Sensitivity Analysis for the Mathematical Modeling Transmission and Control of Rabies Incorporating Vaccination Class

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Abstract

In this paper, the Disease Free Equilibrium (DFE) of the model was obtained. The Basic Reproduction Number R_0 was also computed and used to carry out the sensitivity analysis. The analysis revealed the sensitive parameters for the spread and control of Rabies. It was also shown that contact rate of dog and vaccination rate of the dog are the most sensitive parameters to increase and decrease the transmission of rabies. The reproduction number was presented graphically against the sensitive parameters.

Keywords: Sensitivity analysis; Rabies; incorporating; parameters;

Introduction

Rabies is an acute viral disease of the nervous system of warm-blooded animals including human beings. It is most often transmitted through the bite or scratch of a rabid animal (WHO, 2010 and Tang *et al*, 2005). All species of mammals are susceptible to rabies virus infection, but dog remain the main carrier of rabies and are responsible for most of the human rabies death worldwide (CDC, 2011 and Wiraningsih *et al*, 2010) because of their intense interaction with human being. Transmission among human beings does not happen, but rather there are uncommon instances of the disease transmission through bites or organ transplant from infected individual (Sambo *et al*, 2013). After been bitten by an infected animal, the virus enters the peripheral nervous system of the human being, it then travels along the nerves of the central nervous system.

The symptoms can transform a human into a furious wolf (Gastaut and Miletto, 1955) and causes fear of water. According to WHO (2018), the initial symptoms of rabies includes: pains, headache, fever, burning sensation at the wound site. As the virus spreads to the central nervous systems, progressive and fatal inflammation of the brain and spinal cord develops. Rabies is present in all continents, except Antarctica, with over 95% of human deaths occurring in the Asia and Africa Region (WHO, 2018). Each year, it is estimated that more than 55,000 people die of rabies (Tadesse, 2015).

Hompson *et al*. (2007) observed rabies epidemics cycles with a period of 3-6 years in dog populations in Africa, built a susceptible, exposed, infectious and vaccinated model with an intervention response variable, and showed significant synchrony.

Carrol *et al*. (2010) created a continuous compartmental model to describe rabies epidemiology in dog populations and explored three control methods: vaccination, vaccination plus fertility control, and culling.

Zinsstag *et al*. (2009) extended existing models on rabies transmission between dogs to include dog to human transmission and concluded that combining human Pre-Exposure Prophylaxis (PEP) with a dog vaccination campign is more cost effective in the long run.

Zhang *et al*. (2011) proposed a deterministic model to study the transmission dynamics of rabies in China. The model consist of susceptible, exposed, infected and recovery subpopulations of both dogs and humans and describes the spread of rabies among dogs and from infectious dogs to humans. They used the model to stimulate the human rabies data in China from 1996 to 2010. They performed the sensitivity analysis of basic reproduction R_0 in terms of model parameter. The result shows that reducing dog's birth rate and increasing dog immunization coverage rate are the best way to control human rabies in China.

Donkok *et al*. (2014) also developed an SEIR model with vaccination to predict the spread of dog rabies in Bolgatanga district in Ghana. The results showed the basic reproduction number to be 0.3755 which meant the disease was non- endemic.

Mirjam Laager *et al*. (2018) used a deterministic population-based model of ordinary differential equations extended from Zinsstag *et al*. (2009). They used the data from the N'Djamena vaccination campaigns in 2012 and 2013 to understand if the transmission was interrupted and whether individual immunity loss or population turnover contribute more to the decreasing vaccination coverage.

In this paper the mathematical model of rabies is formulated, the Disease Free Equilibrium DFE and Basic Reproduction Number were computed. The sensitivity analysis of the Basic Reproduction Number with respect to some parameters of the model was carried out to determine the most sensitive parameters that will have both positive and negative impact on the transmission of Rabies.

Materials and Methods

Model Formulation

In this model, two populations are considered; dog and human. We divide each of the population into five compartments; susceptible, exposed, infected, vaccinated and recovered, with dog population denoted by $S_d(t), E_d(t), I_d(t), V_d(t)$, and $R_d(t)$, and human population denoted by $S_h(t), E_h(t), I_h(t), V_h(t)$, and $R_h(t)$, respectively.

