Menemui Matematik (Discovering Mathematics)
Vol. 45, No. 1: 56 -75 (2023)

Modeling the transmission dynamics of Hantavirus infection under the effect of vaccination and other optimal controls

Fauzi Mohamed Yusof [1] and Farayola Musiliu Folarin [2]

[1] Faculty of Science and Mathematics, Sultan Idris Education University, 35900 Tanjong Malim, Perak, Malaysia;
[2] Department of Science in Engineering, International Islamic University Malaysia Kuala Lumpur, Malaysia;
[1] fauzi.my@fsmt.upsi.edu.my, [2] farayola@iium.edu.my

ABSTRACT

This article presents a nonlinear deterministic mathematical model which simulates the transmission dynamics of hantavirus infection in the presence of vaccination as well as other optimal control measures. The model is formulated by improving the previous models and including vaccination as an essential component of its optimal control variable. The model is then analyzed for local stability and the disease reproduction number is obtained. Subsequently, the analysis of the model's optimal controls is done using the Pontryagin maximum principle. The necessary conditions for the optimal solution are obtained and used to formulate the adjoint equations and characterize the optimal controls. The model equations and adjoint equations are then solved in the MATLAB environment and used to simulate the population dynamics of the infected and susceptible humans and rodents. The values for the model parameters used for the simulations are obtained from previous works of literature. Thereafter, the global sensitivity analysis of the model's optimal control variables is performed using infected humans and rodents as the expected outputs. The simulation results indicate that within five months, the populations of rodents and infected humans had approached zero. The population of susceptible humans increased initially but the rate of increase later slowed down. As for the susceptible rodents, the population increased for the first two months to a maximum point, then it decreased and approached zero. The results of the global sensitivity analysis show that the first-order sensitivity index for the vaccination in the infected human is 1.0 and 0.9935 in the infected rodents. Similarly, the total-effect sensitivity index for the vaccination in the infected humans is 0.0142 and -0.0691 in the infected rodents. Lastly, based on the simulation and sensitivity analysis results, the presented model, which integrated vaccination with other optimal control strategies, is the most viable model for Hantavirus.

Keywords: Hantavirus; Vaccination; Pontryagin Maximum Principle; Biodiversity; Sensitivity Analysis

INTRODUCTION

Hantaviruses, which are etiological agents carried by wild rats, are primarily transmitted to people through direct human contact. Such encounters may occur while inhaling polluted air, touching contaminated soils and surfaces, consuming contaminated water and food (Martins et al., 2019), or coming into contact with an infected rodent's excreta, urine, or saliva (Wang et al., 2020). The breakout of hantavirus infections within the human population can be attributed to the ecological interactions between the virus, the humans, and the reservoir (Koishi et al., 2016). In the New World, the Hantavirus Cardiopulmonary Syndrome (HCPS) has been confirmed as a deadly disease caused by Hantavirus. Similarly, in the Old World,

Hemorrhagic Fever with Renal Syndrome (HFRS) which is also carried on by the worm has also been categorized as a deadly disease (Nusshag et al., 2017). Consequently, these viruses have been responsible for over 200,000 yearly human infections, with case fatality rates of 5–15% for HFRS and up to 40% for HCPS. Unfortunately, neither of the disease caused by the virus has an effective cure (Liu et al., 2020). Therefore, it is crucial to carry out research activities to discover a treatment for the virus, halt its spread, or optimally control the spread of the virus. The employment of mathematical models is crucial to achieving this objective.

The use of mathematical models for describing Hantavirus infection was pioneered by Abramson and Kenkre (2002). The authors formulated a nonlinear deterministic model that described the infection's temporal and spatial properties. Apart from this model, several nonlinear deterministic models for Hantavirus have also been developed by other authors (Abdul Karim et al., 2009; Abramson et al., 2003; Abramson, 2008; Kenkre et al., 2007; Goh et al., 2009; Gokdogan et al., 2012; Peixoto and Abramson, 2006; Rida et al., 2012). In continuation, Yusof and Ismail (2019) presented a mathematical model which examined the transmission dynamics of the infection and forecasted the path of the disease. The authors concluded that the elimination of the disease depended on the environmental parameter (k) of the real ecosystem of the model, where humans can get sick from being bitten or scratched by an infected rodent. Furthermore, the authors obtained the reproduction number and discussed its sensitivity with respect to the model parameters. Finally, the bifurcation analysis was done by the authors which resulted in the discovery of the disease-free equilibrium points and the asymptotical stability of the endemic.

Although these previous authors have contributed substantially to the research work of eliminating Hantavirus by developing and analyzing models, certain control mechanisms were still left out in the models. An effective way of eradicating or stopping the spread of an infectious disease is to introduce control measures. As a result of this gap, Yusof et al. (2019) presented a mathematical model that considered two distinct effective control measures that could stop the spread of the infection. According to the authors, the disease can be effectively controlled by reducing the number of rodents that disseminate the Hantavirus infection. Hence, harvesting efforts and biodiversity control measures were included in their proposed model as model parameters. Despite the strong academic effort of the authors, the control measures presented only addressed the population of the infected rodents, thereby overlooking the significant populations of infected as well as susceptible humans, which was the main objective of the research endeavor. As a result, this article presents a multi-species nonlinear deterministic mathematical model simulating the dynamics of Hantavirus transmission and the consequences of the disease in the presence of three essential preventative strategies: vaccination, biodiversity, and harvesting efforts.

Amongst these preventative strategies, the use of vaccination has been described as a successful strategy and has undergone extensive research. According to Mu et al. (2019), vaccination is an effective method of stopping infectious disease transmission. Hugo et al. (2017) studied the effects of chicken vaccination, education campaign, and treatment as the optimal control strategies in curbing the spread of Newcastle disease (ND). According to the scientists, the chicken vaccination introduces latent diseases into the susceptible population, enabling the vaccinated animals to manufacture potent defenses against the frailer pathogens. Thus, the authors concluded that the optimal control measures with chicken vaccination could contribute to the eradication of Newcastle disease (ND) among humans. So, including

vaccination as a control measure in Hantavirus modeling is a significant input Peixoto and Abramson (2006).

The proposed multi-species model in this article is formulated by combining the biodiversity model of Peixoto and Abramson (2006) and the Hantavirus transmission dynamics model of Yusof et al. (2019). This combination allows the biodiversity and harvesting control measures to be included in the proposed model. Thereafter, the effect of vaccination on susceptible and infected humans is included in the proposed model by using the same strategy as used by Hugo et al. (2017) in the chicken vaccination. The proportion of infected rodents and humans in the population is reduced once the model is created using the optimum control theory. According to Bryson (1996), the process of calculating out control and state trajectories for a dynamic system over a period of time in order to minimize a performance index or cost functional is known as optimal control theory. The optimal control theory is defined as a mathematical method derived from the calculus of variations (Gaff and Schaefer, 2009) and it has recently been used to decide optimal strategies for infectious diseases.

This article is divided into sections. The strategy utilized to acquire the results is explained in Section 2. The methodology section is divided into subsections which include the model formulation, the model analysis, the model simulation, and the sensitivity analysis. Section 3 presents the results and discussion. The article is then concluded by stating the summary of this research.

