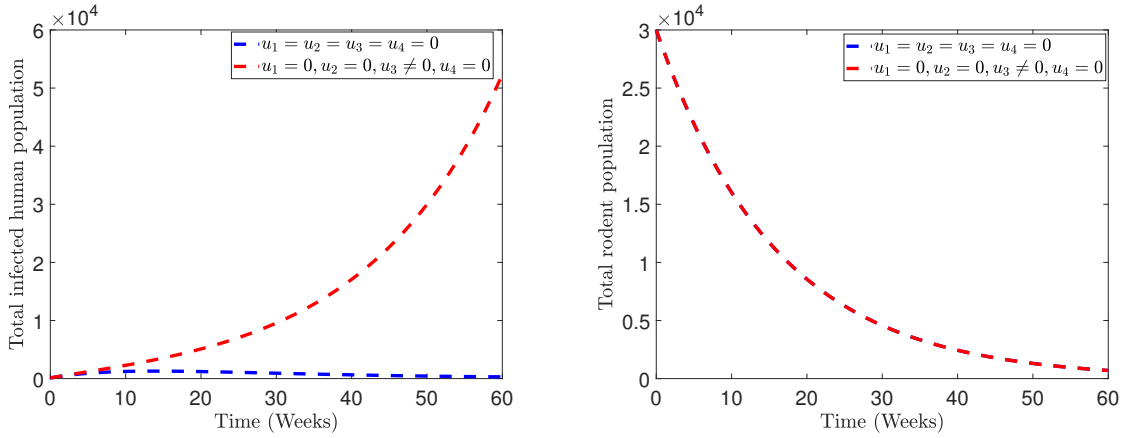


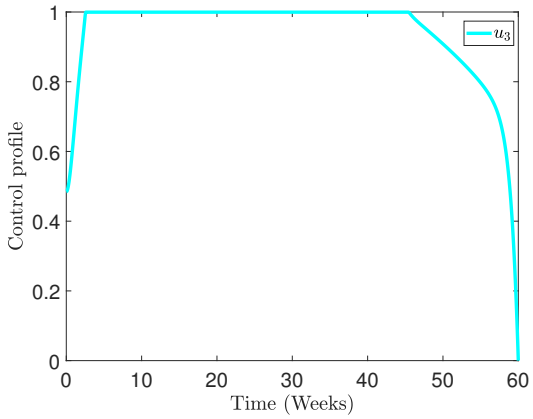
Figure 2: Simulations of the effects of Strategy B optimal control on (a) size of infected human $(E_h + I_h)$; (b) rodent population (N_r); and (c) control profile.

4.1.3. *Strategy C: the optimal use of treatment u_3 only.* In Figure 3, we simulate the effect of the optimal treatment control u_3 on the entire infected human and rodent population. Figure 3(a) shows the effect of this control strategy on the overall infected human population, which is comparable to Figure 1(a). The optimal use of treatment of the infected individuals reduces the burden of Lassa fever in the population due to the higher total Lassa fever infection averted in the population. We note that the optimal use of Strategy C does not have any impact on the total rodent population as shown in Figure 3(b). The control profile of Strategy C is presented in Figure 3(c). For the first four weeks, the optimal treatment usage is increased to the upper

bound and thus kept at the upper limit 100% for 45 weeks of treatment intervention before reducing to the lower bound at the end of the intervention.



(a) (b)



(c)

Figure 3: Simulations of the effects of Strategy C optimal control on (a) size of infected human $(E_h + I_h)$; (b) rodent population (N_r); and (c) control profile.

4.1.4. *Strategy D: optimal use of rodents reduction u_4 only.* In Figure 4, we illustrate the total infected human population and entire rodent population under the effect of the optimal control Strategy D. We see in Figure 4(a) that the optimal reduction of rodents reduces the size of the entire infected human population when compared with the case without optimal control measure. Furthermore, the presence of Strategy D leads to a reduction in the rodent population as depicted in Figure 4(b). This result can be used to inform the public about the importance of

reducing the primary host of Lassa virus in the population as mentioned in [23, 21]. In Figure 4(c), the control profile for the optimal control of treatment usage is maintained at the local maximum for 9 weeks of intervention before declining to the local minimum at the end of the intervention period.