The dog population, σ_d represent the recruitment rate of dogs, some of the dogs in the population are given Pre Exposure Prophylaxis (PREP) vaccine represented by ϕ_d. The susceptible dogs get in contact with infected dogs at rate α_d to get expose to rabies. Some of the dogs that got exposed may develop clinical rabies represented by $\tau_d \lambda_d$ which make them move to the infected class while others may not develop clinical rabies represented by $\tau_d (1-\lambda_d)$. Those dogs with clinical rabies have a small chance of surviving which leads to death due to the infection at rate δ_d and those that were attended to immediately after being exposed to are vaccinated at rate ϕ_d and they were confirmed totally free from rabies move to recovered class at rate γ_d and after sometime a loss of vaccine immunity can occur at rate θ_d and they became susceptible. All dogs in the model have natural mortality rate μ_d

The human population, σ_h represent the recruitment rate of humans. The susceptible humans get in contact with infected dogs at rate α_h to get expose to rabies. Some of the humans that got exposed may develop clinical rabies represented by $\tau_h \lambda_h$ which make them move to the infected class while others may not develop clinical rabies represented by $\tau_h (1-\lambda_h)$. Those humans with clinical rabies have a small chance of surviving which leads to death due to the infection at rate δ_h and those that were attended to immediately after being exposed to by washing the bite with soap and water at rate ψ_h and are vaccinated at rate ϕ_h and they were confirmed totally free from rabies move to recovered class at rate γ_h and after sometime a loss of vaccine immunity can occur at rate θ_h and they became susceptible. All humans in the model have natural mortality rate μ_h. All parameters are positive. Table 3.1 has the definition of variables and parameter.

The model flow diagram is shown in figure 3.1. The arrow from infected dog to the susceptible human shows the infected dog infects the susceptible human.