METHODOLOGY

This section presents the methodology used in obtaining the results. The first part includes the model formulation which is done in three steps. Thereafter, the model analysis is done in two stages. The first stage is the local stability analysis while the second stage is the optimal control analysis. The model simulation is then done in MATLAB by using numerical values from previous literature. Finally, the sensitivity analysis is done and the sensitivity values of the three optimal controls with regard to two model variables (infected humans and infected rodents) are done.

Model derivations

The proposed model is presented in this section in three steps. In the first two steps, the previous models used for the formulation are presented while the third step presents the proposed model.

Step 1

The following describes the Hantavirus model involving the two basic components of infected and susceptible rodents have been proposed by Abramson and Kenkre (2002). This basic two-component model considered the transmission dynamics of the Hantavirus within the populations of a single rodent specie. The populations of the infected and susceptible rodents are represented by S_r and I_r respectively.

$$\begin{aligned}\frac{dS_r}{dt} &= \phi N_r - \rho S_r - \frac{S_r N_r}{e(t)} - \lambda S_r I_r, \\ \frac{dI_r}{dt} &= -\rho I_r - \frac{I_r N_r}{e(t)} + \lambda S_r I_r,\end{aligned} \tag{1}$$

where $N_r(t) = S_r(t) + I_r(t)$ denotes the total population of rodents. The birth rate is represented by ϕ, the natural mortality rate is given by ρ, the transmission rate of Hantavirus is given by λ and this term is also called the aggression parameter. Finally, the environmental parameter is given by e. Based on the Abramson and Kenkre (2002) model, the infection dies away when $e < e_c$, where $e_c = \phi/(\lambda(\phi - \rho))$ and the infection continues to thrive since there is abundant edible resources when $e > e_c$.

The formulation of the proposed model is then continued by including other populations in addition to the two rodents' populations.

Step 2

The populations of aliens and susceptible as well as infected humans are now incorporated into the proposed model. This is accomplished by applying the model of Yusof and Ismail (2019). The model developed by Yusof and Ismail (2019) expanded the model of Peixoto and Abramson (2006), which included biodiversity, by including the impact of human infection on the direct transmission of the propagation of the Hantavirus.
The model is given by Equation 2 below

$$\begin{cases} \dfrac{dS_h}{dt} = \Omega - \beta S_h + \alpha I_h - \partial I_r S_h, \\ \dfrac{dI_h}{dt} = \partial I_r S_h - (\beta + \alpha) I_h, \\ \dfrac{dS_r}{dt} = \phi N_r - \rho S_r - \dfrac{S_r}{e}(N_r + \nu A_z) - \lambda S_r I_h, \\ \dfrac{dI_r}{dt} = -\rho I_r - \dfrac{I_r}{e}(N_r + \nu A_z) + \lambda S_r I_h, \\ \dfrac{dA_z}{dt} = (m - n) A_z - \dfrac{A_z}{e}(A_z + \omega N_r). \end{cases} \tag{2}$$

where, S_h and I_h are the populations of susceptible and infected humans, respectively at any given time *t*. The parameter Ω denotes the human birth rate, β gives human death rate, α denotes the human recovery rate, and ∂ denotes the transmission rate from humans to rodents. As for the alien population, ν denotes influence of the alien population and $A_z(t)$ represents the population of aliens. For the alien population, m, n and ω denote the corresponding parameters for obtaining resources from the other species and e denotes the environmental parameter.

To include control strategies in the proposed model, the dynamical Newcastle disease model of Hugo et al. (2017), which incorporated chicken vaccination, is used with the model of Yusof and Ismail (2019). The Newcastle disease model is given below by Equation (3).

$$\begin{cases} \dfrac{dS_1}{dt} = r\left(1-\dfrac{S_1}{k}\right)S_1 - (1-u_1(t))\beta_1 S_1 I_1 - \dfrac{b_1 S_1 S_2}{a_1+S_1} - \dfrac{b_2 S_1 S_2}{a_2+S_1}, \\ \dfrac{dI_1}{dt} = (1-u_1(t))\beta_1 S_1 I_1 - (m+u_1(t))I_1 - \dfrac{c_1 S_1 S_2}{n_1+I_1} - \dfrac{c_2 S_1 S_2}{n_2+I_1}, \\ \dfrac{dS_2}{dt} = \dfrac{\alpha_1 b_1 S_1 S_2}{a_1+S_1} - \dfrac{\alpha_2 c_1 I_1 S_2}{n_1+I_1} - (1-u_2(t))\beta_2 S_2 I_1 - \mu_2 S_2 + \theta R_2, \\ \dfrac{dI_2}{dt} = (1-u_2(t))\beta_2 S_2 I_1 - (u_3(t)+\gamma)I_2 - \mu_2 I_2 + \dfrac{\alpha_3 b_2 S_1 I_2}{a_2+S_1} - \dfrac{\alpha_4 c_1 I_1 I_2}{n_2+I_1}, \\ \dfrac{dR_2}{dt} = (u_3(t)+\gamma)I_2 - (\theta+\mu_2)R_2. \end{cases} \quad (3)$$

where $S_1(t)$ and $I_1(t)$ represent the populations of susceptible chicken and infected chicken, respectively. As for the human populations, the susceptible humans is denoted by $S_2(t)$, the infected humans is given by $I_2(t)$, and the human recovery class is denoted by $R_2(t)$. The parameters of Equation (3) are described in Table 1.

Table 1: Details of the variables utilised in Equation (3).

Symbol	Description
R	The intrinsic growth rate of chickens
K	The carrying capacity of the population
β_1	The force of the infection
β_2	The infection of Humans as a result of force of infection
μ_1	The natural death rate of chickens
M	The death rate caused by the disease
μ_2	The loss suffered by the human population as result of the natural death rate
θ	The rate of recovery
γ	The treatment rate
b_1, c_1, b_2, c_2	The predation functional response of humans towards susceptible and infected chicken rate
a_1, a_2, n_1, n_2	The half saturation constant rate
$\alpha_1, \alpha_2, \alpha_3, \alpha_4$	The consumed susceptible and infected chickens are converted into a human at an efficient rate
$u_1(t)$	Control variable for the chicken vaccination
$u_2(t)$	Control variable based on the human education campaign
$u_3(t)$	Control variable used to measure the effectiveness of treatment of infected humans.

Step 3

The proposed model is then formulated by using Equation (2) and (3). Equation (2) is used as the reference and the chicken vaccination strategy in Equation (3) is integrated into Equation (2). The vaccination strategy for susceptible and infected chickens in Equation (3) is now used as a vaccination strategy for susceptible and infected humans in Equation (2). Subsequently,

the second control measure of harvesting efforts (removal of the populations of infected rodents and susceptible) is included in Equation (2). Finally, the control measure of biodiversity is included in the alien population of Equation (2). Therefore, the proposed optimal control strategy for eliminating Hantavirus from rodent and human populations is a combination of these three strategies (vaccination, harvesting activities, and biodiversity). The proposed model is then given in Equation (4).

$$\begin{cases} \frac{dS_h}{dt} = \Omega - \beta S_h + \alpha I_h - (1-\Lambda_1(t))\partial I_r S_h, \\ \frac{dI_h}{dt} = (1-\Lambda_1(t))\partial I_r S_h - (\beta+\alpha) I_h, \\ \frac{dS_r}{dt} = \phi N_r - \rho S_r - \frac{S_r}{e}(N_r + \nu A_z) - \lambda S_r I_h - \Psi(t) S_r, \\ \frac{dI_r}{dt} = -\rho I_r - \frac{I_r}{e}(N_r + \nu A_z) + \lambda S_r I_h - -\Psi(t) I_r, \\ \frac{dA_z}{dt} = (m-n) A_z - \frac{A_z}{e}(A_z + (1-\Lambda_2(t))\omega N_r). \end{cases} \quad (4)$$

where $\Lambda_1(t)$, $\Psi(t)$ and $\Lambda_2(t)$ are the control variables for human vaccination, the harvesting efforts, and biodiversity respectively. The fraction of the rodent population that is removed during each period is referred to as the harvesting efforts. The supply and profusion of alien and rodent species within an ecosystem are referred to as biodiversity.

