

Research Article

Mathematical Modeling of Culling and Vaccination for Dog Rabies Disease Transmission with Optimal Control and Sensitivity Analysis Approach

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Abstract

Objective: In this work, a five-compartment mathematical model is developed to investigate the transmission dynamics of rabies infection in dog populations, incorporating vaccination and culling as control interventions. The study also includes an optimal control analysis and a cost-effectiveness evaluation of the proposed interventions.

Methods: Local and global stability analyses of the disease-free equilibrium (E_0) and the endemic equilibrium (E^*) are established through Jacobian and Lyapunov function techniques, alongside the calculation of the effective reproductive number (Re). A sensitivity analysis is conducted by normalized forward index method to identify key parameters influencing Re . Optimal control and cost-effectiveness techniques were employed to find the optimal and suitable control strategies for the disease control.

Results: The study findings indicate that, vaccination rate η , and force of infection β are the most influential parameters negatively and positively for reducing and increasing Re by -0.8197 and +1.0000 respectively. Also, the work identifies that, combined strategy of vaccination and culling is the most effective approach for controlling rabies within short time, just within 3y, while implementation by using single intervention takes control profile of 4.5y to eliminate the disease. Moreover, the cost-effectiveness analysis shows that, control strategy B is more economically best choice with less incremental cost-effectiveness ratio (ICER) compared to strategies A and C.

Conclusions: Therefore, it is recommended that vaccination and culling be implemented simultaneously to significantly reduce the population of exposed and infected dogs, leading to better control of rabies transmission.

Keywords: dog rabies, effective reproductive number, vaccination, culling; optimal control

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1 INTRODUCTION

The Lyssavirus-based disease Rabhas, which means violence in Sanskrit, is a zoonotic carnivore disease that has been known about since 3,000 BC. It has been known for a very long time-more than 4,300 years-and is steadily expanding over numerous nations and locations^[1]. An estimated 59,000 people die from the rabies virus each year worldwide^[2-4], with roughly 36.4% of those deaths taking place in Africa and 60% in Asia^[5,6]. According to WHO^[7], this disease causes over 21,000 human deaths per year in the African continent. In 1912, the first cases in the East African

region were found in Kenya's Machakos District^[8].

Even though the disease has been combated with several measures, its annual death toll in the region is still rising, from 210 to 290 for the human population and 4,400 to 6,500 for dogs. In addition to dogs, rabies can infect cats, foxes, skunks, raccoons, and other mammals that carry the virus. Even among different species, dogs continue to be the principal source of rabies disease transmission to humans. When a rabid or sick dog bites another animal or dog, their broken skin, wounds, or scratches get contaminated with virus-laden saliva, which then spreads the disease^[9].

In the study of Addo^[10], the rabies virus enters the spinal cord by the motor pathway, where it becomes infected and quickly spreads to the central nervous system. As soon as the viruses spread to the brain, many behavioral abnormalities started to occur as a result of neuronal defection. The loss of the neurological system causes brain inflammation in the organism, which ultimately leads to death. One way to stop the spread of dog rabies is through vaccination and treatment. Rabies vaccinations for canine or canine populations are administered to susceptible population groups by injection or oral route. By doing this, susceptible dogs who are more prone to contract the disease when socializing with infected dogs will be better protected.

Theoretically and experimentally, vaccination is deemed to be successful when it is administered to roughly 70% of the dog population. On the other side, when a dog or canine bites the suspect rabid dog before the infectious stage has formed, a treated population group is enforced^[11]. This protects all attacked dogs who have not yet displayed indications of disease infection, but as symptoms emerged, infected dogs stopped receiving treatment and eventually perished. All wounds or scratches should be cleaned and washed completely right away with soap and a clean enough amount of water for around 15mins while also providing supportive care to a victim in any event of a dog bite or any suspected rabid animal^[12].

The rabies virus continues to be a problem in many places, causing both animal and human deaths, a decline in production due to mortality or incapacity, and the expense of vaccination and treatment operations. More efforts are required to reduce disease spread and fatalities because the disease continues to be prevalent in animal and human populations, particularly in young age groups^[13]. The development of effective disease control strategies and a better understanding of the dynamics of infectious disease transmission in a community have both benefited from the use of mathematical models^[14]. The several works about the disease infection with various intervention techniques are listed below.

In the Bongo District of Ghana, Addo investigated the Susceptible, S(t)Exposed, E(t)-Infected, I(t) and Recovered, R(t) model for rabies transmission infection in the dog population group considering vaccination control intervention. Based on the results, the minimal population coverage of dogs that needed to be immunized was 24.6%. Corresponding to this, the basic reproduction number, R_0 , with vaccination found as 0.3755 and suggests $R_0 < 1$, whereas without vaccination intervention it is 1.3267 and implies $R_0 > 1$, thus indicating endemic disease status. Similar models were provided by Tulu^[15] with the addition of Susceptible, S(t)-Exposed Prodromal, E(t) Infectious, $I_1(t)$ -Furious Infectious, $I_2(t)$ -Recovery, R(t), which involved the importation of diseased immigrants with the purpose of preventing the spread of the disease among the dog population.

In a confined dog population group found in the Machakos

District of Kenya, Kital et al.^[16] established a model with five classes namely; Susceptible, S(t) Vaccination, V(t)-Latent, L(t)-Infectious, I(t) (SVLI) to investigate the transmission of dog rabies disease with vaccine control techniques. In addition to the analysis of sensitivities, immunization was seen as the best way to stop the spread of disease among dogs. Once more, Carroll et al.^[17], and Laager^[18] developed a Susceptible, S(t)-Vaccination, V(t)-Exposed, E(t)-Infectious, I(t) model classes in the spreading dynamics of rabies between dog populations by employing immune-contraception method to reduce the number of dogs in cities and towns by means of vaccination alongside dog birth rates control or surgical sterilizing that decreases newborn puppies.

Additionally, the model with classes Susceptible, S(t)-Vaccination, V(t)Exposed, E(t)-Infectious, I(t) was proposed by Fitzpatrick et al.^[19] and Bilinski et al.^[20], incorporating with a vaccination strategy for rabies disease infection spread control where cost-effectiveness was analyzed for Carnivorous vaccination aim for stopping rabies increase among Ngorongoro and Serengeti districts in Tanzania through controlling dog along with other wildlife community groups. A similar model was also created by Ndii et al.^[21] combining crisp and fuzzy techniques, with the primary aspects of transmission being the availability of vaccinations and the rate at which infections spread. Leung and Davis^[22] suggested a similar mathematical model for administering rabies immunization to the population of owned, free-roaming, and stray dogs.