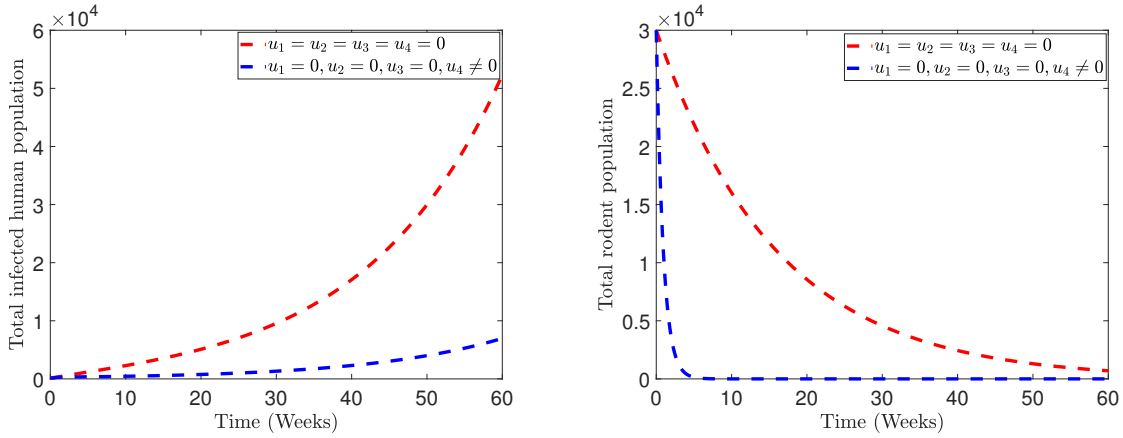


Figure 4: Simulations of the effects of Strategy D optimal control on (a) size of infected human $(E_h + I_h)$; (b) rodent population (N_r); and (c) control profile.

4.1.5. *Strategy E: the optimal use of educational campaign u_1, and rodents reduction u_4 only.* The combined effect of educational campaign u_1 and rodent control u_4 (described as Strategy E) on the entire infected human and rodent population is depicted in Figure 5. In Figure 5(a) and Figure 5(b), we see that throughout the intervention period the total infected human and rodent population sizes are decreased magnificently when compared to the scenario with no control strategy. The optimal control of Strategy E portrayed in Figure 5(c) shows that optimal control of u_1 is at the upper bound for nine weeks before declining to the lower bound. Similarly, the optimal use of rodent control u_4 is maintained at the maximum peak for eleven weeks before declining to the lower bound at the end of the sixty weeks intervention period.