The efficiency of the vaccine is denoted by $(1-\Lambda_1(t))$ and the value $(1-\Lambda_2(t))$ is used to lessen the impact of the Hantavirus infection. The control variables being engaged, $\Lambda_1(t)$, $\Psi(t)$ and $\Lambda_2(t)$ are constrained by Lebesgue measurable functions on $[0,1]$. The main objective of these control variables is to minimize the population of infected humans and rodents meanwhile maximize the populations of susceptible human populations. In the following section, the model is analyzed for stability after formulating created.

MODEL ANALYSIS

The analysis of the model Equation (4) is presented in this section. The first analysis is the local stability analysis behavior of the model Equation (4) at various positive equilibrium points.

Local Stability Analysis

The equilibrium point is found by setting $\frac{dS_h}{dt} = \frac{dI_h}{dt} = \frac{dS_r}{dt} = \frac{dI_r}{dt} = \frac{dA_z}{dt} = 0$. In the absence of infection, the model Equation (4) has a steady state, E_0 called the disease-free equilibrium, where $E_0\left(\frac{\Omega}{\beta}, 0, e(\phi - \rho - \Psi(t)), 0, 0\right)$. According to Van den Driessche and Watmough (2002), linear stability E_0 is formed using the next-generation operator method on the model Equation (4). The matrices of the new infection terms (*F*) and the terms of the vital dynamics (*V*) are given as

$$F=\begin{bmatrix} 0 & (1-\Lambda_1(t))\partial\left(\dfrac{\Omega}{\beta}\right) \\ 0 & 0 \end{bmatrix}, \quad V=\begin{bmatrix} \beta+\alpha & 0 \\ -\lambda Q_1 & \rho+\dfrac{Q_1}{e}+\Psi(t) \end{bmatrix}$$

where $Q_1 = e(\phi-\rho-\Psi(t))$. Therefore, the disease reproduction number (R_0) for optimal control strategies in the model Equation (4) is given as the dominant eigenvalue of FV^{-1}:

$$R_0 = \frac{(\Lambda_1(t)-1)\lambda e\partial\Omega Q_1}{\beta(e(\rho+\Psi(t))+Q_1)}. \tag{5}$$

Optimal Control Analysis

The optimal control analysis for the model Equation (4) is done by following the method of Momoh and Fügenschuh (2018). The Pontryagin maximum principle is then use to control the required conditions for the optimal control of the propagation of the Hantavirus infection. To achieve optimal control, it is necessary to reduce the number of infected humans and rodents disseminating the Hantavirus infection. The controls are vaccination, harvesting efforts, and biyodiversity controls. The technique for minimizing the number of infected rodents and human disseminating this infection is obtained by using the functional given by:

$$J(\Lambda_1(t),\Psi(t),\Lambda_2(t)) = \int_0^T \left[(M_1 I_h + M_2 S_r + M_3 I_r) + \frac{1}{2}\left(K_1\Lambda_1^2 + K_2\Psi^2 + K_3\Lambda_2{}^2\right)\right] dt$$

Thereafter, the bounded Lebesgue measurable functions are used to determine the objective functional. This is given by Equation (6),

$$J(\Lambda_1(t),\Psi(t),\Lambda_2(t)) = \min \int_0^T \left[(M_1 I_h + M_2 S_r + M_3 I_r) + \frac{1}{2}\left(T_1\Lambda_1^2 + T_2\Psi^2 + T_3\Lambda_2{}^2\right)\right] dt, \tag{6}$$

where K_1, K_2 and are weight constants for human vaccination, harvesting efforts, and biodiversity respectively. As for the objective functional, the weight constant of infected humans is represented by M_1, the weight constant of susceptible rodents is given by M_2, and the weight constant of infected rodents is represented by M_3.

Afterward, the optimal control strategies $(\Lambda_1^*(t),\Psi^*(t),\Lambda_2^*(t))$ are sought such that

$$J(\Lambda_1(t),\Psi(t),\Lambda_2(t)) = \min\{J(\Lambda_1(t),\Psi(t),\Lambda_2(t)) \mid \Lambda_1(t),\Psi(t),\Lambda_2(t)\in U\},$$

where the control set is represented by

$$U = \{(\Lambda_1(t),\Psi(t),\Lambda_2(t)) \text{ are Lebesque measureable, } 0\le(\Lambda_1(t),\Psi(t),\Lambda_2(t))\le 1, t\in[0,T]\}$$

The Lagrangian for the optimal control problem is given as

$$L = M_1 I_h + M_2 S_r + M_3 I_r + \frac{1}{2}\left(K_1 \Lambda_1^2 + K_2 \Psi^2 + K_3 {\Lambda_2}^2\right).$$

The maximum principle of Pontryagin [21] gives the necessary requirements the optimal solution must fulfill. With this principle, the model Equation (4) and Equation (6) are converted into a problem of diminishing point-wise Hamiltonian H, $\Psi(t)$ and $\Lambda(t)$ as shown by Equation (7)

$$H = L(I_h, S_r, I_r, \Lambda_1(t), \Psi(t), \Lambda_2(t)) + \gamma_1 \frac{dS_h}{dt} + \gamma_2 \frac{dI_h}{dt} + \gamma_3 \frac{dS_r}{dt} + \gamma_4 \frac{dI_r}{dt} + \gamma_5 \frac{dA_z}{dt}$$

$$= M_1 I_h + M_2 S_r + M_3 I_r + \frac{1}{2}\left(K_1 \Lambda_1^2 + K_2 \Psi^2 + K_3 {\Lambda_2}^2\right) + \gamma_1 \frac{dS_h}{dt} + \gamma_2 \frac{dI_h}{dt} + \gamma_3 \frac{dS_r}{dt} + \gamma_4 \frac{dI_r}{dt} + \gamma_5 \frac{dA_z}{dt}$$

$$= M_1 I_h + M_2 S_r + M_3 I_r + \frac{1}{2}\left(K_1 \Lambda_1^2 + K_2 \Psi^2 + K_3 {\Lambda_2}^2\right) + \gamma_1(\Omega - \beta S_h + \alpha I_h - (1 - \Lambda_1(t))\partial I_r S_h) + \quad (7)$$

$$+ \gamma_2((1 - \Lambda_1(t))\partial I_r S_h - (\beta + \alpha) I_h) + \gamma_3\left(\phi N_r - \rho S_r - \frac{S_r}{e}(N_r + \nu A_z) - \lambda S_r I_h - \Psi(t) S_r\right) +$$

$$\gamma_4\left(-\rho I_r - \frac{I_r}{e}(N_r + \nu A_z) + \lambda S_r I_h - -\Psi(t) I_r\right) + \gamma_5\left((m - n) A_z - \frac{A_z}{e}\left(A_z + (1 - \Lambda_2(t))\omega N_r\right)\right),$$

where $\gamma_1, \gamma_2, \gamma_3, \gamma_4$ and γ_5 are the adjoint variables or co-state variables.