The Susceptible, S(t)-Exposed, E(t)-Infectious, I(t)-Recovered, R(t) model was created and examined by Asamoah et al.^[23] and Wiraningsih et al.^[24], while Yang and Lou^[25] constructed the Susceptible, S(t)-Vaccination, V(t) Exposed, E(t)-Infectious, I(t) model compartments for the dynamics of rabies disease transmission between dog-human interaction groups with vaccine control measures. In addition, Huang et al.^[26] established a comparable model for rabies disease transmission patterns interacting dogs, humans, and Chinese ferret badger communities found in China Zhenjiang Region, while Ega et al.^[27] provided a similar work composed of three population groups namely; dogs, human and livestock for analyzing rabies infection transmission employing vaccination control measure in Ethiopia, particularly in Addis Ababa city. In addition, Tian et al.^[28] created the model to investigate the trends of the re-emergence of rabies illness spreading in domesticated dogs in Yunnan town, China, and their study used a vaccination control technique incorporating environmental variables to construct a Susceptible, S(t)-Vaccinated, V(t)Exposed, E(t)-Infectious, I(t) model composed of dog and human interacting groups. Furthermore, Zinsstag et al.^[29] built the Susceptible, S(t)-Vaccination, V(t)-Exposed, E(t)-Infectious, I(t) mathematical model with vaccination based on the dog population, purposefully for the spread control of rabies illness between the dog-to-human contacting populations in N'Djamena town, Chad. As others did, their study considered vaccination as a useful approach to illness prevention.

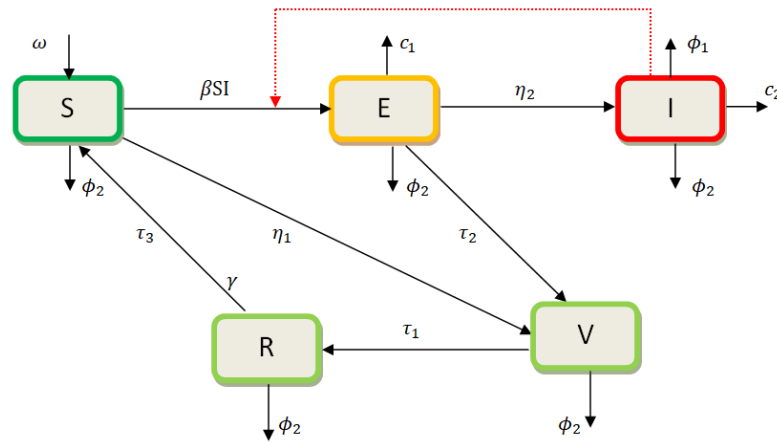


Figure 1. Dog Rabies Disease Schematic Model Diagram.

In recent times, fractional calculus has gained considerable attention for its application in the study of infectious disease dynamics. Fractional-order models offer a more accurate representation of biological systems by incorporating memory effects, which allow for more realistic descriptions of the spread and control of diseases. These models have been successfully applied to investigate the dynamics of various diseases, including HIV and its interaction with the immune system using non-integer derivatives^[30], as well as the dynamics of coronavirus infections under preventive interventions through fractional-calculus analysis^[31]. Similarly, the study of plant infections and the implementation of preventive policies have benefited from the dynamical analysis offered by fractional calculus^[32].

In the context of vector-borne diseases, fractional models have provided valuable insights into the transmission dynamics of dengue, accounting for memory, re-infection, and vaccination^[33]. Moreover, chikungunya infection has been studied through fractional calculus, with a focus on evaluating the effects of saturated incidence functions^[34]. These studies underscore the significance of fractional-order models in capturing the complexities of infectious disease dynamics more effectively than classical models.

Indeed, the current study developed and analyzed a mathematical model of the dog population with classes namely SVEIR (Susceptible, $S(t)$; Vaccinated, $V(t)$; Exposed, $E(t)$; Infectious, $I(t)$; and Recovery, $R(t)$), for investigating the most influential and potential parameters for dog rabies disease infection spread among the dogs by considering dog vaccination and culling interventions. Additionally, the work made more mathematical applications for its disease optimal control and cost-effectiveness evaluation part for the best use options among the interventions suggested. This aims to control the transmission of disease infection among dogs at minimal cost but with great achievement. Hence, since most of the studies surveyed above missed this angle, this work played a necessary highlight in disease control by considering appropriate and relevant budget use options to attain the planned target.

2 MODEL FORMULATION

The model presented here incorporates vaccination for both susceptible and exposed dogs, as well as culling for both exposed and infected dogs as control measures. This model is structured into five compartments, including $S(t)$, $V(t)$, $E(t)$, $I(t)$, and $R(t)$.

Following this, the total population is then given by $N(t) = S(t) + V(t) + E(t) + I(t) + R(t)$. Dogs are recruited into the susceptible population group $S(t)$ at the rate of ω . The dog rabies disease infection among the dogs occurs at the rate of β . Vaccination is administered to the susceptible $S(t)$ and exposed $E(t)$ dog groups at the rate of η_1 and τ_2 respectively, for which some will gain temporary immunity and therefore join to recovered group $R(t)$ through the rate of τ_1 . Each dog group diminishes due to the natural mortality rate, ϕ_2 , while the infected dogs $I(t)$ also die due to rabies at the rate of ϕ_1 . The exposed dog class $E(t)$ develops infection and enters into the infected group $I(t)$ through the rate η_2 . In both, exposed $E(t)$ and infected $I(t)$ groups, culling c_1 and c_2 interventions are introduced to control dogs' reproduction rates growth respectively. The recovered dog group $R(t)$ joins into the susceptible $S(t)$ dogs at the rate of τ_3 subject to immune loss. Through these variables and parameters, the following schematic diagram with a set of non-linear ordinary differential equations is established. (Figure 1)

$$\begin{cases} \frac{dS}{dt} = \omega + \tau_3 R - \beta SI - (\eta_1 + \phi_2)S \\ \frac{dV}{dt} = \eta_1 S + \tau_2 E - (\tau_1 + \phi_2)V \\ \frac{dE}{dt} = \beta SI - (\eta_2 + \tau_2 + \phi_2 + c_1)E \\ \frac{dI}{dt} = \eta_2 E - (\phi_1 + \phi_2 + c_2)I \\ \frac{dR}{dt} = \tau_1 V - (\phi_2 + \tau_3)R \end{cases} \quad (1)$$

With the initial conditions; $S(0) \geq 0$, $V(0) \geq 0$, $E(0) \geq 0$, $I(0) \geq 0$, $R(0) \geq 0$.

2.1 Model Analysis

In this section, a region in which solutions of the model system (1) are uniformly bounded in the proper subset $\Omega \in \mathbb{R}^5$.

The total population at any time t is given by $N(t)=S(t)+V(t)+E(t)+I(t)+R(t)$ and

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dV}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} \quad (2)$$

Substituting Equation (1) into Equation (2) simplified to

$$\frac{dN}{dt} = \omega - \phi_2 N + c_1 E - (\phi_1 + c_2) I, \quad (3)$$

In the absence of culling and mortality due to rabies, it becomes

$$\frac{dN}{dt} \leq \omega - \phi_2 N \quad (4)$$

By solving Equation (4), we obtain $0 \leq N(t) \leq \omega/\phi_2$.