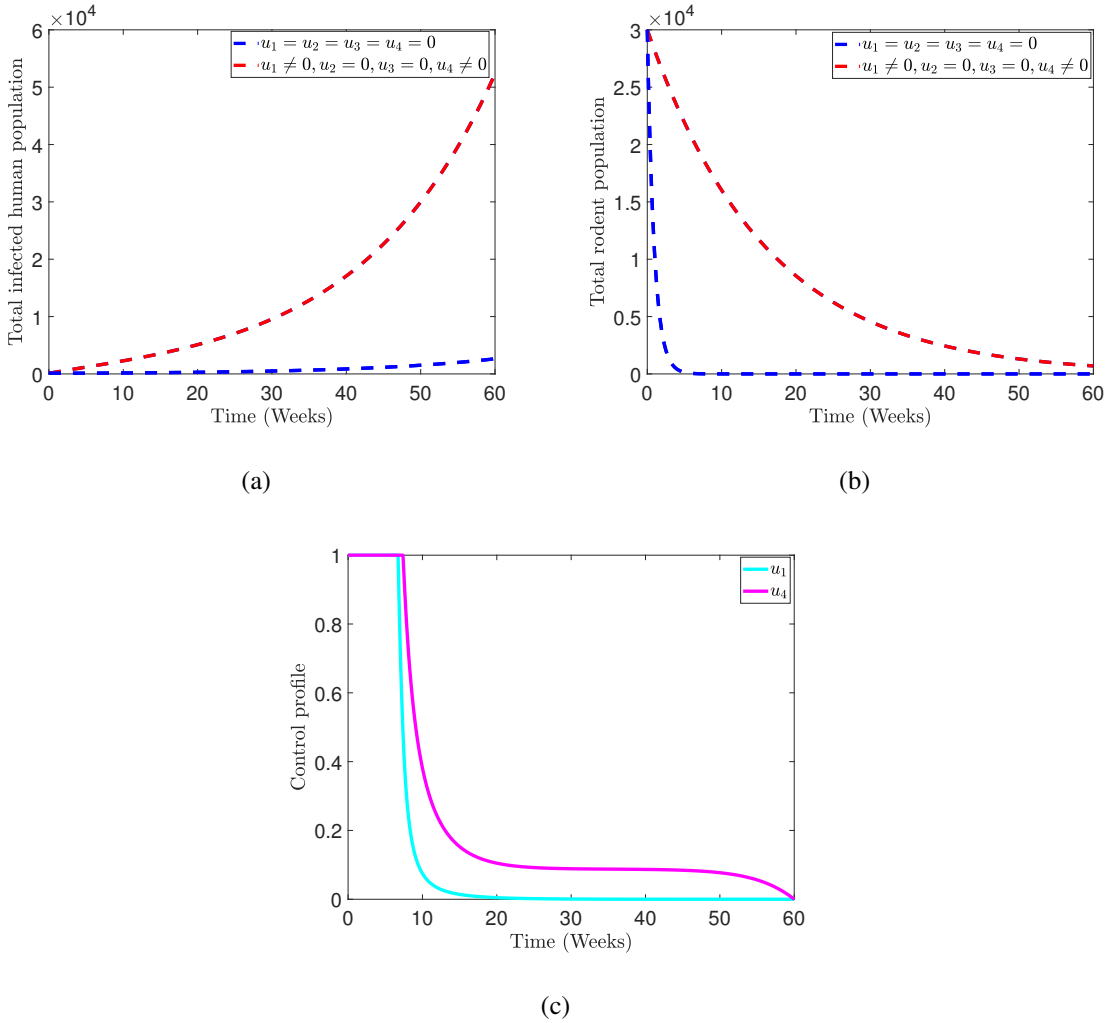


Figure 5: Simulations of the effects of Strategy E optimal control on (a) size of infected human $(E_h + I_h)$; (b) rodent population (N_r); and (c) control profile.

4.1.6. *Strategy F: optimal condom usage u_2, and rodents reduction u_4 only.* In Figure 6, we illustrate the effects of Strategy F (combination of condom usage u_2 and rodent reduction u_4) on the entire infected human and rodent population. The result observed here is similar to the one depicted in Figure 5(a) and Figure 5(b). The respective control profile of the two combined strategies is depicted in Figure 6(c). The optimal condom usage is maintained at the upper bound for fifty-eight weeks, while the optimal use of rodent control is sustained for just eight weeks before declining to the lower bound at the end of the intervention period.