From Equation (7), the subsequent adjoint equations are generated as follows in Equation (8)

$$\frac{d\gamma_1}{dt} = -\frac{\delta H}{\delta S_h} = \gamma_1(\beta + (1 - \Lambda_1(t))\partial I_r) - \gamma_2((1 - \Lambda_1(t))\partial I_r)$$

$$\frac{d\gamma_2}{dt} = -\frac{\delta H}{\delta I_h} = -M_1 - \gamma_1\alpha + \gamma_2(\beta + \alpha) + (\gamma_3 - \gamma_4)\lambda S_r$$

$$\frac{d\gamma_3}{dt} = -\frac{\delta H}{\delta S_r} = -M_2 - \gamma_3\left(\phi - \rho - \frac{1}{e}(2S_r + I_r + \nu A_z) - \lambda I_h - \Psi(t)\right) - \gamma_4\left(-\frac{I_r}{e} + \lambda I_h\right) -$$

$$\gamma_5\left(-\frac{A_z}{e}((1 - \Lambda_2(t))\omega)\right) \quad (8)$$

$$\frac{d\gamma_4}{dt} = -\frac{\delta H}{\delta I_r} = -M_3 + \gamma_1((1 - \Lambda_1(t))\partial S_h) - \gamma_2((1 - \Lambda_1(t))\partial S_h) - \gamma_3\left(\rho - \frac{S_r}{e}\right)$$

$$-\gamma_4\left(-\rho - \frac{1}{e}(S_r + 2I_r + \nu A_z) - \Psi(t)\right) - \gamma_5\left(-\frac{A_z}{e}((1 - \Lambda_2(t))\omega)\right)$$

$$\frac{d\gamma_5}{dt} = -\frac{\delta H}{\delta A_z} = \gamma_3\left(\frac{\nu}{e} S_r\right) + \gamma_4\left(\frac{\nu}{e} I_r\right) - \gamma_5\left((m - n) - \frac{1}{e}(2A_z + (1 - \Lambda_2(t))\omega N_r)\right),$$

with transversality condition (or the boundary condition) given below
$\gamma_1(t_{end}) = \gamma_2(t_{end}) = \gamma_3(t_{end}) = \gamma_4(t_{end}) = \gamma_5(t_{end}) = 0$.

The Hamiltonian H is then differentiated into $\Lambda_1(t)$, $\Psi(t)$ and $\Lambda_2(t)$, and set to be $\frac{\delta H}{\delta \Lambda_1(t)} = \frac{\delta H}{\delta \Psi(t)} = \frac{\delta H}{\delta \Lambda_2(t)} = 0$.

Therefore,

$$\frac{\delta H}{\delta \Lambda_1(t)} = K_1 \Lambda_1(t) + (\gamma_1 - \gamma_2) \partial I_r S_r = 0,$$

$$\frac{\delta H}{\delta \Psi(t)} = K_2 \Psi - \gamma_3 S_r - \gamma_4 I_r = 0,$$

$$\frac{\delta H}{\delta \Lambda_2(t)} = K_3 \Lambda_2(t) + \frac{\gamma_5 \omega}{e} N_r A_z = 0.$$

Further, solving for the optimal controls $\left(\text{i.e.} \frac{\delta H}{\delta \Lambda_1(t)} = \frac{\delta H}{\delta \Psi(t)} = \frac{\delta H}{\delta \Lambda_2(t)} = 0 \right)$, yields

$$\Lambda_1(t)^C = \frac{(\gamma_2 - \gamma_1)}{K_1} \partial I_r S_h,$$

$$\Psi(t)^C = \frac{1}{K_2} (\gamma_3 S_r + \gamma_4 I_r),$$

$$\Lambda_2(t)^C = -\frac{\gamma_5 \omega}{e K_3} N_r A_z.$$

Then the second derivate of the Lagrangian function to $\Lambda_1(t)$, $\Psi(t)$ and $\Lambda_2(t)$ are obtained. The values of these second derivatives which are given below are all positive and this implies that the optimal control strategy approaches the minimum at controls $\Lambda_1(t)$, $\Psi(t)$ and $\Lambda_2(t)$ (Lenhart and Workman, 2007).

$$\frac{\delta^2 H}{\delta \Lambda_1^2(t)} = K_1 > 0$$

$$\frac{\delta^2 H}{\delta \Psi^2(t)} = K_2 > 0$$

$$\frac{\delta^2 H}{\delta \Lambda_2{}^2(t)} = K_3 > 0$$

Therefore, the problem is associated with a decrease in the of the populations of infected humans and rodents with optimal control strategies since the second derivative is greater than zero (Lenhart and Workman, 2007).

Finally, the characterization of the optimal controls $\Psi(t)^*$ and $\Lambda(t)^*$ are given by Equation (9) below

$$\left.\begin{aligned} \Lambda_1(t)^* &= \max\left\{\min\left\{\frac{(\gamma_2-\gamma_1)}{K_1}\partial\, I_r S_h\,, 1\right\}, 0\right\} \\ \Psi(t)^* &= \max\left\{\min\left\{\frac{1}{K_2}(\gamma_3 S_r + \gamma_4 I_r), 1\right\}, 0\right\} \\ \Lambda_2(t)^* &= \max\left\{\min\left\{-\frac{\gamma_5\omega}{eK_3} N_r A_z, 1\right\}, 0\right\}. \end{aligned}\right\} \tag{9}$$

By using standard arguments that involve the limitations on the controls, the optimal controls can be written as shown below

$$\Lambda_1(t)^* = \begin{cases} 0 & \text{if } \Lambda_1(t)^C \le 0, \\ \Lambda_1(t)^C & \text{if } 0 < \Lambda_1(t)^C < 1, \\ 1 & \text{if } \Lambda_1(t)^C \ge 1, \end{cases}$$

$$\Psi(t)^* = \begin{cases} 0 & \text{if } \Psi(t)^C \le 0, \\ \Psi(t)^C & \text{if } 0 < \Psi(t)^C < 1, \\ 1 & \text{if } \Psi(t)^C \ge 1, \end{cases}$$

$$\Lambda_2(t)^* = \begin{cases} 0 & \text{if } \Lambda_2(t)^C \le 0, \\ \Lambda_2(t)^C & \text{if } 0 < \Lambda_2(t)^C < 1, \\ 1 & \text{if } \Lambda_2(t)^C \ge 1. \end{cases}$$

MODEL SIMULATION

This section presents the model simulation to describe the affects of the optimal control strategies of vaccination, harvesting efforts, and biodiversity on the dynamics of the Hantavirus. The model simulation is done in the MATLAB environment. The model Equation (4) and adjoint Equation (8) are solved simultaneously in MATLAB software which makes a total of ten equations. The dependent model variables in Equation (4) are the populations of the rodents (i.e., infected and susceptible), humans (i.e., infected and susceptible), and aliens while the dependent model variables in Equation (8) are the adjoint variables. As illustrated in Equation (9), the adjoint variables are employed to obtain the optimal control variables $\left(\Lambda_1(t), \Psi(t), \Lambda_2(t)\right)$, which are then used in the ten equations. The MATLAB inbuilt code (ode45) was used for solving the ten equations (model Equation (4) and adjoint variables Equation (8)). The time interval was chosen as [0,5] which signified five months.