Therefore, the feasible solutions set of the system (1) of the model remain in the region such that:

$$\Omega = \left\{ (S(t), V(t), E(t), I(t), R(t)) \in \mathbb{R}_+^5 : (S + V + E + I + R) \leq \frac{\omega}{\phi_2} \right\}$$

2.2 Non-Existence of Rabies Disease Equilibrium Point, and Effective Reproduction Number R_e

The model system (1) has a disease-free equilibrium point (DFE) obtained by setting the right-hand sides of the equation in the model to zero given by $E_0 = (S_0, V_0, E_0, I_0, R_0)$, such that

$$E_0 = \left[\frac{\omega}{\phi_2 + \eta_1}, \frac{\omega \eta_1}{\phi_2 + \eta_1}, 0, 0, 0 \right] \quad (5)$$

The effective reproduction number of the model system (1), R_e is calculated using the Next Generation Matrix method as

$$R_e = \frac{\beta \omega \eta_2}{(\eta_2 + \tau_2 + \phi_2 + c_1)(\phi_2 + \phi_1 + c_2)(\phi_2 + \eta_1)} \quad (6)$$

2.3 Rabies Disease Existence Equilibrium Point

The endemic equilibrium point E_1 and defined as a steady state for the model system (1). This occurs when there is a persistence of the disease. It can be obtained by equating the system of Equation (1) to zero. Then we obtain

$$E^* = [S^*, V^*, E^*, I^*, R^*] \quad (7)$$

such that:

$$\begin{aligned} S^* &= \frac{(\eta_2 + \tau_2 + \phi_2 + c_1)(\phi_2 + \phi_1 + c_2)}{\beta \eta_2} \\ V^* &= \frac{\eta_1 S^* + \tau_2 E^*}{\phi_2 + \tau_1} \\ E^* &= \frac{(\phi_2 + \phi_1 + c_2)}{\eta_2} \times I^* \\ I^* &= \frac{(\eta_2 + \tau_2 + \phi_2 + c_1)}{\beta S^*} \times E^* \\ R^* &= \frac{\tau_1 V^*}{\tau_3 + \phi_2} \end{aligned}$$

2.4 Local Stability of Non-existence of Dog Rabies Disease Steady State E_0

We linearize the system in (1) to obtain the Jacobian Matrix $J(E_0)$ at E_0 to determine the local stability of DFE dog rabies as;

$$J(E_0) = \begin{pmatrix} -(\phi_2 + \eta_1) & 0 & 0 & -\beta S & \tau_3 \\ \eta_1 & -(\phi_2 + \tau_1) & 0 & 0 & 0 \\ 0 & 0 & -(\phi_2 + \eta_2 + \tau_2 + c_1) & \beta S & 0 \\ 0 & 0 & \eta_2 & -(\phi_2 + \phi_1 + c_2) & 0 \\ 0 & \tau_1 & 0 & 0 & -(\phi_2 + \tau_3) \end{pmatrix} \quad (8)$$

From Equation (8), trace-determinant approach is applied to determine local stability analysis^[35], in which for trace $TrJ(E_0)$ we get $TrJ(E_0) = -5\phi_2 - \tau_1 - \eta_1 - c_1 - \eta_2 - \tau_2 - c_2 - \phi_1 - \tau_3$;

$$\therefore TrJ(E_0) < 0. \quad (9)$$

Consequently, the determinant $Det J(E_0)$ is obtained as

$$\begin{aligned} DetJ(E_0) &= (\beta \omega \eta_2 (\phi_2 + \tau_1)(\phi_2 + \tau_3) - k_2) \\ &\quad - (\beta \omega \eta_2 (\phi_2 + \tau_1)(\phi_2 + \tau_3)) \\ &\quad - k_1 (\phi_2 + \eta_2 + \tau_2 + c_1) (\phi_2 + \phi_1 + c_2 - k_2) \end{aligned} \quad (10)$$

Through several simplifications and substitutions, obvious $Det J(E_0) > 0$, if the following achieved

$$DetJ(E_0) = k_1 (\phi_2 + \eta_2 + \tau_2 + c_1) (\phi_2 + \phi_1 + c_2) + 2k_2 [1 - R_e] \quad (11)$$

By using the condition in Equation (11) clearly, $Det J(E_0) > 0$ for $R_e < 1$, which implies that, biologically, rabies disease infection will be easily exited from the particular population, and this establishes the following theorem:

Theorem 1. The DFE point of the model (1), given by E_0 , is locally asymptotically stable (LAS) if $R_e < 1$ and unstable if $R_e > 1$.

2.5 Global Stability Analysis of Non-existence of Dog Rabies Disease Equilibrium Point

To compute the global stability of E_0 , we choose and employ the Lyapunov function L technique below^[36]

$$\begin{aligned} L &= \left(S - S_0 - S_0 \ln \frac{S}{S_0} \right) + \left(V - V_0 - V_0 \ln \frac{V}{V_0} \right) \\ &\quad + r_1 E + r_2 I + (R - R_0 - R_0 \ln \frac{R}{R_0}) \end{aligned} \quad (12)$$

Taking derivatives in Equation (12) with respect to time t we obtain;

$$\begin{aligned} \frac{dL}{dt} &= \left(1 - \frac{S}{S_0} \right) \frac{dS}{dt} + \left(1 - \frac{V}{V_0} \right) \frac{dV}{dt} \\ &\quad + r_1 \frac{dE}{dt} + r_2 \frac{dI}{dt} + \left(1 - \frac{R}{R_0} \right) \frac{dR}{dt} \end{aligned} \quad (13)$$

Using substitutions, Equation (13) becomes:

$$\begin{aligned} \frac{dL}{dt} &= \left(1 - \frac{S}{S_0} \right) [\omega + \tau_3 R - \beta SI - (\eta_1 + \phi_2) S] \\ &\quad + \left(1 - \frac{V}{V_0} \right) [\eta_1 S + \tau_2 E - (\tau_1 + \phi_2) V] \\ &\quad + r_1 [\beta SI - (\eta_2 + \tau_2 + \phi_2 + c_1) E] \\ &\quad + r_2 [\eta_2 E - (\phi_1 + \phi_2 + c_2) I] \\ &\quad + \left(1 - \frac{R}{R_0} \right) [\tau_1 V - (\phi_2 + \tau_3) R] \end{aligned} \quad (14)$$

Explicitly, assume that; $S \leq S_0$, $V \leq V_0$, and $R \leq R_0$, consequently Equation (15) is obtained through substitution and simplifications in Equation (14).

$$\frac{dL}{dt} \leq r_1 (R_e - 1) \quad (15)$$

Therefore, by considering positive constants r_1 and r_2 in the trivial equilibrium points E_0 , it is obvious that Equation (15) derives the following theorem:

Theorem 2. If $R_e \leq 1$, then the disease-free equilibrium

point E_0 is globally asymptotically stable, while for $R_e > 1$ will be unstable in the region Ω .