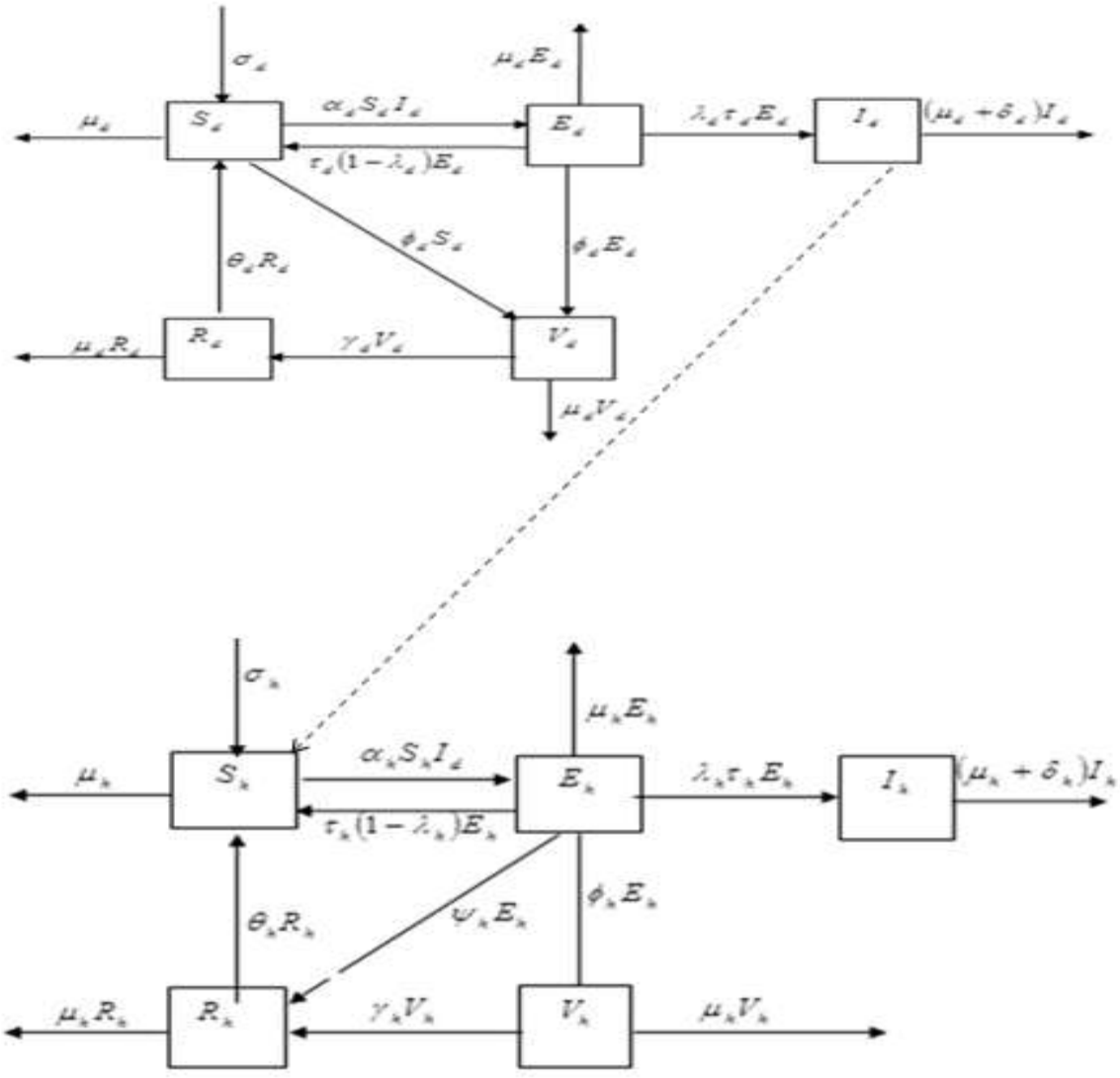

Figure 3.1: Schematic Diagram of the Model

$$\frac{dS_d(t)}{dt} = \sigma_d - \alpha_d S_d I_d + \tau_d(1-\lambda_d)E_d + \theta_d R_d - (\mu_d + \phi_d)S_d \quad (1)$$

$$\frac{dE_d(t)}{dt} = \alpha_d S_d I_d - (\mu_d + \tau_d + \phi_d)E_d \quad (2)$$

$$\frac{dI_d(t)}{dt} = \tau_d \lambda_d E_d - (\mu_d + \delta_d)I_d \quad (3)$$

$$\frac{dV_d(t)}{dt} = \phi_d Sd + \phi_d E_d - (\mu_d + \gamma_d)V_d \quad (4)$$

$$\frac{dR_d(t)}{dt} = \gamma_d V_d - (\theta_d + \mu_d)R_d \quad (5)$$

$$\frac{dS_h(t)}{dt} = \sigma_h - \alpha_h S_h I_d + \tau_h(1-\lambda_h)E_h + \theta_h R_h - \mu_h S_h \quad (6)$$

$$\frac{dE_h(t)}{dt} = \alpha_h S_h I_d - (\mu_h + \tau_h + \phi_h + \psi_h)E_h \quad (7)$$

$$\frac{dI_h}{dt} = \tau_h \lambda_h E_h - (\mu_h + \delta_h)I_h \quad (8)$$

$$\frac{dV_h}{dt} = \phi_h E_h - (\mu_h + \gamma_h)V_h \quad (9)$$

$$\frac{dR_h(t)}{dt} = \gamma_h V_h + \psi_h E_h - (\theta_h + \mu_h)R_{\mathrm{h}} \quad (10)$$

Table 3.1: Notation and definition of variables and parameter

Symbol	Description
$S_d(t)$	Susceptible dogs at time t
$E_d(t)$	Exposed dogs at time t
$I_d(t)$	Infected dogs at time t
$V_d(t)$	Vaccinated dogs at time t
$R_d(t)$	Recovered dogs at time t
$S_h(t)$	Susceptible humans at time t
$E_h(t)$	Exposed humans at time t
$I_h(t)$	Infected humans at time t
$V_h(t)$	Vaccinated humans at time t

$R_h(t)$	Recovered humans at time t
σ_d	Recruitment rate of dog population
σ_h	Recruitment rate of human population
α_d	Contact rate of dog population
α_h	Contact rate of human population
τ_d	Incubation rate of dog population
τ_h	Incubation rate of human population
λ_d	Risk of developing rabies for exposed dog
λ_h	Risk of developing rabies for exposed human
$\tau_d \lambda_d E_d$	The exposed dog develops rabies
$\tau_h \lambda_h E_h$	The exposed human develops rabies
$\tau_d (1-\lambda_d) E_d$	The exposed dog do not develops rabies
$\tau_h (1-\lambda_h) E_h$	The exposed human do not develops rabies
ϕ_d	Vaccination rate for the dog populations
ϕ_h	Vaccination rate for the human populations
θ_d	Loss of vaccine immunity in the dog populations
θ_h	Loss of vaccine immunity in the human populations
ψ_h	Washing of the bite area with soap and water
μ_d	Natural death rate of dog populations

μ_h	Natural death rate of human populations
δ_d	Disease-induced death rate of dog populations
δ_h	Disease-induced death rate of human populations
γ_d	recovery rate of dog populations due to effective vaccination
γ_h	recovery rate of human populations due to effective vaccination

Equilibrium State of the Model

At equilibrium

$$\frac{dS_d}{dt}=\frac{dE_d}{dt}=\frac{dI_d}{dt}=\frac{dV_d}{dt}=\frac{dR_d}{dt}=\frac{dS_h}{dt}=\frac{dE_h}{dt}=\frac{dI_h}{dt}=\frac{dV_h}{dt}=\frac{dR_h}{dt}=0 \qquad (11)$$