The values for the model parameters used in the simulation were obtained from previous literature [20, 14]. The weight constant values in the objective functional were

chosen as $M_1 = 0.25$, $M_2 = 0.75$, $M_3 = 0.5$, $K_1 = 0.16$, $K_2 = 0.11$ and $K_3 = 0.15$. According to Momoh and Fügenschuh (2018), the factors M_i $(\text{for } i = 1, 2, 3)$ are higher than the K_j $(\text{for } j = 1, 2, 3)$ factors, this is to emphasize the size of the groups that should be smaller during optimization. The list of the values of the model parameters for Equation (4) and Equation (8) and their corresponding descriptions and references are presented in Table 2. The initial values for the populations of the rodents (i.e., infected and susceptible), humans (i.e., infected and susceptible), and aliens were set as 5 during the simulations while the initial values for the adjoint variables were set as 0. The simulation findings for the dynamics of the infected human, susceptible human, infected rodent, and susceptible rodent populations are shown in Figures 1-4, respectively.

Table 2: Parameter Values of Equation (4)

Symbol	Description	Parameter value	References
Ω	Birth rate (Humans)	6.75	Li and Blakeley (2011)
β	Death rate (Humans)	0.15	Li and Blakeley (2011)
α	Recovery rate (Humans)	3.075	Li and Blakeley (2011)
∂	Transmission rate from humans to rodents	0.03	Li and Blakeley (2011)
ϕ	Birth rate (Rodents)	1	Peixoto and Abramson (2006)
ρ	Death rate (Rodents)	0.6	Peixoto and Abramson (2006)
λ	The transmission rate of Hantavirus	0.1	Peixoto and Abramson (2006)
e	The environmental parameter	200	Assumed
ν	Competitive effect of rodents on alien species	0.2	Peixoto and Abramson (2006)
m	Birth rate (Aliens)	1	Peixoto and Abramson (2006)
n	Death rate (Aliens)	0.5	Peixoto and Abramson (2006)
ω	Competitive effect of rodents on alien species	0.1	Peixoto and Abramson (2006)