2.5.1 Global Stability for the Disease Existence Equilibrium

To determine the global stability of rabies disease existence endemic equilibrium E_* , appropriate Lyapunov function W technique is selected and is defined as:

$$W(x_1, \dots, x_n) = \sum_{i=1}^5 \frac{1}{2} [x_i - x_i^*]^2 \quad (16)$$

where x_i presents all dog population compartments and implies dog classes dominated with rabies disease infection at E_* .

Then Equation (16) can be expressed as

$$W(S(t), V(t), E(t), I(t), R(t)) = \frac{1}{2} [(S - S^*) + (V - V^*)^2 + (E - E^*) + (I - I^*) + (R - R^*)] \quad (17)$$

Taking derivatives with respect to time t in Equation (17) leads to

$$\frac{dW}{dt} = [(S - S^*) + (V - V^*) + (E - E^*) + (I - I^*) + (R - R^*)] \frac{d}{dt} [S + V + E + I + R] \quad (18)$$

Remember Equation (2), where we get:

$$\frac{dN(t)}{dt} = \frac{d}{dt} [S + V + E + I + R] \quad (19)$$

By employing Equation (2), and using Equation (1) and Equation (19) followed by simplifications gives:

$$\frac{dN(t)}{dt} = \omega - \phi_2 N(t), \quad (20)$$

Similarly, we have also:

$$S^* + V^* + E^* + I^* + R^* = \frac{\omega}{\phi_2} \quad (21)$$

By combining Equations (20), and (21), then Equation (18) is simplified to:

$$\frac{dW}{dt} = [N(t) - \frac{\omega}{\phi_2}] [\omega - \phi_2 N(t)] \quad (22)$$

Consequently, by simplifying and re-arranging in Equation (22), we obtain:

$$\frac{dW}{dt} = -\frac{1}{\phi_2} [\omega - \phi_2 N(t)]^2 < 0 \quad (23)$$

Hence, Equation (23) concludes the proof of global stability (GS) at E_* such that $dW/dt < 0$ a strictly Lyapunov function achieved indicates that, at E_* dog rabies disease is globally asymptotically stable and is contained in the defined region Ω . This leads to the following theorem:

Theorem 3. If $R_e > 1$, then the existing endemic equilibrium point E_* is globally asymptotically stable (GAS) which is contained in the defined region Ω .

2.6. Sensitivity Analysis

Conducting a sensitivity analysis allows us to assess how the model parameters influence the effective reproduction number (R_e) and, consequently, disease transmission^[37]. This analysis provides insights into which parameters and initial conditions influence the model's outcomes and

helps pinpoint parameters that warrant further numerical investigation^[38].

The normalized sensitivity index (SI) of the variable R_e depends on the differentiability of a parameter l that is defined as;

$$Y_l^{R_e} = \frac{\partial R_e}{\partial l} \times \frac{l}{R_e},$$

where l is any parameter presented in effective reproduction number R_e . For example, the sensitivity index of R_e corresponding to the parameter ϕ_1 is given as

$$Y_{\phi_1}^{R_e} = \frac{\partial R_e}{\partial \phi_1} \times \frac{\phi_1}{R_e} = -0.621118$$

Other indices are calculated using a similar approach and the results are displayed in Table 1.

From indices in Table 1, we have a SI profile which can be presented in bar graph as shown in Figure 2.

Figure 2 illustrates the SI profile of R_e concerning all parameters within the model system (1). A negative value signifies that an augmentation in the parameter value results in a reduction of R_e , whereas a positive value denotes that an increase in the parameter value leads to an elevation in R_e . Consequently, β exhibits an index value of +1.0000, making it the most positively sensitive parameter, while η_1 holds an index value of -0.8197, signifying it as the most negatively sensitive parameter.

2.6.1 Interpretation of the sensitivity

The sensitivity analysis of the model's parameters revealed valuable insights. Parameters β and η_2 exhibited positive indices, indicating their significant impact on the model. Notably, β had the highest positive index, suggesting that increasing this parameter would elevate the effective reproduction number R_e and, consequently, the risk of a disease outbreak.

Conversely, parameters such as c_1 , c_2 , τ_2 , ϕ_2 , ϕ_1 , and η_1 displayed negative indices, indicating their potential to reduce R_e when their values increase. Among these, the Susceptible vaccination rate ($\eta_1 = -0.819672$) was the most influential in decreasing the disease burden among dogs.

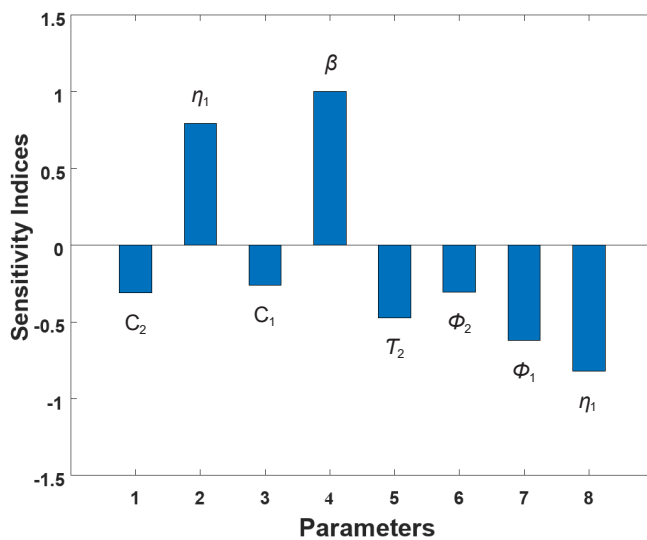
In summary, the sensitivity analysis underscores the importance of enhancing the efficacy of vaccination by targeting the S class and implementing vaccination for the E class, along with culling for E and I classes, and considering the natural death rate. Additionally, reducing the contact rate between S and I dogs can also effectively curb the spread of Dog rabies. Therefore, it is crucial to maintain and expand vaccination and culling programs as vital strategies to combat the transmission of Dog rabies infection.

2.7 Optimal Control Formulation

We apply optimal control techniques to the model system (1) in this section. Our goals are to reduce the number of cases of dog rabies as well as the expenses related to control measures. To stop the spread of dog rabies, we add culling u_2 ($0 \leq u_2 \leq 1$) and vaccination u_1 ($0 \leq u_1 \leq 1$) as

Table 1. Parameter Values and Sensitivity Indices (SI) of the Model corresponding to R_e .