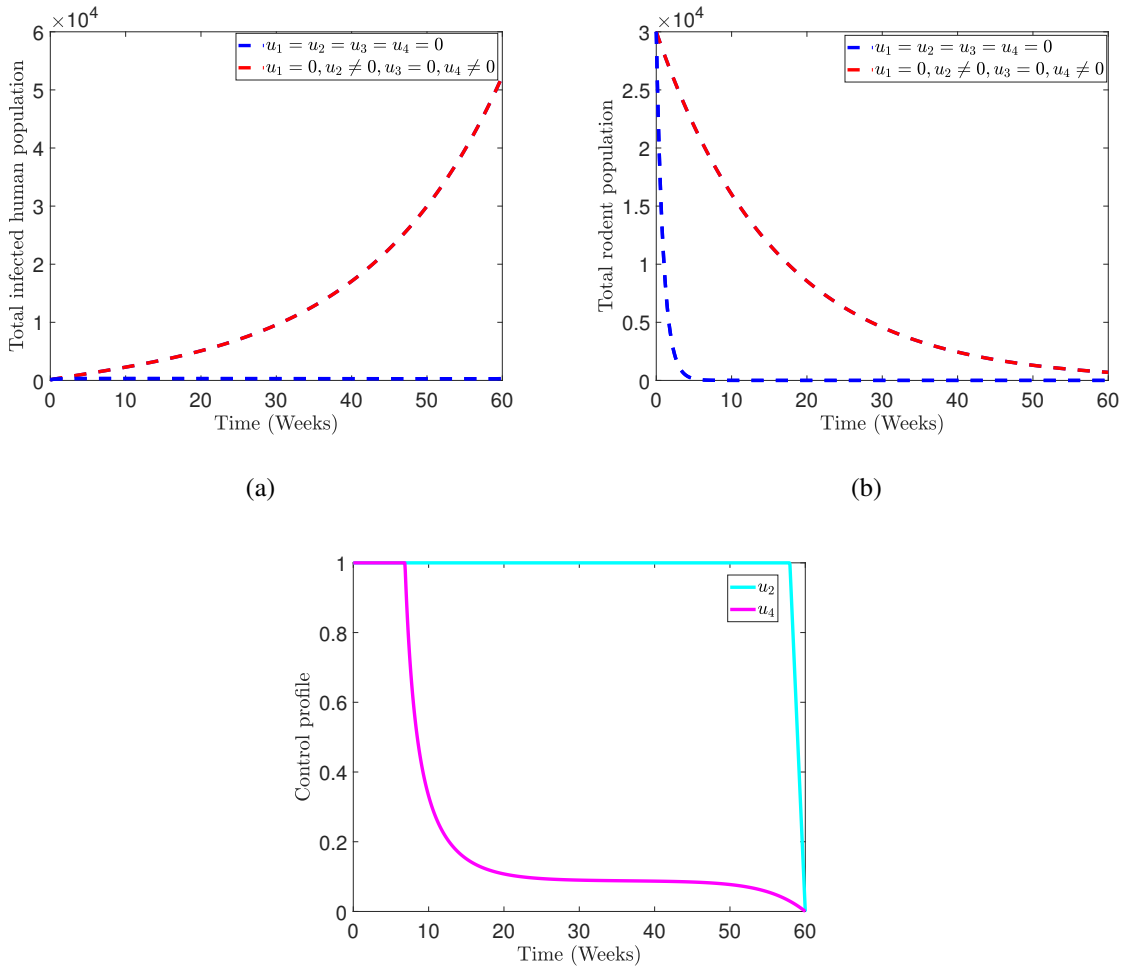
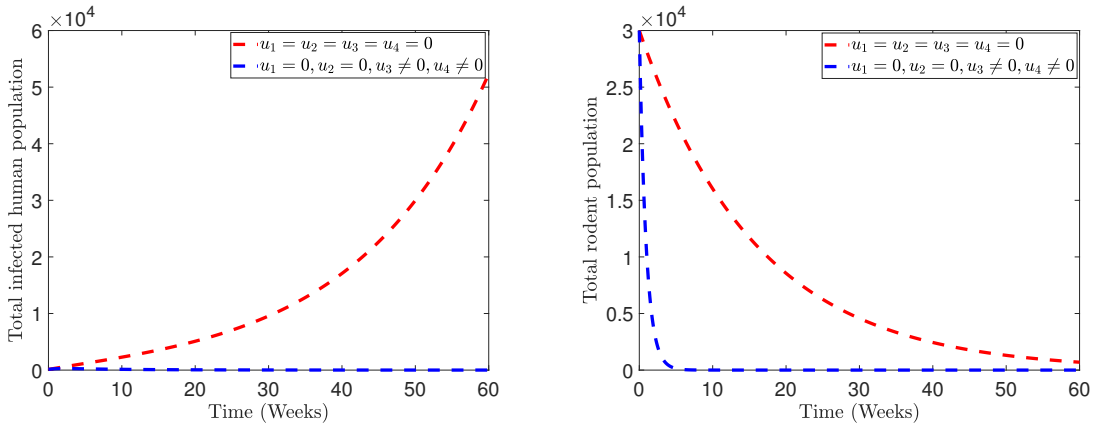


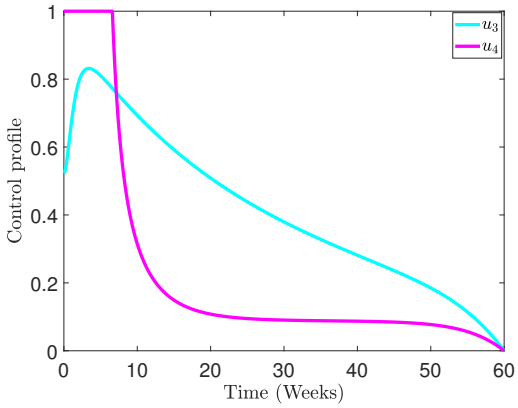
Figure 6: Simulations of the effects of Strategy F optimal control on (a) size of infected human $(E_h + I_h)$; (b) rodent population (N_r); and (c) control profile.

4.1.7. *Strategy G: the optimal use of treatment u_3, and rodents reduction u_4 only.* In Figure 7, we show the effects of the optimal control of treatment care u_3 and rodent control u_4 on the entire infected human and rodent population. We see a huge decrease in the size of the total infected human and total rodent population in the presence of optimal control when compared to the case with no control in Figure 7(a) and Figure 7(b) respectively. The respective control profile of the two combined strategies is depicted in Figure 7(c). For the first five weeks, the optimal treatment usage is increased to the higher bound of 82% and thus decreases to the lower bound throughout the intervention, while the optimal control of rodent reduction is maintained at upper bound 100% for nine weeks before decreasing to the lower bound at the end of the control intervention period.