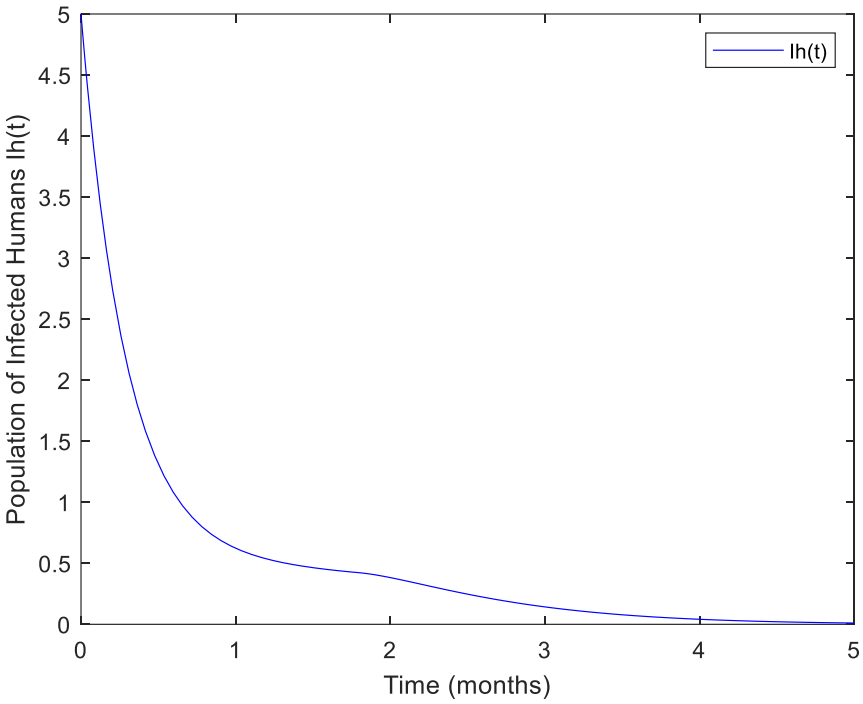

Figure 1. The population dynamics of infected humans within 5 months

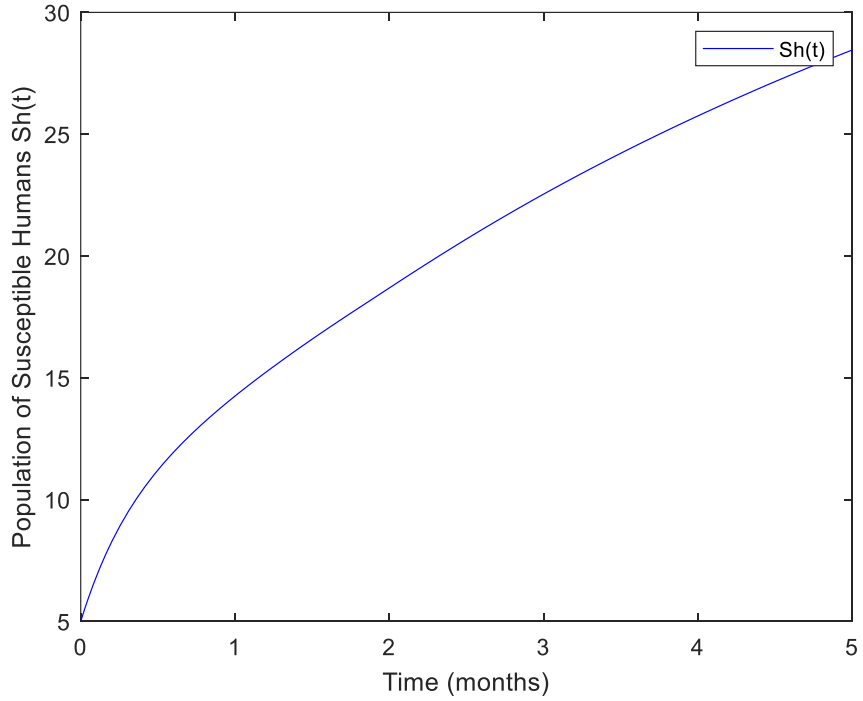

Figure 2. The population dynamics of susceptible humans within 5 months

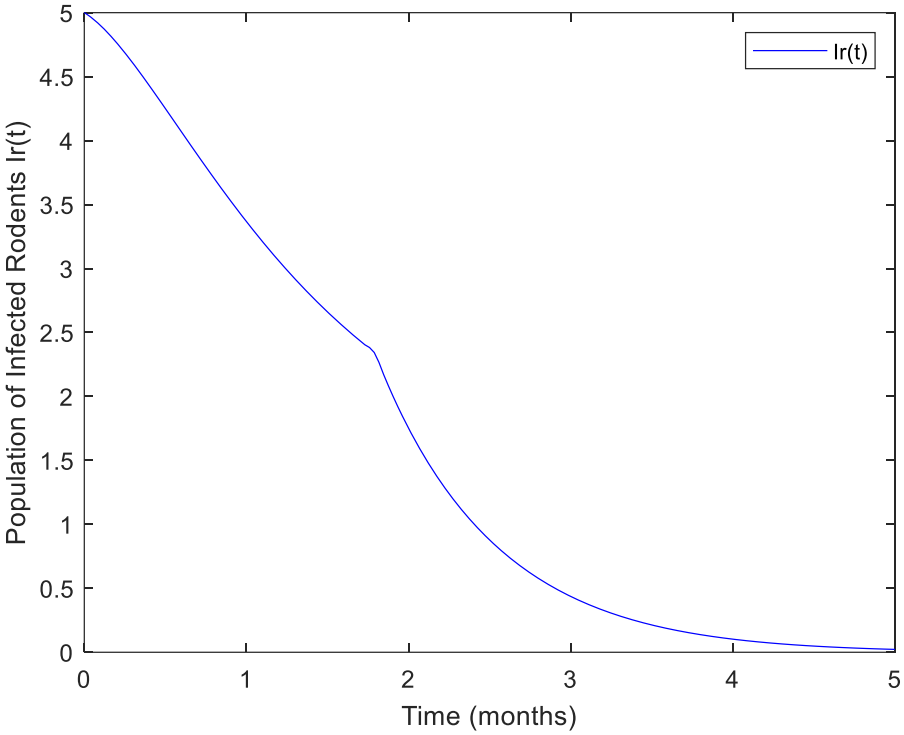

Figure 3. The population dynamics of infected rodents within 5 months

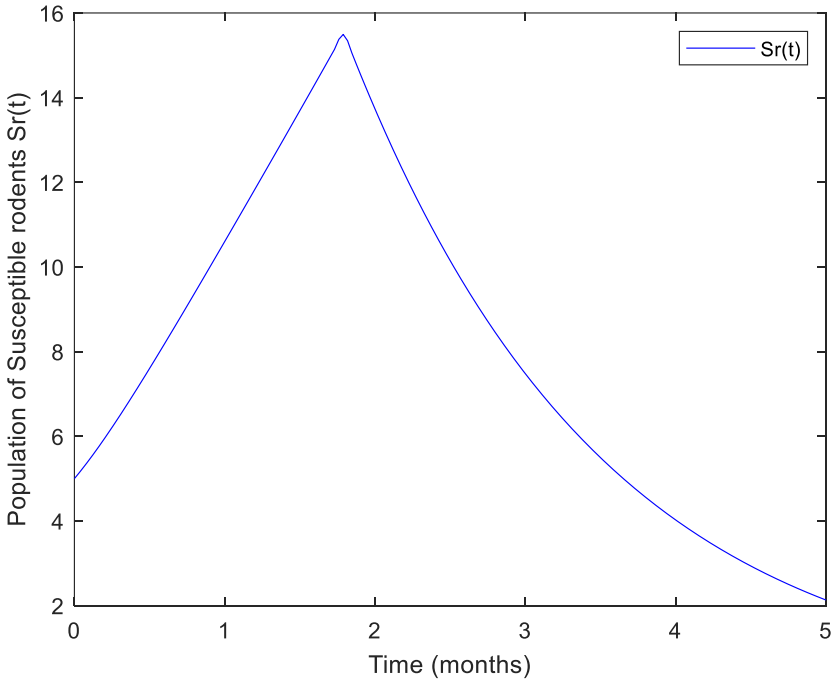

Figure 4. The population dynamics of susceptible rodents within 5 months

The sensitivity analysis for the optimal control variables $\Lambda_1(t)$, $\Psi(t)$ and $\Lambda_2(t)$ are presented in the next section.

SENSITIVITY ANALYSIS

Finding out how each model input factor contributes to the indecision in the output factor is the main goal of sensitivity analysis. The sensitivity analysis establishes the impact of changes in these input factors on the accuracy of the output factor's prediction. Thus, it is possible to establish the order of relevance and relative significance of the model input factors. The significance of an input factor to the precision of an output factor increases with its sensitivity. For the sensitivity analysis, the populations of infected humans and infected rodents are the chosen model output factors, while the chosen model's input factors are the optimal controls, which include vaccination, harvesting efforts, and biodiversity $\left(\Lambda_1(t), \Psi(t), \Lambda_2(t)\right)$.

As a result, the values of the sensitivity indices of the optimal control factors $\left(\Lambda_1(t), \Psi(t), \Lambda_2(t)\right)$ establish their relative significance in the outcome of populations of infected humans (I_h) and infected rodents (I_r). The procedures for the sensitivity analysis of the model input factors are described in the next section. The steps include the mathematical method, the computational process, and the sensitivity values. These steps are presented below.

The Mathematical Method

The variance-based method, which is appropriate for global sensitivity analysis, is the mathematical technique used. The first-order sensitivity indices and the total-effect sensitivity indices of the model input factors are found by using the variance-based method. A model input factor's proportional importance to an output factor is shown by the first-order sensitivity index. The significance of the factor increases with the first-order index's magnitude. The significance of the interaction of an input factor with other input factors is shown by the total-effect sensitivity index. Using the formulae below, the model's sensitivity indices are calculated (Saltelli et al., 2008; Farayola et al., 2020).

$$S_i = \frac{V\left[E\left(Y \mid X_i\right)\right]}{V(Y)} \tag{10}$$

$$S_{Ti} = 1 - \frac{V\left[E\left(Y \mid X_{\sim i}\right)\right]}{V(Y)}, \tag{11}$$

where S_i is the first-order sensitivity index of the model input factor X_i, $V\left[E\left(Y \mid X_i\right)\right]$ is the variance of the conditional expectation of the model input factor X_i, $V(Y)$ is the unconditional variance of the model input factor X_i, S_{Ti} is the total-effect sensitivity index of the input index X_i, and $V\left[E\left(Y \mid X_{\sim i}\right)\right]$ is the variance of the conditional expectation of all input factors except X_i.

The method for calculating the model factors' sensitivity indices is shown in the following section. This is accomplished in MATLAB by utilizing the computational method proposed by Saltelli et al. (2008).

The Computational Process

The computational process is done in steps as suggested by Saltelli et al. (2008). The steps are presented below.

Step 1

A random matrix X0 with dimension (101, 6) was built. The 6 columns were selected since 3 model factors $\left(\Lambda_1(t), \Psi(t), \Lambda_2(t)\right)$ were to be analyzed. The MATLAB sobolset function was used to produce random integers, which were then applied to the matrix X0. The produced sobolset's sample space within interval (0,1).

Step 2

Two matrices MATA and MATB with dimensions (101, 3) each, were built. The values of the random matrix X0 (101, 1-3) were assigned to matrix MATA and X0 (101, 4-6) were assigned to matrix MATB. Four more matrices A1, MATΛ1 (for storing $\Lambda_1(t)$), MATΨ1 (for storing $\Psi(t)$), and MATΛ2 (for storing $\Lambda_2(t)$) with dimensions (101,1) each, were built. The values of the model factor to be analyzed (X_i) were then assigned to the matrix A1. This was done by solving Equation (4) and (8) in MATLAB with inbuilt function ode45 and the results were used in Equation (9) to obtain the optimal control values of $\Lambda_1(t)$, $\Psi(t)$, $\Lambda_2(t)$ which were then stored in arrays MATΛ1, MATΨ1, and MATΛ2 respectively. The values of the array MATΛ1, MATΨ1, or MATΛ2 were then transferred to the array A1 depending on which optimal control value was to be analyzed. Therefore, the entries in all the rows of array A1 were the optimal control values to be analyzed.