3.6 Disease Free Equilibrium State

Let $E^0=\left(S_d,E_d,I_d,V_d.R_d,S_h,E_h,I_h,V_h.R_h\right)=\left(S_d^0,E_d^0,I_d^0,V_d^0.R_d^0,S_h^0,E_h^0,I_h^0,V_h^0,R_h^0\right)$

(12)

be the DFE point

Therefore, the system (1) to (10) become

$$\sigma_d-\alpha_d S_d I_d+\tau_d(1-\lambda_d)E_d+\theta_d R_d-A_1 S_d=0 \qquad (13)$$

$$\alpha_d S_d I_d-A_2 E_d=0 \qquad (14)$$

$$\tau_d\lambda_d E_d-A_3 I_d=0 \qquad (15)$$

$$\phi_d S_d + \phi_d E_d - A_4 V_d = 0 \tag{16}$$

$$\gamma_d V_d - A_5 R_d = 0 \tag{17}$$

$$\sigma_h - \alpha_h S_h I_d + \tau_h (1-\lambda_h) E_h + \theta_h R_h - \mu_h S_h = 0 \tag{18}$$

$$\alpha_h S_h I_d - A_6 E_h = 0 \tag{19}$$

$$\tau_h \lambda_h E_h - A_7 I_h = 0 \tag{20}$$

$$\phi_h E_h - A_8 V_h = 0 \tag{21}$$

$$\gamma_h V_h + \psi_h E_h - A_9 R_h = 0 \tag{22}$$

where,

$$\left.\begin{array}{l} A_1 = (\mu_d + \phi_d),\ A_2 = (\mu_d + \tau_d + \phi_d),\ A_3 = (\mu_d + \delta_d),\ A_4 = (\mu_d + \gamma_d) \\ A_5 = (\theta_d + \mu_d),\ A_6 = (\mu_h + \tau_h + \phi_h + \psi_h),\ A_7 = (\mu_h + \delta_h) \\ A_8 = (\mu_h + \gamma_h),\ A_9 = (\theta_h + \mu_h) \end{array}\right\} \tag{23}$$

Solving (13) to (22) gives

Therefore the Disease Free Equilibrium DFE state is given as

$$E^0 = (S_d^0, E_d^0, I_d^0, V_d^0 . R_d^0, S_h^0, E_h^0, I_h^0, V_h^0, R_h^0) = \left(\begin{array}{l} \dfrac{\sigma_d A_4 A_5}{A_1 A_4 A_5 - \phi_d \gamma_d \theta_d}, 0, 0, \dfrac{\sigma_d \phi_d A_5}{A_1 A_4 A_5 - \phi_d \gamma_d \theta_d}, \\ \dfrac{\sigma_d \phi_d \gamma_d}{A_1 A_4 A_5 - \phi_d \gamma_d \theta_d}, \dfrac{\sigma_h}{\mu_h}, 0, 0, 0, 0 \end{array} \right) \tag{24}$$

3.7 Basic Reproduction Number (R_0)

Basic reproduction number R_0 is used to measure the transmission potential of a disease. The basic reproduction number R_0 of an infectious agent such as rabies virus is defined as the average number of secondary infections produced by an infected individual in an otherwise susceptible host population (Anderson and May, 1991). The basic reproduction number R_0 can also mean the number of individuals infected during his or her entire infectious period, in a population which is entirely susceptible (Heffernan, Smith and Wahl, 2005). The basic reproduction number R_0 has no unit. When $R_0 < 1$, the disease will die out in the population. Otherwise, when $R_0 > 1$, the disease becomes endemic. In this model, the next generation matrix method as described in (Driessche and Watmough, 2002) is used to get the basic reproduction number R_0.

Basic reproduction number $(R_0) = \rho(FV^{-1})$, where $f_i(x)$ be the rate of appearance of new infections in compartment i, V_i^+ the rate of transfer of individuals into compartment i by all other means and V_i^- the rate of transfer of individuals out of compartment i.

In the model equation (13) to 22), the infectious compartments include E_d, I_d, E_h, I_h and the expected secondary infections depend on these classes. The rate of appearance of new infections in compartment i is given by the matrix,

$$f = \begin{pmatrix} \alpha_d S_d I_d \\ 0 \\ \alpha_h S_h I_d \\ 0 \end{pmatrix} \qquad (25)$$

The jacobian matrix of F evaluated at the disease free equilibrium point is given by

F=$\left(\frac{\partial f_i\left(E^0\right)}{\partial x_j}\right)$, where $x_j = E_d, I_{d,} E_h, I_h$ for j=1, 2, 3, 4 and E^0 is the disease free equilibrium.