4.1.8. *Strategy H: the optimal use of educational campaign u_1, condom usage u_2, treatment u_3, and rodents reduction u_4.* Figure 8 shows the dynamic of the total infected human and total rodent population on the effect of the combination of all control strategies considered in this study. Figure 8(a) and Figure 8(b) show that the total infected human population and the total rodent population reduce enormously when all the controls are applied compared to the scenario without control. The control profile Strategy H (combination of all strategies) is depicted in Figure 8(c). We see that the optimal use of educational campaign and rodent control are at the maximum peak for five weeks and eight weeks respectively, while the optimal condom usage and treatment care are at an average bound of 40% and 58% respectively before decreasing to the lower bound throughout the intervention period. We considered 55 weeks of control intervention for this strategy because of the simulation processing time.



(a) (b)



(c)

Figure 7: Simulations of the effects of Strategy G optimal control on (a) size of infected human $(E_h + I_h)$; (b) rodent population (N_r); and (c) control profile.

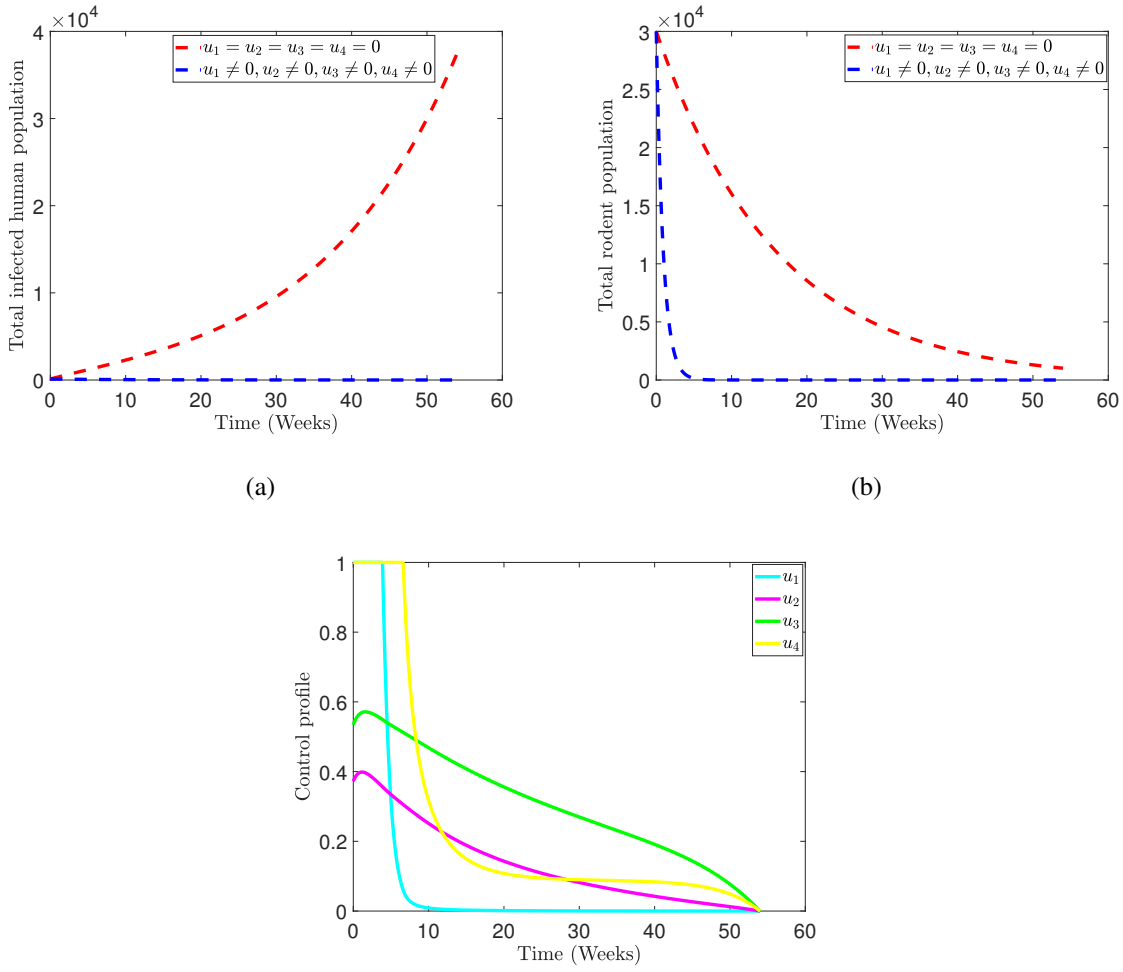


Figure 8: Simulations of the effects of Strategy H optimal control on (a) size of infected human $(E_h + I_h)$; (b) rodent population (N_r); and (c) control profile.