Step 3

For the sensitivity analysis of each of the optimal control values, the values of the A1 are then transferred to the appropriate column of the array MATA. For instance, the values of A1 (from MATΛ1) were transferred to column 1 of the array MATA for the sensitivity analysis of $\Lambda_1(t)$. Similarly, the values of A1 (from MATΨ1, or MATΛ2) were transferred to columns 2 or 3 of the array MATA for the sensitivity analysis of $\Psi(t)$ or $\Lambda_2(t)$ respectively.

Step 4

The values of MATB are then transferred to MATC. Next, the values of A1 are transferred to the appropriate columns of the MATC as done in the case of MATA. This implied that matrix MATC consists of resampled values of MATA apart from the column to which A1 was assigned. The values of the 3 columns of each row were used in solving Equation (4) and (8) with $\Lambda_1(t)$ in the equations being replaced by the values of column 1 in MATA, $\Psi(t)$ being replaced by values in column 2 in MATA, and $\Lambda_2(t)$ replaced by values of column 3 in MATA. The only outputs taken into account for the sensitivity analysis were the rodent and

human populations that were infected. The outputs of the infected human and rodent populations were stored in column matrices FA1 and FB1 respectively.

Step 5

Similar procedures were used for the matrices MATB and MATC and their outputs were stored in arrays (FA12, FB12) and (FA13, FB13) respectively. The sensitivity indices were calculated using the output matrices and the algorithm provided below. The sensitivity algorithms were used to compute the first-order and total-effect sensitivity indices of $\Lambda_1(t)$, $\Psi(t)$, and $\Lambda_2(t)$ in the model (Equation (4) and (8)) to the values of the infected humans and infected rodents.

The first-order sensitivity index is given as

$$\begin{aligned} S_i &= \frac{V\left[E\left(Y \mid X_i\right)\right]}{V(Y)} \\ &= \frac{FA1FA13 - \left(E(X)\right)^2}{FA1FA1 - \left(E(X)\right)^2}, \\ &= \frac{\left(1/N\right)\sum_i^N \left(FA1\right)^i \left(FA13\right)^i - \left(E(X)\right)^2}{\left(1/N\right)\sum_i^N \left(\left(FA1\right)^i\right)^2 - \left(E(X)\right)^2} \end{aligned} \tag{12}$$

The total-effect sensitivity index is given as

$$\begin{aligned} S_{Ti} &= 1 - \frac{V\left[E\left(Y \mid X_{\sim i}\right)\right]}{V(Y)} \\ &= 1 - \frac{FA12FA13 - \left(E(X)\right)^2}{FA1FA1 - \left(E(X)\right)^2}, \\ &= 1 - \frac{\left(1/N\right)\sum_i^N \left(FA12\right)^i \left(FA13\right)^i - \left(E(X)\right)^2}{\left(1/N\right)\sum_i^N \left(\left(FA1\right)^i\right)^2 - \left(E(X)\right)^2} \end{aligned} \tag{13}$$

The N is the number of rows in the matrices, and the expected value $E(X)$, in Equation (12) and (13), is the mean value of the expected output. These are the mean value of the infected rodents (I_r) and infected humans (I_h). These mean values are obtained by solving the model (Equation (4) and (8)) and storing the populations of the infected humans and rodents in 2 matrices from which their means were obtained. The sensitivity indices thus provided deviations from the accurate value. This computational method is very efficient because the total computational cost for each model factor is N(3 + 2), as against N^2 which is the computational cost for using the direct brute-force method Saltelli et al. (2008). The matrices

$(FA1, FA12, FA13)$ were used when the output was the population of the infected humans while the matrices $(FB1, FB12, FB13)$ were used when the output was the population of the infected rodents.

The Sensitivity Values

The values of the sensitivity indices of the optimal control variables $\Lambda_1(t)$, $\Psi(t)$, and $\Lambda_2(t)$ are presented in Table 3-Table 4. The sensitivity indices should be between 0 and 1, and the higher the magnitude of the first-order index, the higher the importance of the factor in the model equations. The values of the total-effect sensitivity index represent the interaction between the model factor and other factors.

Table 3: Sensitivity Values (Infected Humans as output) $E(X)$=1.2613

Model factors	S_i	S_{Ti}
$\Lambda_1(t)$	1.0	0.0142
$\Psi(t)$	0.9986	0.0016
$\Lambda_2(t)$	0.9997	-0.0012

Table 4: Sensit.ivity Values (Infected Rodents as output) $E(X) =$ 2.2551

Model factors	S_i	S_{Ti}
$\Lambda_1(t)$	0.9935	-0.0691
$\Psi(t)$	0.9940	0.2564
$\Lambda_2(t)$	0.9975	-0.0945

RESULTS AND DISCUSSION

From the outcomes of the model simulations, as obtainable in Figure 1-4, the transmission dynamics of the Hantavirus infections as well as the population changes can be analyzed. As for the infected humans, shown in Figure 1, the population decreased and became zero within five months. This shows that the infection was eliminated within the human population. This implied that the optimal control measures of vaccination, harvesting efforts, and biodiversity were effective in eradicating the Hantavirus infection.

The population changes in the susceptible humans were presented in Figure 2, and as expected, the population increased initially but the rate of increase decreased over time. The initial increase was due to the exposure of people to the Hantavirus and the later decline is because of the optimal control measures. Figure 3 shows the population changes in the infected rodents. The population of the infected rodents also declined and became zero within five months. This is due to the harvesting efforts of removing the infected rodents from the ecosystem. The last figure, Figure 4, shows the population changes in the susceptible rodents. The population increased initially and got to the maximum turning point within two months and it then decreased and tended towards zero. This is due to the control measure of harvesting efforts and biodiversity. The turning point experienced in Figure 4 was also

observed in Figure 1 (population dynamics of infected humans) and Figure 3 (population dynamics of infected rodents) as points of inflexions. These turning points showed that the optimal control measures changed the trends of the populations. Without control measures, the population of the susceptible rodents would have continued to increase, and the populations of the infected humans and rodents would not have tended towards zero.

From the outcomes of the sensitivity analysis, the relative importance of the optimal control measures in the model equations can be obtained. For obtaining the population of the infected humans, when the model's output is I_h, the most sensitive model factor was vaccination $\Lambda_1(t)$. This was shown in Table 1 with its first-order sensitivity value of 1.0. The model factors of biodiversity and harvesting efforts followed suit in terms of sensitivities. These results show that simulating accurate population changes of the infected humans, including the control measures is significant with the vaccination being the most important model factor. As for their relative importance in terms of their interactions with one another, this can be obtained from their total-effect sensitivity values. Generally, they all have low total-effect sensitivity values, showing that the effects of their interactions with one another are low. Furthermore, when the model's output is infected rodents r_i, the most sensitive model factor is biodiversity. This was illustrated in Table 2. However, the three control measures have relatively high first-order sensitivity values, showing their significance in the model. As for their relative importance, in terms of interactions, the harvesting effort is the only important factor with a total-effect sensitivity value of 0.2564. The other two had relatively low total-effect sensitivity values.