The Jacobian matrix of (25) evaluated at the disease free equilibrium point is given

$$F = \begin{pmatrix} 0 & \frac{\alpha_d \sigma_d A_4 A_5}{A_1 A_4 A_5 - \phi_d \gamma_d \theta_d} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & \frac{\alpha_h \sigma_h}{\mu_h} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{26}$$

The rate of transfer of individuals in and out of the infectious compartment i is given by the matrix,

$$v = v^- - v^+ = \begin{pmatrix} A_2 E_d \\ A_3 I_d - \tau_d \lambda_d E_d \\ A_6 E_h \\ A_7 I_h - \tau_h \lambda_h E_h \end{pmatrix} \tag{27}$$

Where

$$v^- = \begin{pmatrix} A_2 E_d \\ A_3 I_d \\ A_6 E_h \\ A_7 I_h \end{pmatrix} \tag{28}$$

And $v^+ = \begin{pmatrix} 0 \\ \tau_d \lambda_d E_d \\ 0 \\ \tau_h \lambda_h E_h \end{pmatrix}$ (29)

The jacobian matrix of (27) evaluated at the disease free equilibrium point is given by,

$$V = \left(\frac{\partial v_i (x_0)_i}{\partial x_j} \right) = \begin{pmatrix} A_2 & 0 & 0 & 0 \\ -\tau_d \lambda_d & A_3 & 0 & 0 \\ 0 & 0 & A_6 & 0 \\ 0 & 0 & -\tau_h \lambda_h & A_7 \end{pmatrix} \tag{30}$$

Where $x_j = E_d, I_{d,} E_h, I_h$ for j=1, 2, 3, 4 and x_0 is the disease free equilibrium

The inverse of V is computed using guass Jordan method

$$V^{-1} = \begin{pmatrix} \frac{1}{A_2} & 0 & 0 & 0 \\ \frac{\tau_d \lambda_d}{A_2 A_3} & \frac{1}{A_3} & 0 & 0 \\ 0 & 0 & \frac{1}{A_6} & 0 \\ 0 & 0 & \frac{\tau_h \lambda_h}{A_6 A_7} & \frac{1}{A_7} \end{pmatrix} \tag{31}$$

The next generated matrix FV^{-1} is given by;

$$FV^{-1} = \begin{pmatrix} \frac{\alpha_d \sigma_d \tau_d \lambda_d A_4 A_5}{A_2 A_3 (A_1 A_4 A_5 - \phi_d \gamma_d \theta_d)} & \frac{\alpha_d \sigma_d A_4 A_5}{A_3 (A_1 A_4 A_5 - \phi_d \gamma_d \theta_d)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\alpha_h \sigma_h \tau_d \lambda_d}{\mu_h A_2 A_3} & \frac{\alpha_h \sigma_h}{\mu_h A_3} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{32}$$

$\rho(FV^{-1})$ is the dominant eigenvalue of the (FV^{-1}) matrix.

The eigenvalue is gotten using $|FV^{-1} - \lambda I| = 0$,

$$\begin{vmatrix} \frac{\alpha_d \sigma_d \tau_d \lambda_d A_4 A_5}{A_2 A_3 \left(A_1 A_4 A_5 - \phi_d \gamma_d \theta_d\right)} - \lambda & \frac{\alpha_d \sigma_d A_4 A_5}{A_3 \left(A_1 A_4 A_5 - \phi_d \gamma_d \theta_d\right)} & 0 & 0 \\ 0 & -\lambda & 0 & 0 \\ \frac{\alpha_h \sigma_h \tau_d \lambda_d}{\mu_h A_2 A_3} & \frac{\alpha_h \sigma_h}{\mu_h A_3} & -\lambda & 0 \\ 0 & 0 & 0 & -\lambda \end{vmatrix} = 0 \qquad (33)$$

$$\left(\frac{\alpha_d \sigma_d \tau_d \lambda_d A_4 A_5}{A_2 A_3 \left(A_1 A_4 A_5 - \phi_d \gamma_d \theta_d\right)} - \lambda\right)(-\lambda)(\lambda\lambda) = 0 \qquad (34)$$

$$\left(\frac{\alpha_d \sigma_d \tau_d \lambda_d A_4 A_5}{A_2 A_3 \left(A_1 A_4 A_5 - \phi_d \gamma_d \theta_d\right)} - \lambda_1\right) = 0 \text{ or } (-\lambda_2) = 0 \text{ or } (\lambda_3 \lambda_4) = 0 \qquad (35)$$

$$\lambda_1 = \frac{\alpha_d \sigma_d \tau_d \lambda_d A_4 A_5}{A_2 A_3 \left(A_1 A_4 A_5 - \phi_d \gamma_d \theta_d\right)} \qquad (36)$$

$$\text{Then, } R_0 = \frac{\alpha_d \sigma_d \tau_d \lambda_d A_4 A_5}{A_2 A_3 \left(A_1 A_4 A_5 - \phi_d \gamma_d \theta_d\right)} \qquad (37)$$