Parameter	Description	Value	Source	SI
ω	Dogs Increment Rate	0.9897	[39]	-
η_1	Vaccination Rate for Susceptible	0.5	[39]	-0.8197
β	Rabies Disease Infection Rate	0.0198	[39]	+1.0000
ϕ_1	Death Rate Due to Dog Rabies	1	[40]	-0.6211
η_2	Exposed Transfer Rate	0.4	[41]	+0.7917
τ_1	Recovery Rate Due to Vaccination	0.6	Assumed	-
τ_3	Immune Lose Rate	0.5	Assumed	-
ϕ_2	Dogs Natural Mortality Rate	0.11	Assumed	-0.3059
c_1	Exposed Dogs Culling Rate	0.5	Assumed	-0.3260
c_2	Infected Dogs Culling Rate	0.5	Assumed	-0.3106
τ_2	Exposed Dogs Vaccination Rate	0.91	Assumed	-0.4740

**Figure 2. Graph of sensitivity indices of R_e with respect to the model parameters.**

time-dependent controls to the model system (1). Next, the model system (1) turns into

$$\begin{cases} \frac{dS}{dt} = \omega + \tau_3 R - \beta SI - (1 + u_1)\eta_1 S - \phi_2 S \\ \frac{dV}{dt} = (1 + u_1)\eta_1 S + (1 + u_1)\tau_2 E - (\tau_1 + \phi_2)V \\ \frac{dE}{dt} = \beta SI - (1 + u_1)\tau_2 E - (\eta_2 + \phi_2)E - (1 + u_2)c_1 E \\ \frac{dI}{dt} = \eta_2 E - (\phi_1 + \phi_2)I - (1 + u_2)c_2 I \\ \frac{dR}{dt} = \tau_1 V - (\phi_2 + \tau_3)R \end{cases} \quad (24)$$

to study the optimal control level of the controls, the control set U , which is Lebesgue measurable is defined as $U = \{(u_1, u_2) : 0 \leq u_1 \leq 1, 0 \leq u_2 \leq 1, 0 \leq t \leq t_f\}$.

The purpose of introducing the controls in the model system is to find the optimal level of the intervention strategy to reduce the spread of dog rabies disease and the cost of implementing the controls. The control variables u_1 and are minimized subject them to the differential Equation (24), where we formulate the objective function as

$$J(u_1, u_2) = \int_0^{t_f} [A_1 E + A_2 I + \frac{1}{2}(c_1 u_1^2 + c_2 u_2^2)] dt \quad (25)$$

where t_f is the final time, while A_1 , A_2 , c_1 and c_2 are positive

weights. The expression $\frac{1}{2}(c_1 u_1^2 + c_2 u_2^2)$ represents the costs associated with the control u_1 and u_2 . The objective function (25) involves minimizing the number of dog rabies infections (E and I) as well as the cost of applying the control strategies u_1 and u_2 . Thus, we seek to find the optimal controls u_1^* and u_2^* such that

$$J(u_1^*, u_2^*) = \text{Min}\{J(u_1, u_2) : u_1, u_2 \in U\} \quad (26)$$

where; $U = \{(u_1, u_2) : 0 \leq u_1 \leq 1, 0 \leq u_2 \leq 1, 0 \leq t \leq t_f\}$.

By using Potryagin's maximum principle^[42], we drive the necessary conditions for our optimal control and corresponding states. This principle converts the system of Equations (25) and (26) into the problem of minimizing point-wise a Hamiltonian (H), with respect to $u_1(t)$ and $u_2(t)$

$$\begin{aligned} H = & A_1 E + A_2 I + \frac{1}{2} c_1 u_1^2 + \frac{1}{2} c_2 u_2^2 \\ & + \lambda_1 [\omega + \tau_3 R - \beta SI - (1 + u_1)\eta_1 S - \phi_2 S] \\ & + \lambda_2 [(1 + u_1)\eta_1 S + (1 + u_1)\tau_2 E - (\tau_1 + \phi_2)V] \\ & + \lambda_3 [\beta SI - (1 + u_1)\tau_2 E - (\eta_2 + \phi_2)E - (1 + u_2)c_1 E] \\ & + \lambda_4 [\eta_2 E - (\phi_1 + \phi_2)I - (1 + u_2)c_2 I] + \lambda_5 [\tau_1 V - (\phi_2 + \tau_3)R] \end{aligned} \quad (27)$$

where $\lambda_1, \lambda_2, \lambda_3, \dots, \lambda_5$ are the co-state variables or the adjoint variables associated by S, V, E, I and R . The adjoint equations are obtained by

$$\begin{cases} \frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S} = (\lambda_1 - \lambda_2)(1 + u_1)\eta_1 + (\lambda_1 - \lambda_3)\beta I + \lambda_1 \phi_2 \\ \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial V} = (\lambda_2 - \lambda_5)\tau_1 + \lambda_2 \phi_2 \\ \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial E} = -A_1 + \lambda_3(\phi_2 + (1 + u_2)c_1) + (\lambda_3 - \lambda_4)\eta_2 \\ \quad + (\lambda_3 - \lambda_2)(1 + u_1)\tau_2 \\ \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial I} = -A_2 + (\lambda_1 - \lambda_3)\beta S + \lambda_4(\phi_1 + \phi_2 + (1 + u_2)c_2) \\ \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial R} = (\lambda_5 - \lambda_1)\tau_3 + \lambda_5 \phi_2 \end{cases} \quad (28)$$

with the final time conditions (transversality conditions):

$$\lambda_1(T_f) = \lambda_2(T_f) = \lambda_3(T_f) = \lambda_4(T_f) = \lambda_5(T_f) = \lambda_6(T_f) = 0 \quad (29)$$

Moreover, the control set (u_1^*, u_2^*) is characterized by;

$$\frac{\partial H}{\partial u_i} = 0 \Rightarrow \frac{\partial H}{\partial u_1} = \frac{\partial H}{\partial u_2} = 0 \quad (30)$$

then,

$$\begin{cases} \frac{\partial H}{\partial u_1} = c_1 u_1 + (\lambda_2 - \lambda_1)\eta_1 S + (\lambda_2 - \lambda_3)\tau_2 E, \\ \frac{\partial H}{\partial u_2} = c_2 u_2 + \lambda_3 c_1 E - \lambda_4 c_2 I \end{cases} \quad (31)$$