The outcomes of the model simulations show the effectiveness of the model in simulating the population dynamics of the Hantavirus infection while the sensitivity analysis shows the importance of the optimal control measures in the model. It can be inferred that the vaccination of the human population contributed significantly to the elimination of the infection within the infected humans while the biodiversity and harvesting efforts also contributed to the elimination of infected and susceptible rodents. Although previous authors had presented models for Hantavirus elimination, the absence of vaccination in those models might have reduced their viabilities since human vaccination is the most effective clinical way of curbing an epidemic. Therefore, the presented model in this article has incorporated the most effective clinical control measure which is the human vaccination.

CONCLUSION

In the present paper, a mathematical model with optimal control for Hantavirus infection was developed and analyzed to inspect the greatest strategy for governing Hantavirus infection in the populations of humans and rodents. The local stability analysis of the model was done from which the disease reproduction number R_0 was obtained. The optimal Hantavirus infection control conditions were established using the Pontryagin Maximum Principle. The developed model incorporated the optimal control strategies of vaccination, harvesting efforts, and biodiversity. The model was then utilised to simulate the population dynamics of the susceptible and infected humans and rodents. Furthermore, the global sensitivity analysis was done for the optimal control variables by using infected humans and infected rodents as outputs. The results of the simulations showed that the Hantavirus will be eliminated from the populations of the infected humans and rodents within five months. The outcomes of the sensitivity analysis showed that vaccination is the model factor that can most accurately

simulate the population of infected humans. Finally, it was concluded that the optimal control strategies will prevent further propagation of the Hantavirus infection, and the presented model which incorporated vaccination is the most viable.

REFERENCES

Abdul Karim, M. F., Ismail, A. I. M. & Ching, H. B. (2009). Cellular automata modeling of hantavirus infection. *Chaos, Solitons & Fractals*, **41(5):** 2847-2853.

Abramson, G. (2008). Mathematical Modeling of hantavirus: from the mean field to the individual level. *Progress in Mathematical Biology Research Editor: James T. Kelly*, **219:**1-27.

Abramson, G. & Kenkre, V. M. (2002). Spatiotemporal patterns in the hantavirus infection. *Physical Review E, **66*:** 011912-1-5.

Abramson, G., Kenkre, V. M., Yates, T. L., & Parmenter, B. R. (2003). Traveling waves of infection in the Hantavirus epidemics. *Bulletin of Mathematical Biology*, **65(3)**: 519-534.

Bryson, A. E. (1996). Optimal control-1950 to 1985. *IEEE Control Systems Magazine*, **16(3)**: 26-33.

Farayola, M. F., Shafie, S., Siam, F. M. & Khan, I. (2020). Mathematical modeling of radiotherapy cancer treatment using Caputo fractional derivative, *Computer Methods and Programs in Biomedicine*, **188:** 105306.

Gaff, H. & Schaefer, E. (2009). Optimal control applied to vaccination and treatment strategies for various epidemiological models. *Mathematical Biosciences and Engineering*, **6(3):** 469-492.

Goh, S. M., Ismail, A. I. M., Noorani, M. S. M. & Hashim, I. (2009). Dynamics of the hantavirus infection through variational iteration method (VIM). *Nonlinear Analysis: Real World Applications*, **10(4):** 2171-2176.

Gokdoğan, A., Merdan, M. & Yildirim, A. (2012). A multistage differential transformation method for approximate solution of Hantavirus infection model. *Commun Nonlinear Sci Numer Simulat*, **17:** 1-8.

Hugo, A., Makinde, O. D., Kumar, S. & Chibwana, F. F. (2016). Optimal control and cost effectiveness analysis for Newcastle disease eco-epidemiological model in Tanzania. *Journal of Biological Dynamics*, **11(1)**:190-209.

Kenkre, V. ,Giuggioli, L., Abramson, G. & Camelo-Neto, G. (2007). Theory of hantavirus infection spread incorporating localized adult and itinerant juvenile mice, *The European Physical Journal B*, **55:** 461-470.

Koishi, A. C., Aoki, M. N., Jorge, T. R., Suzukawa, A. A., Zanluca, C., Lewis, S. & Duarte dos Santos, C. N. (2016). Development and validation of a point-of-care test for detectinghantavirus antibodies in human and rodent samples. *Diagnostic Microbiology and Infectious Disease*, **85(3):** 323-327.

Lenhart, S. & Workman, J. T. (2007). Optimal control applied to biological models, *Chapman and Hall/CRC*.

Li, J. & Blakeley, D. (2011). The failure of R_0, *Computational and Mathematical Methods in Medicine*, **2011**.

Liu, R., Ma, H., Shu, J., Zhang, Q., Han, M., Liu, Z., Jin, X., Zhang, F. & Wu, X. (2020). Vaccines and therapeutics against hantaviruses, *Frontiers in Microbiology*, **10:** 2989.

Martins, G., Gogola, J. L., Caetano, F. R., Kalinke, C., Ricciardi-Jorgeb, T., Santos, C. N. D., Bergaminia, M. F. & Marcolino-Junior, L. H. (2019). Quick electrochemical immunoassay for hantivirus detection based on biochar platform. *Talanta*, **204(1):** 163-171.

Momoh, A. A. & Fügenschuh, A. (2018). Optimal control of intervention strategies and cost effectiveness analysis for a Zika virus model. *Operations Research for Health Care*, **18:** 99-111.

Mu, X., Zhang, Q. & Rong, L. (2019). Optimal vaccination strategy for an SIRS model with imprecise parameters and Lévy noise. *Journal of the Franklin Institute*, **356(18):** 11385-11413.

Nusshag, C., Osberghaus, A., Baumann, A., Schnitzler, P., Zeier, M. & Krautkrämer, E. (2017). Deregulation of levels of angiopoietin-1 and angiopoietin-2 is associatedwith severe courses of hantavirus infection. *Journal of Clinical Virology*, **94:** 33-36.

Peixotu, I. D., and Abramson, G. (2006). The effect of biodiversity on the Hantavirus epizootic. *Ecology*, **87(4):** 873-879.

Pontryagin, L. S. (1987). Mathematical theory of optimal processes, *CRC press*, 1987.

Rida, S. Z., Abdel Rady, A. S., Arafa, A. A. M. & Khalil, M. (2012). The effect of the environmental parameter on the Hantavirus infection through a fractional-order SI model. *Int. J. Basic Appl. Sci*., **1(2):** 88-99.

Saltelli, A., Ratto, M., Andres, T., Campolongo, F., Cariboni, J., Gatelli, D., Saisana, M. & Tarantola, S. (2008). Global sensitivity analysis: the primer, *John Wiley & Sons*.

van den Driessche, P. & Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, **180:** 29-48.

Wang, X., Shen, W., Qin, Y., Ying, L., Li, H., Lu, J., Lu, J., Zhang, N., Li, Z., Zhou, W., Tang, F., Zhu, F., Hu, J. & Bao, C. (2020). A case-control study on the risk factors for hemorrhagic fever with renal syndrome. *BMC Infectious Diseases*, **20(1):** 1-7.

Yusof, F. M. & Ismail, A. I. Md. (2019). Modeling the transmission dynamics on the spread of Hantavirus Infection, *Menemui Matematik* (*Discovering Mathematics*), **41:** 96-111.

Yusof, F. M., Abdullah, F. A., and Ismail, A. I. Md. (2019). Modeling and optimal control on the spread of hantavirus infection, *Mathematics*, **7:** 1192.