Result and Discussions

Sensitivity Analysis

Table 2 is the table of values for sensitivity indices for the sensitivity analysis of the Basic Reproduction Number R_0 with respect to some parameters of the model.

Table 2: Sensitivity Indices of R_0 to the Parameters of the Model

parameters	Value	Sensitivity Index
α_d	0.0158	1.000000000
ϕ_d	0.9	-0.9884039105
γ_d	0.75	0.2334460790
θ_d	0.5	0.3541940511
δ_d	0.75	-0.9036144578

Graphical representation of Basic Reproduction Number R_0 against Sensitive Parameters

Figures 4.1 to 4.5 are the graphical representations of Basic Reproduction Number R_0 against Sensitive Parameters.

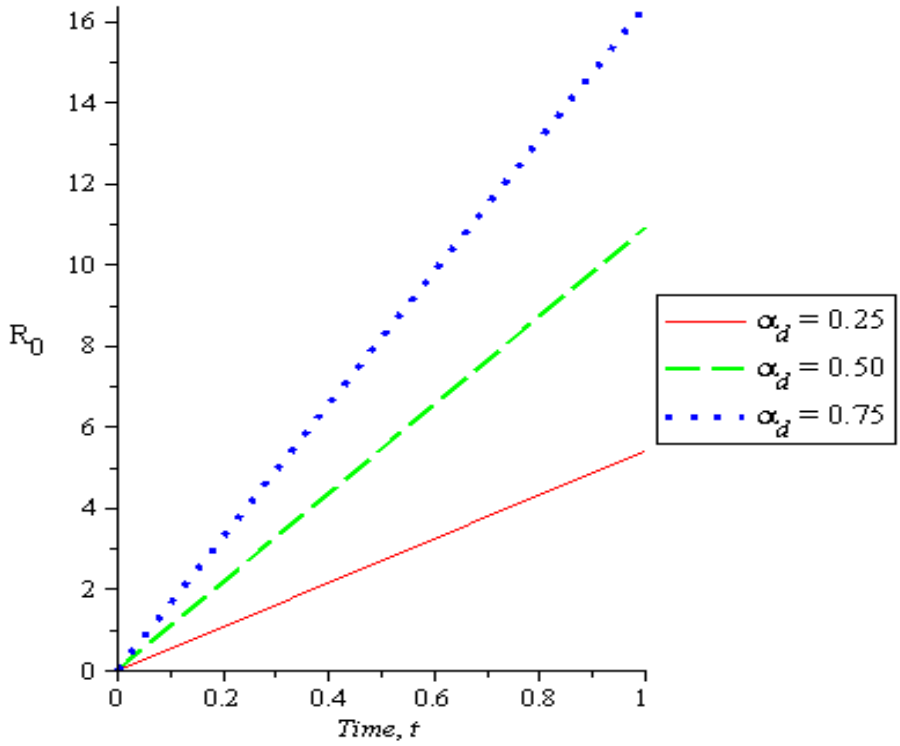

Figure 4.1: The Effect of Contact Rate of Dog on Reproduction Number

Figure 4.1 shows that, the increase in contact rate of dogs with time give rise to increase in the reproduction number. This shows that no matter how small is the contact of the infected dog with the susceptible dog or human will spread the transmission of rabies.