Overall, the result of the numerical simulations shows that the optimal use of different control strategies has a positive impact in reducing the total human infected population. Particularly, from Figure 4 through Figure 8, we deduce that to effectively reduce the incidence of Lassa fever in the population, both the total infected human and total rodent population must be reduced through the implementation of at least combined control strategies that includes rodent reduction u_4 and any other alternative control strategies considered in this study. Thus, the next section will focus on the cost-effectiveness analysis of at least a combination of two different strategies.

4.2. Cost-effectiveness analysis. Here, we undertake a cost-effectiveness analysis to determine the most efficient optimal control strategy with minimal cost, among different combinations of controls. It must be noted that we consider a combination of at least two different control strategies such that all combination includes the control of rodents in the population. These strategies are as given in Strategy E to Strategy H, such that $\triangle_1$ is the combination of educational campaign and rodent control (u_1, u_4), $\triangle_2$ is the combination of condom usage and rodent control (u_2, u_4), $\triangle_3$ is the combination of treatment care and rodent control (u_3, u_4), and $\triangle_4$ is the combination of all the control strategies (u_1, u_2, u_3, u_4). We use the incremental cost-effectiveness ratio (ICER) as presented in [28, 29]. The incremental cost-effectiveness ratio method is used in comparing the difference between multiple contending strategies in relation to their health benefits and costs of implementation. This is calculated by

$$\text{ICER} = \frac{\text{Difference in total costs between control strategies}}{\text{Difference in total infection averted by control strategies}} \tag{10}$$

The total infection averted and the respective total cost for the selected intervention strategies are tabulated in Table 1.

Strategies	Total Infection Averted	Total Cost
$\triangle_1$: u_1, u_4	10,769,790	7,314
$\triangle_2$: u_2, u_4	11,064,220	28,314
$\triangle_3$: u_3, u_4	11,308,195	15,563
$\triangle_4$: u_1, u_2, u_3, u_4	11,350,229	12,431

Table 1: Total infection averted and total cost for the selected intervention strategies

To obtain the most cost-effective strategy among the controls, we present the total Lassa fever infection averted, total cost, and ICER in the increasing order of the total infection averted in Table 2. The calculation of the ICER is given below.

Strategies	Total Infection Averted	Total Cost	ICER
$\triangle_1$: u_1, u_4	10,769,790	7,314	0.00068
$\triangle_2$: u_2, u_4	11,064,220	28,314	0.07132
$\triangle_3$: u_3, u_4	11,308,195	15,563	-0.05226
$\triangle_4$: u_1, u_2, u_3, u_4	11,350,229	12,431	-0.07451

Table 2: ICER in the increasing order of Lassa fever averted by selected strategies

$$\text{ICER}(\triangle_1) = \frac{7314}{10769790} = 0.00068$$

$$\text{ICER}(\triangle_2) = \frac{28314 - 7314}{11064220 - 10769790} = 0.07132$$

$$\text{ICER}(\triangle_3) = \frac{15563 - 28314}{11308195 - 11064220} = -0.05226$$

$$\text{ICER}(\triangle_4) = \frac{12431 - 15563}{11350229 - 11308195} = -0.07451$$

From Table 2, we compare Strategy $\triangle_1$ and Strategy $\triangle_2$. It is observed that the ICER($\triangle_2$) is greater than the ICER($\triangle_1$). This means that Strategy $\triangle_1$ is strongly dominated by Strategy $\triangle_2$, this infers that Strategy $\triangle_2$ is more costly to implement than Strategy $\triangle_1$. Thus, we will remove the costliest Strategy such that the remaining competing strategies are given in Table 3, and the calculation of the respective ICER is shown below.

Strategies	Total Infection Averted	Total Cost	ICER
$\triangle_1$: u_1, u_4	10,769,790	7,314	0.00068
$\triangle_3$: u_3, u_4	11,308,195	15,563	0.01532
$\triangle_4$: u_1, u_2, u_3, u_4	11,350,229	12,431	-0.07451