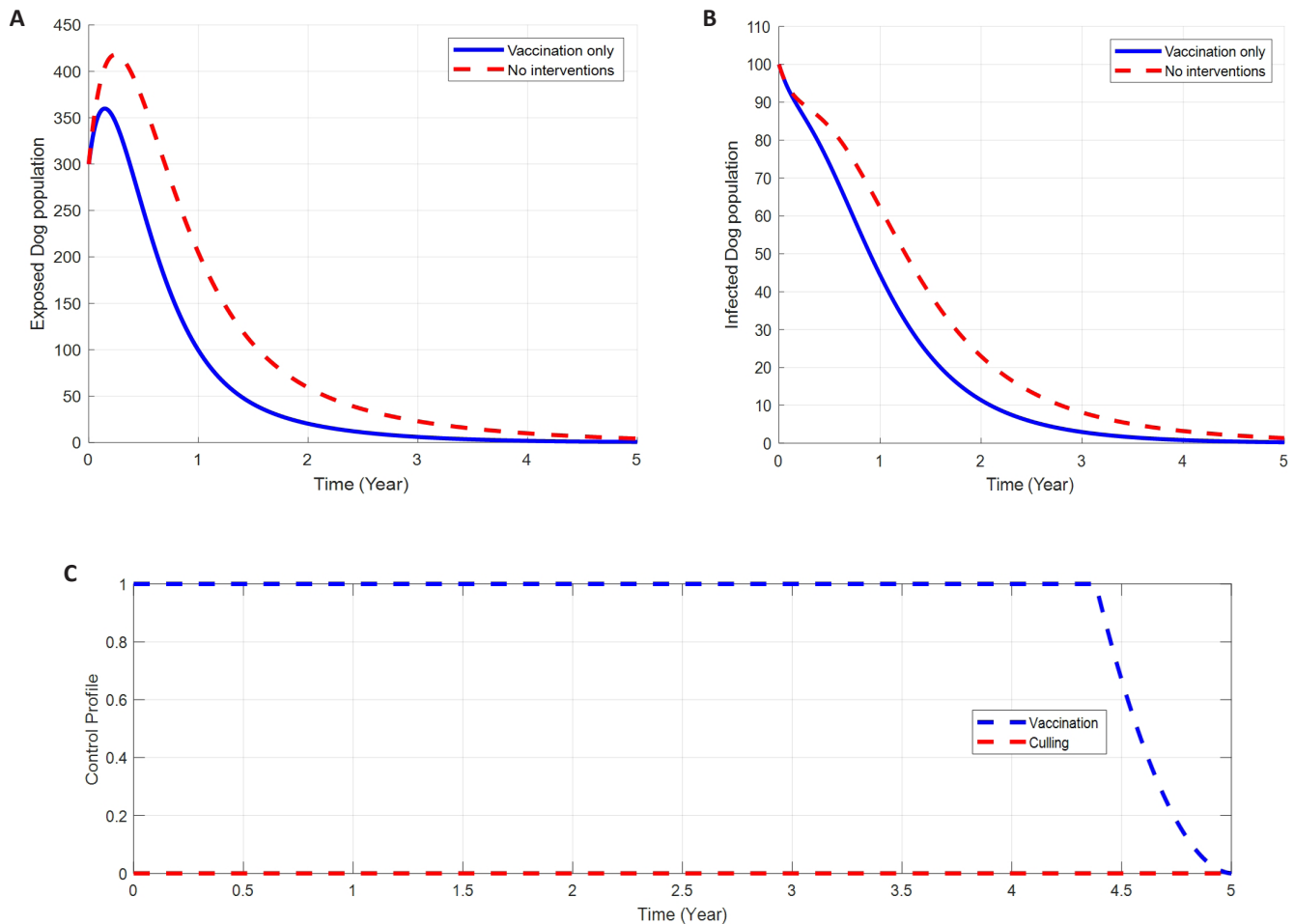


Figure 3. The Impact of Vaccination on Dog Rabies Diseases Dynamics. A: Impacts of vaccination on exposed dogs. B: Impacts of vaccination on infected dogs. C: Profile control of dog rabies disease through vaccination intervention alone.

Solving (31) for u_1^* and u_2^* when $\partial H/\partial u_i = 0$ gives;

$$\begin{cases} u_1^* = \frac{(\lambda_1 - \lambda_2)\eta_1 S^* + (\lambda_3 - \lambda_2)\tau_2 E^*}{c_1}, \\ u_2^* = \frac{\lambda_3 c_1 E^* - \lambda_4 c_2 I^*}{c_2} \end{cases} \quad (32)$$

Therefore,

$$\begin{aligned} u_1^* &= \min \left\{ 1, \max \left\{ 0, \frac{(\lambda_1 - \lambda_2)\eta_1 S^* + (\lambda_3 - \lambda_2)\tau_2 E^*}{c_1} \right\} \right\}, \\ u_2^* &= \min \left\{ 1, \max \left\{ 0, \frac{\lambda_3 c_1 E^* - \lambda_4 c_2 I^*}{c_2} \right\} \right\} \end{aligned} \quad (33)$$

2.8 Numerical Simulation

In this section, the forward and backward fourth-order Runge-Kutta methods implemented in MATLAB (R2022a) software were used to solve the optimal system results within an interval of [0,5] years. The method was chosen because of its accuracy, versatility, stability, and ease of implementation. Simulation of the model system (1) was done using the parameters in the Table 1, and we use the initial population of dogs as; $S=1000$, $V=600$, $E=300$, $I=100$, $R=200$.

To ensure, a balanced consideration of terms within the objective function aimed at minimizing infectious impacts, equal weight constants are chosen, resulting in $A_1=A_2=1$. Additionally, the weight constants used to gauge the

expenses associated with implementing control strategies are specified as $C_1=10$, and $C_2=10$.

2.8.1 Control with Vaccination Alone

Figure 3 shows how the single implementation of Vaccination, $u_1(t)$, affects the spread of dog rabies dynamics in the population. The results in Figure 3A and B show a significant difference in the number of infected individuals in the Exposed, and infected stages with vaccination control compared to the number without control. Due to control u_1 , the number of infected dogs decreases from 100 to approaching zero after 3 years duration, while the exposed were declined from nearly 350 to about non-existence during the 2.5th year.

However, vaccination has shown a greater impact on Exposed dogs compared to Infected Dogs. Figure 3C shows the control profile of (u_1) in which the control u_1 is at the upper bound until the time $t=4.5$ years, before slowly dropping to the lower bound at the final time.

2.8.2 Control with Culling alone

Figure 4 shows how the single implementation of the Culling control strategy, $u_2(t)$, affects the transmission dynamics of Dog Rabies disease in a population. The results in Figure 4A-B show a significant difference in the number of infected Dogs in the Exposed and Infected stages with