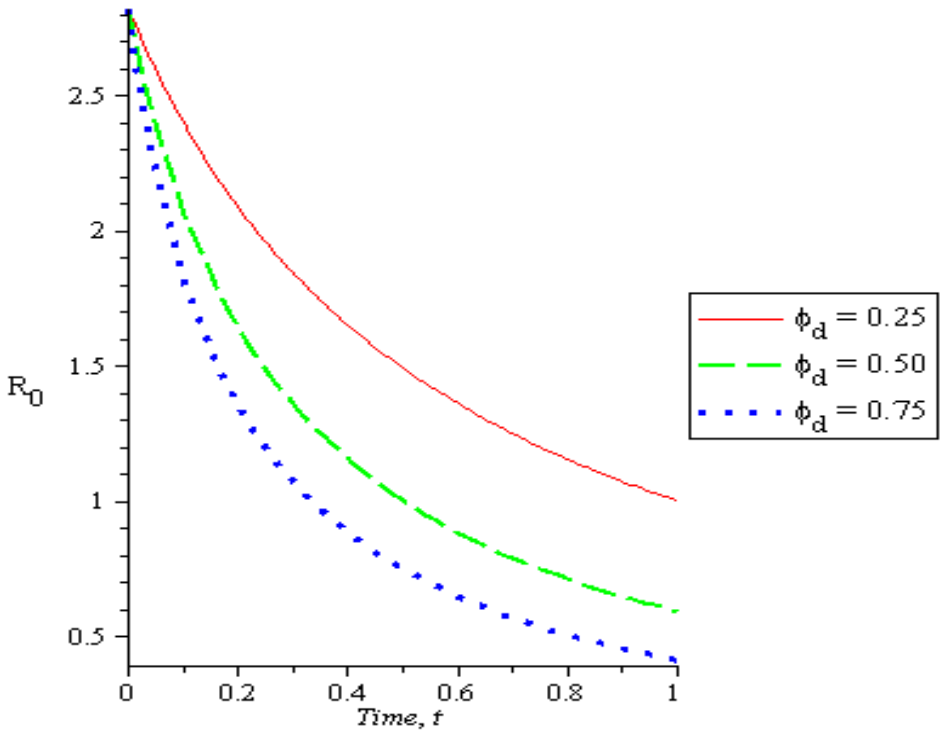

Figure 4.2: The Effect of Vaccination Rate for the Dog Populations on Reproduction Number

Figure 4.2 reveal that, as vaccination rate for the dog increases with time the reproduction number decreases. This had shown that the vaccination is the best to curb the transmission of the rabies.

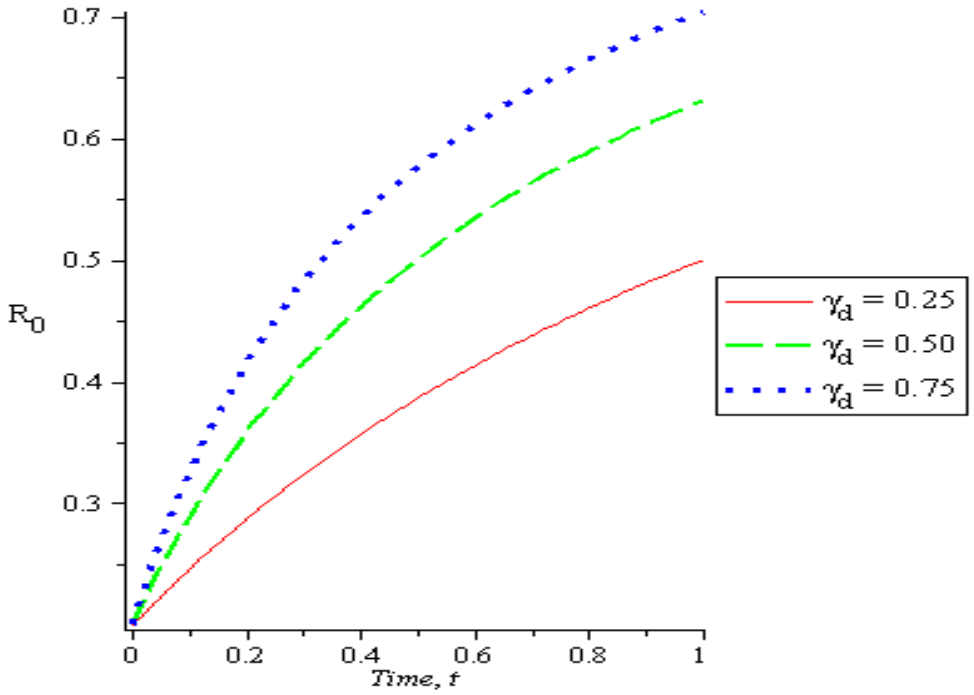

Figure 4.3: The Effect of Recovery Rate of Dog Populations on Reproduction Number