Table 3: ICER in the increasing order of Lassa fever averted by selected strategies

$$\text{ICER}(\triangle_1) = \frac{7314}{10769790} = 0.00068$$

$$\text{ICER}(\triangle_3) = \frac{15563-7314}{11308195-10769790} = 0.01532$$

$$\text{ICER}(\triangle_4) = \frac{12431-15563}{11350229-11308195} = -0.07451$$

Using Table 3, we compare Strategy $\triangle_1$ and Strategy $\triangle_3$. The incremental cost-effectiveness ratio of Strategy $\triangle_3$ is greater than that of Strategy $\triangle_1$. This result implies that Strategy $\triangle_3$ strongly dominates Strategy $\triangle_1$, which indicates that Strategy $\triangle_1$ is less costly to implement than Strategy $\triangle_3$. Consequently, we eliminate Strategy $\triangle_3$ to further examine the most cost-effectiveness among the alternative strategies. Thus the total infection averted, total cost, and ICER of the remaining control strategies $\triangle_1$ and $\triangle_4$ are presented in Table 4, and the calculation of the respective ICER is shown below.

Strategies	Total Infection Averted	Total Cost	ICER
$\triangle_1$: u_1, u_4	10,769,790	7,314	0.00068
$\triangle_4$: u_1, u_2, u_3, u_4	11,350,229	12,431	0.00882

Table 4: ICER in the increasing order of Lassa fever averted by selected strategies

$$\text{ICER}(\triangle_1) = \frac{7314}{10769790} = 0.00068$$

$$\text{ICER}(\triangle_4) = \frac{12431-7314}{11350229-10769790} = 0.00882$$

By comparing Strategy $\triangle_1$ and Strategy $\triangle_4$, we observed a cost-saving of 0.00882 for Strategy $\triangle_4$ over Strategy $\triangle_1$. The higher ICER obtained from Strategy $\triangle_4$ indicates that this strategy dominates Strategy $\triangle_1$, which means that Strategy $\triangle_1$ is less costly when compared to Strategy $\triangle_4$. Thus, the most cost-effective strategy among all combinations of control considered in this study is Strategy $\triangle_1$, which is the optimal control combination of an educational campaign about preventive measures u_1, and rodents control u_4.

5. CONCLUSION

To investigate the effective control measure of Lassa fever, we integrated four-time dependent control variables into an existing deterministic mathematical model: educational campaign, condom usage, treatment care, and rodent reduction. Using the well-known Pontryagin's maximal principle method, the optimum solutions to the optimal control problem and their characterization were found. We model the impacts of eight different combinations of controls on the total number of infected individuals and the total number of rodents to evaluate the impact of optimal control measures on the spread and control of Lassa fever in the populace. When compared to the scenario with no control strategy, the results reveal that each of the control strategies is effective in reducing the overall number of infected humans. As a result, we use the ICER to determine the most cost-effective optimal control approach among the four selected combinations of controls. Among the four combined techniques studied in this study, the combination of preventative strategies through educational campaigns and rodent reduction in the environment was shown to be the most efficient and cost-effective. As a result of the findings of this study, it is recommended that the most cost-effective optimal control method be used to reduce the community's risk of Lassa fever.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

REFERENCES

[1] S. Günther, O. Lenz, Lassa virus, Critic. Rev. Clinic. Lab. Sci. 41 (4) (2004), 339–390.

[2] J. Ter Meulen, I. Lukashevich, K. Sidibe, et al. Hunting of peridomestic rodents and consumption of their meat as possible risk factors for rodent-to-human transmission of lassa virus in the republic of guinea, Amer. J. Trop. Med. Hyg. 55 (6) (1996), 661–666.

[3] S. Horak, K. Killoran, K. Leedom Larson, Porcine sapelovirus. swine health information center and center for food security and public health (2016).

[4] D. U. Ehichioya, D. A. Asogun, J. Ehimuan, et al. Hospital-based surveillance for lassa fever in Edo State, Nigeria, 2005–2008, Trop. Med. Int. Health 17 (8) (2012), 1001–1004.

[5] World Health Organization. Emergencies preparedness, response: Lassa Fever- Nigeria. (2020).

[6] R. Gibb, L. M. Moses, D. W. Redding, K. E. Jones, Understanding the cryptic nature of lassa fever in West Africa, Pathogens Glob. Health 111 (6) (2017), 276–288.

[7] O. Ogbu, E. Ajuluchukwu, C. Uneke, et al., Lassa fever in West African sub-region: an overview, J. Vector Borne Dis. 44 (1) (2007), 1.

[8] R. Hewson, Lessons learnt from imported cases and onward transmission of lassa fever in europe support broader management of viral haemorrhagic fevers, Eurosurveillance 22 (39) (2017), 17–00661.

[9] I. S. Lukashevich, P. Pushko, Vaccine platforms to control lassa fever, Expert Rev. Vacc. 15 (9) (2016), 1135–1150.