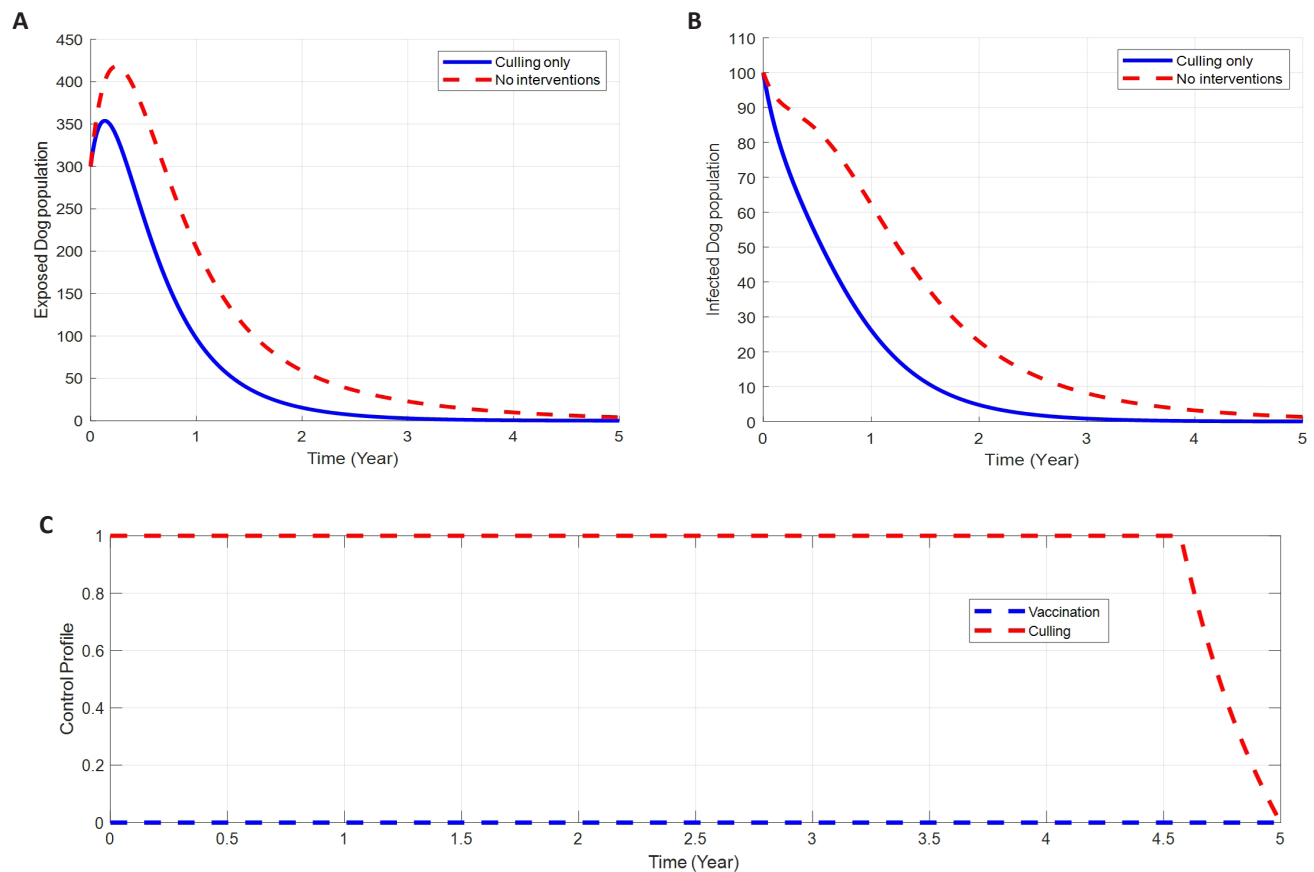


Figure 4. The Impact of Culling on Dog Rabies Diseases Dynamics. A: Impacts of culling on exposed dogs. B: Impacts of culling on infected dogs. C: Profile control of dog rabies disease through culling intervention alone.

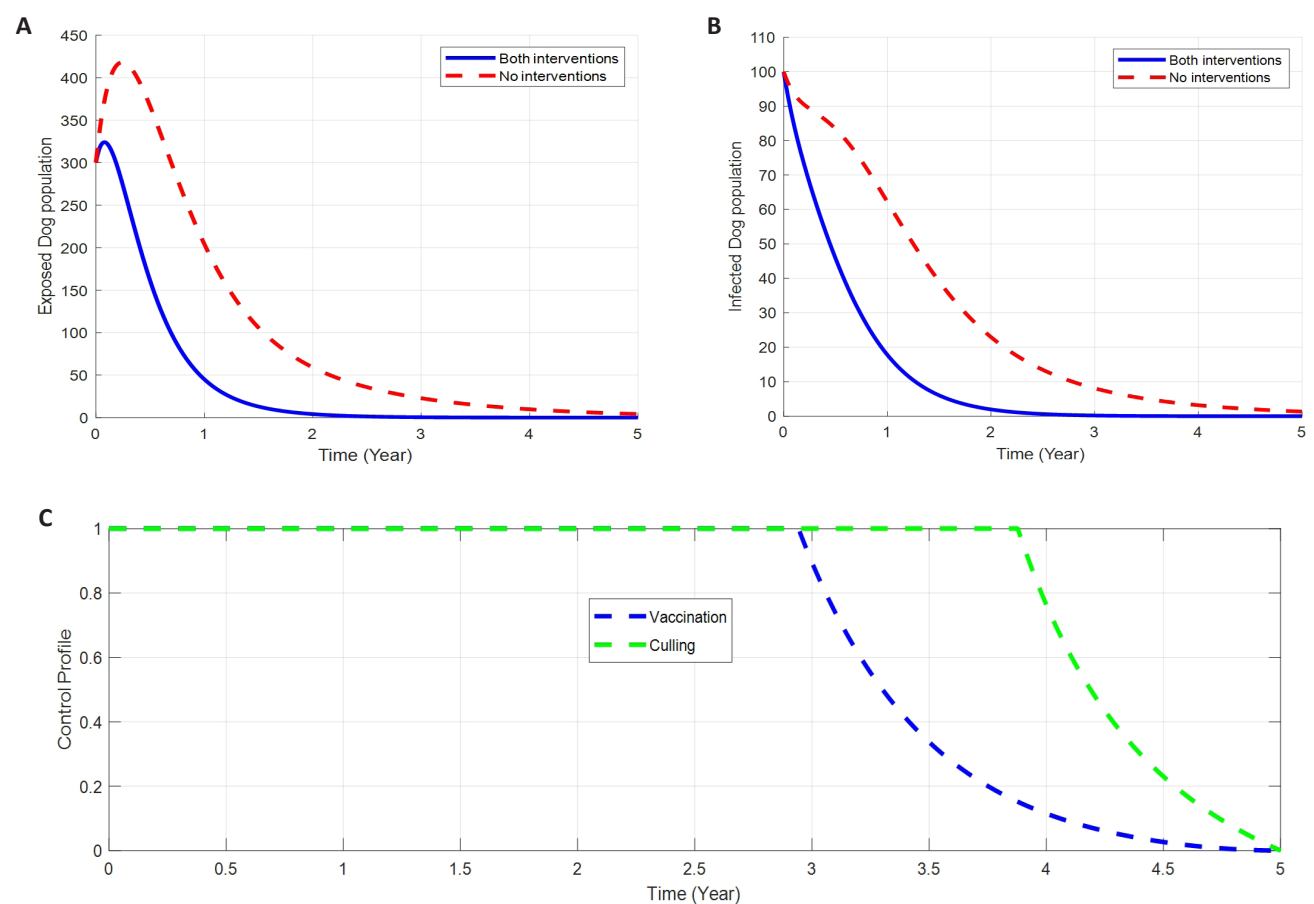


Figure 5. The Impact of Both Interventions (Vaccination And Culling) on Dog Rabies Disease Dynamics. A: Impacts of vaccination and culling on exposed dogs. B: Impacts of vaccination and culling on infected dogs. C: Profile control of dog rabies disease through vaccination and culling intervention.