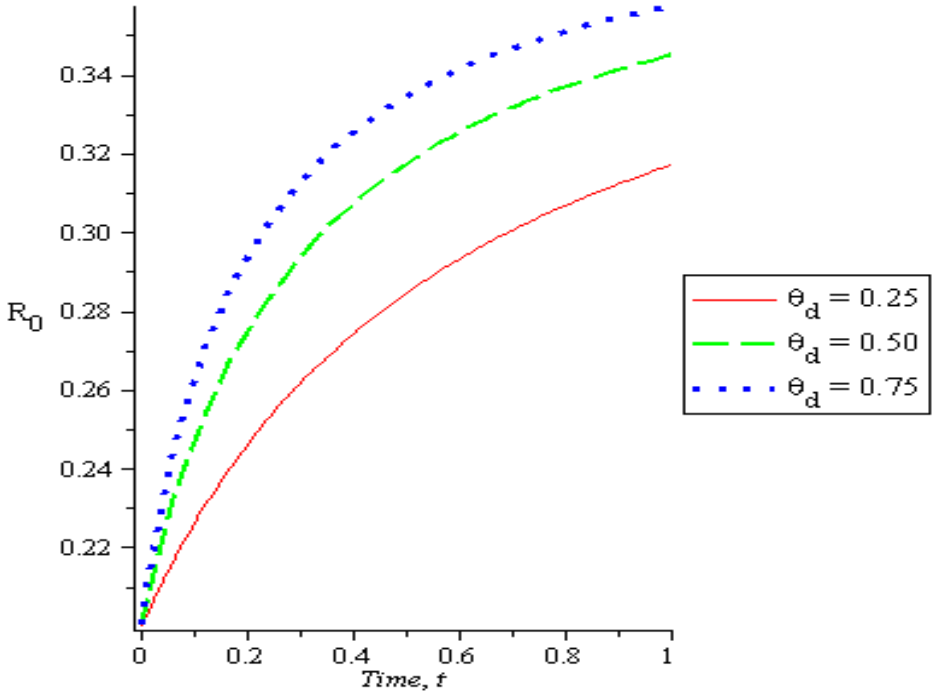

Figure 4.4: The Effect of Loss of Vaccine Immunity in the Dog Populations on Reproduction Number

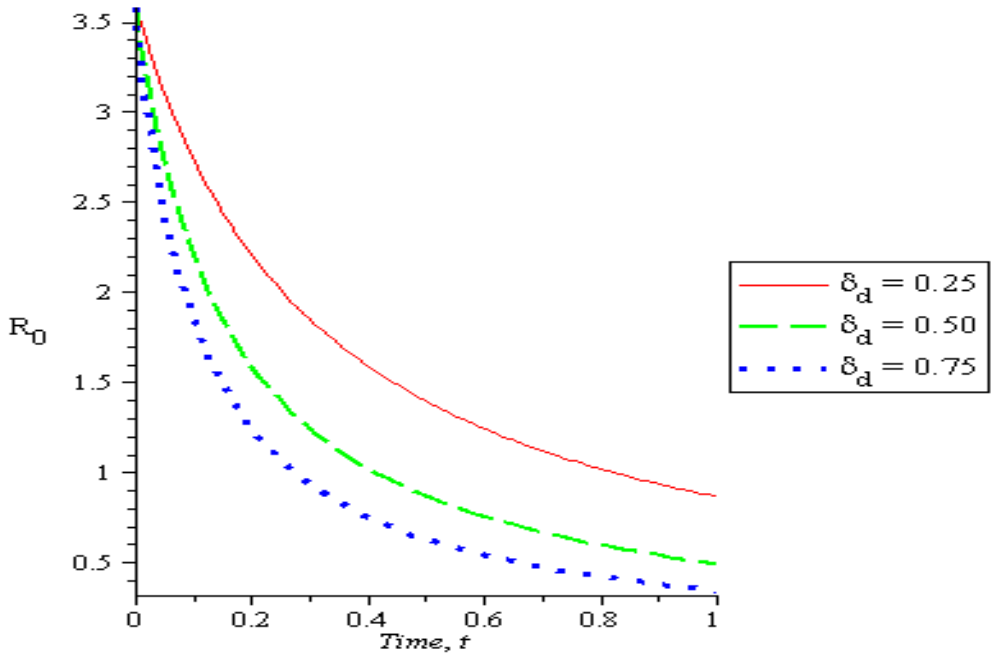

Figure 4.5: The Effect of Disease-Induced Death Rate of Dog Populations on Reproduction Number

Conclusion

Sensitivity analysis of the Basic Reproduction Number with respect to some parameters of the model was carried out. The analysis revealed the sensitive parameters that will increase and decrease the transmission of Rabies. Contact rate of dog was found to be most sensitive parameter to increase the transmission of Rabies while vaccination rate for the dog was the most sensitive parameter to reduce the transmission of Rabies. The analysis was also presented graphically for better understanding.

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