[10] A. B. Woyessa, L. Maximore, D. Keller, et al. Lesson learned from the investigation and response of lassa fever outbreak, Margibi County, Liberia, 2018: Case report, BMC Infect. Dis. 19 (1) (2019), 1–6.

[11] M. M. Ojo, E. F. Doungmo Goufo, Assessing the impact of control interventions and awareness on malaria: a mathematical modeling approach, Commun. Math. Biol. Neurosci. 2021 (2021), 93.

[12] M. O. Adeniyi, S. I. Oke, M. I. Ekum, T. Benson, M. O. Adewole, Assessing the Impact of Public Compliance on the Use of Non-pharmaceutical Intervention with Cost-Effectiveness Analysis on the Transmission Dynamics of COVID-19: Insight from Mathematical Modeling, in: A.T. Azar, A.E. Hassanien (Eds.), Modeling, Control and Drug Development for COVID-19 Outbreak Prevention, Springer International Publishing, Cham, 2022: pp. 579–618.

[13] M. Ojo, F. Akinpelu, Lyapunov functions and global properties of seir epidemic model, Int. J. Chem. Math. Phys. 1 (1) (2017), 11-16.

[14] S. I. Oke, M. M. Ojo, M. O. Adeniyi, M. B. Matadi, Mathematical modeling of malaria disease with control strategy, Commun. Math. Biol. Neurosci. 2020 (2020), 43.

[15] E.F. Doungmo Goufo, S.C. Oukouomi Noutchie, S. Mugisha, A fractional seir epidemic model for spatial and temporal spread of measles in metapopulations, Abstr. Appl. Anal. 2014 (2014), 781028.

[16] M. Ojo, F. Akinpelu, Sensitivity analysis of ebola virus model, Asian Res. J. Math. 2 (2017), 1–10.

[17] E. F. D. Goufo, M. K. Pene, S. Mugisha, Stability analysis of epidemic models of ebola hemorrhagic fever with non-linear transmission, J. Nonlinear Sci. Appl. 9 (6) (2016), 4191–4205.

[18] M. Ojo, B. Gbadamosi, A. Olukayode, O. R. Oluwaseun, Sensitivity analysis of dengue model with saturated incidence rate, Open Access Lib. J. 5 (03) (2018), 1.

[19] B. Gbadamosi, M. M. Ojo, S. I. Oke, M. B. Matadi, Qualitative analysis of a dengue fever model, Math. Comput. Appl. 23 (3) (2018), 33.

[20] M. M. Ojo, E. F. D. Goufo, Modeling, analyzing and simulating the dynamics of lassa fever in Nigeria, J. Egypt. Math. Soc. 30 (1) (2022), 1–31.

[21] M. M. Ojo, B. Gbadamosi, T. O. Benson, O. Adebimpe, A. Georgina, Modeling the dynamics of lassa fever in Nigeria, J. Egypt. Math. Soc. 29 (1) (2021), 1–19.

[22] O. J. Peter, A. I. Abioye, et al. Modelling and optimal control analysis of lassa fever disease, Inform. Med. Unlocked. 20 (2020), 100419.

[23] J. Mariën, B. Borremans, F. Kourouma, et al. Evaluation of rodent control to fight lassa fever based on field data and mathematical modelling, Emerg. Micr. Infect. 8 (1) (2019), 640–649.

[24] I. S. Onah, O. C. Collins, P.-G. U. Madueme, G. C. E. Mbah, Dynamical system analysis and optimal control measures of lassa fever disease model, Int. J. Math. Math. Sci. 2020 (2020), 7923125.

[25] W. H. Fleming, R. W. Rishel, Deterministic and stochastic optimal control, Vol. 1, Springer Science & Business Media, 2012.

[26] L. Pontryagin, V. Boltyanskii, R. Gamkrelidze, E. Mishchenko, The maximum principle, The Mathematical Theory of Optimal Processes. John Wiley and Sons, New York. (1962).

[27] O. A. Adepoju, S. Olaniyi, Stability and optimal control of a disease model with vertical transmission and saturated incidence, Sci. Afr. 12 (2021), e00800.

[28] F. Agusto, M. Leite, Optimal control and cost-effective analysis of the 2017 meningitis outbreak in Nigeria, Infect. Dis. Model. 4 (2019) 161–187.

[29] J. K. K. Asamoah, E. Okyere, A. Abidemi, et al. Optimal control and comprehensive cost-effectiveness analysis for COVID-19, arXiv preprint arXiv:2107.09595. (2021).