Table 2. Number of Infections Averted and Total Cost of Each Strategy

Strategies	Infections	Infections Averted	Cost (\$)	ICER($\tau_2 C / \tau_2 E$)
No control	1.3092×10^6	0	0	0
Strategy A	8.2484×10^5	484360	1.3889×10^3	0.00028675
Strategy B	7.2314×10^5	585790	361.5597	-0.01012856
Strategy C	5.0668×10^5	802520	1.4012×10^3	0.00479694

Culling control compared to the number without control. Due to the control u_2 , the number of exposed and infected Dogs decreases from 350 and 100 respectively to nearly zero after 2.5th time duration. However, Culling therapy has shown a greater impact on Infected.

Dogs' population compared to Exposed. Figure 4C shows the control profile of (u_2) in which the control u_2 is at the upper bound until the time $t=4.7$, before slowly dropping to the lower bound at the final time.

2.8.3 Control with Both Interventions (Vaccination and Culling)

In this strategy, the implementation of both control strategies, Vaccination (u_1), and Culling (u_2), is used to minimize the objective function in (25). The results in Figure 5A-B demonstrate a significant reduction in the number of exposed and infected Dogs with the existence of combined control strategies compared to when the control strategies are not in place. Figure 5C shows the control profile in which the control strategy (u_1) is maintained at a maximum effort of 100% until $t=3$, (u_2) is maintained at the maximum effort of 100% until $t=4$ for infected individuals in the population, before gradually dropping to the lower bound at the final time. Therefore, it is clear that, employing both strategies brings quicker impacts in reducing the number of exposed and infected dogs compared with the application of single strategy intervention.

2.9 Cost-Effectiveness Analysis

In this section, we conduct a cost-effectiveness analysis (CEA) with the aim of identifying the most cost-effective control measure, whether it's a single strategy or a combination of two, in order to minimize disease infections while optimizing cost-efficiency. To accomplish this, we employ the Incremental Cost-Effectiveness Ratio (ICER). The ICER plays a crucial role in discerning the most economically efficient strategy for mitigating the spread of Dog Rabies disease by comparing any two competing measures. This methodology is particularly valuable when allocating limited resources for disease control, as explained by Olaniyi et al.^[43]

$$ICER = \frac{\text{Change in the total costs of control measures}}{\text{Change in the number of infections averted}} \quad (34)$$

Change in the number of infections averted

$$total\ Cost(C_T) = \int_0^{T_f} (C_1 u_1 (S(t) + E(t)) + C_2 u_2 (E(t) + I(t)) dt, \quad (35)$$

where C_1 and C_2 correspond to per dog unit cost based on the

use of Vaccination (u_1) and per Dog unit cost of Culling (u_2) of susceptible, Exposed, and Infected Dogs respectively.

The results obtained (as depicted in Table 2) reveal that the ICER value for strategy C surpasses that of strategy A. This implies that implementing all control measures is more expensive and less effective than when solely employing control u_1 (Vaccination). Consequently, strategy C is excluded from the roster of viable control strategies.

By examining results in Table 2, the competing strategy A with strategy B it becomes evident that the Incremental Cost-Effectiveness Ratio (ICER) for strategy A exceeds the ICER value for strategy B. This signifies that strategy A is decidedly inferior, implying higher costs and lower effectiveness compared to strategy B. As a result, strategy B, which involves culling, emerges as the most economically efficient option among the three strategies.

Consequently, the adoption of culling is deemed the optimal and most cost-effective intervention for significantly reducing the prevalence of Dog Rabies disease within the population.

3 DISCUSSION

In this study, we developed and analyzed the dog rabies disease model comprises of five compartments of dog population to evaluate the impacts of vaccination and culling intervention approaches for the disease control. Effective reproduction number (R_e) was computed by the Next Generation method which is potential key for the disease prevalence. Again, both equilibrium points for disease free and endemic were determined accordingly followed by their respective analyses. Analytically, we observed that at disease free equilibrium point (E_0) potentially $R_e < 1$ exists, which implies that the dog rabies disease is weak, and consequently easily for its elimination and control. However, for the endemic equilibrium point (E_*) we see the reverse that $R_e > 1$ persists suggesting that the disease is strong enough to remain in the population at significant time duration. Furthermore, we computed for the sensitivity analysis to identify the most and significant influential parameters that contribute to the existence and elimination of the disease in the population.

The study also introduces an optimal control model aimed at evaluating the effectiveness of various strategies for managing rabies transmission in dog populations. The model investigates time-dependent control measures, such as vaccinating both susceptible and exposed dogs, as well

as implementing culling strategies to reduce the number of infected animals. To identify the optimal control conditions, Pontryagin's Maximum Principle is applied, followed by numerical simulations using the forward and backward fourth-order Runge-Kutta methods.

Our findings show that, with the implementation of a single control strategy either vaccination (u_1) or culling (u_2) alone brings a little impact on reducing the dog rabies disease infection as it takes almost 2.5 to 3 years duration to eliminate the number of exposed and infected dogs in the population as seen and discussed in [Figure 3](#) and [Figure 4A-B](#). Moreover, the disease control profile time for single intervention is more prolonged to almost 4.5 years before bringing its impacts on the disease control (refer [Figures 3](#) to [4C](#)).

On the other hand, the study suggesting that, the utilization of both interventions simultaneously, that's vaccination and culling give more significant reduction of exposed and infected number of dogs from its peak of 350 and 100 respectively, to approaching zero for about 1.5y duration ([Figure 5A-B](#)). Additionally, double interventions (vaccination and culling) bring a potential impact on the disease control profile time from 4.5 to 3 and 4 years for the vaccination and culling respectively.

Furthermore, from the [Table 2](#) above, a cost-effectiveness analysis further identifies culling (strategy B) as the most economically efficient approach, showing the lowest incremental cost-effectiveness ratio -0.01012856 compared with other strategies (A=0.00028675 and C=0.00479694), particularly when implemented on a larger scale. However, this option is convincing economically, but not sufficient in combating infection spread in the dog population timely.

These findings align with previous studies on infectious disease control, where fractional-calculus-based models have provided deeper insights into the dynamics of diseases like monkey-pox and HIV^[44]. Fractional calculus has proven useful in capturing memory effects and variable transmission factors, as seen in models for diseases such as Hand-Foot-Mouth Disease^[45]. Furthermore, the study's use of optimal control strategies is consistent with approaches seen in modelling water-borne diseases, where non-singular and non-local kernels are employed to reflect the complex nature of disease transmission^[46]. The inclusion of fractional derivatives could enhance future rabies models by accounting for long-term effects and delayed responses, as demonstrated in the analysis of HIV transmission dynamics via the Galerkin method^[47].

4 CONCLUSION

Ultimately, this study suggests that effective rabies control can be achieved by simultaneously implementing vaccination and culling, particularly targeting the exposed and infectious dog populations, which plays a critical role in sustaining the disease, although on the economical basis does not give optimal solution for combination of control strategy

alternatives obtained.

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Conflicts of Interest

The authors declared no conflict of interest.

Data Availability

All supportive data regarding this work are included.

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