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Impact of early treatment programs on Swine flu infection with optimal controls: Mathematical model

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Abstract

This manuscript focuses on the impact of early treatment programs on swine flu disease transmission among the population. In this manuscript, a nonlinear Susceptible-Exposed-Infected-Recovered (SEIR) model with early Treatment programs are developed to examine the transmission dynamics of Swine flu infection with the help of the system of ordinary differential equations. The characteristics of the model are investigated by the basic reproduction number. We analyzed that the model exhibits using stability theory of differential equations, the disease-free equilibrium is linearly stable for R01. Also, conditions for non-linear stability are derived. Sensitivity indices for basic reproduction and also optimal control measures for swine flu are obtained. Further, numerical simulation for the model is supported by relevant graphs.

Keywords: Swine flu and Early Treatment Programs, SEIR Model, Basic Reproduction Number, Stability, Sensitivity Analysis, Optimal controls.
2010 MSC: 34D20, 34D23, 37C75, 49Q12, 90C31, 93C15, 93D05.

1. Introduction

Swine flu is an infectious disease caused by influenza virus of type A more specifically H1N1 virus. This flu spreads easily in person through direct or indirect contact with infected pigs or swine flu infected person [1]. Swine flu spreads rapidly among the population mainly in crowded circumstances. Cold and dry weather enables the virus to more active than in other conditions [7].Unhygienic

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surroundings, lack of awareness, low immunity and migration are some more issues regarding spread of swine flu [2]. High fever, muscular pain, nasal secretions, headache, sore throat, weakness and uneasiness are symptoms of swine flu disease. The symptom of the virus is noticed after two days [8]. Vaccination is principle measure or best treatment for swine flu infections which helps to prevent and reduce the risk of epidemics in humans and pigs. The U.S. Centers for Disease Control and Prevention (CDC) recommends real time PCR as the technique to diagnose H1N1. Two antiviral drugs; zanamivir (Relenza) and oseltamivir (Tamiflu) are introduced to prevent or reduce symptoms of swine flu. If the symptoms already have been present for 48 hours or more, then these drugs are not prescribed. Patients with a severe flu infection may require special or additional supportive measures, hospitalization and ventilation support against treatment for infection. Some researchers argued that Tamiflu and Relenza are not effective. On Dec. 22, 2014, the FDA recommended the first new anti-influenza drug namely, Peramivir injection (Rapivab) for H1N1 and other influenza virus types in 15 years [3, 4, 5].

In modern era, Mathematical models are well-known and helpful tools to analyze the mechanism of spread, effect of treatment and control of the diseases. Various models on swine flu outbreak have been designed to explain the transmission dynamics. In particular, Misra et al. [7] analyzed a SVIR model to describe the spread and control of influenza in two dissimilar groups. They evaluated basic reproduction number and executed linear and non-linear stability around disease free and endemic equilibrium points. Rahman et al. [9] proposed a SIT model to observe the impact of early treatment programs on HIV epidemics. Kharis et al. [10] suggested a SITR model on Seasonal Influenza with Treatment in constant population. They observed that when $R_0 < 1$ then disease free points is stable and when $R_0 > 1$ then endemic points is stable. Shrivastav el al. [8] gave a SEIQR model on the symptomatic and asymptomatic infections of swine flu with optimal control. They calculated basic reproduction number and studied the local and global stabilities of equilibrium points of the model. More over, the optimal control model was analyzed using Pontryagin's Maximum Principle. Goswami et al. [11] presented a SITR Mathematical Model for Stability and Treatment of Influenza. They calculated basic reproduction number and compared the theoretical results with findings. The effect of treatment was depicted by the graphs. Further, Chitnis et al. [6], Marsudi et al. [12] and Rani et al. [20] have done sensitivity analysis for various epidemiological models. Move over, Athithan et al. [13], Srivastav et al. [8], Sisodiya et al. [15] and Goswami et al. [14] have measured optimal controls in several models for underlying diseases. The purpose to see the impact of early treatment programs on spread of swine flu epidemics and its control motivate us to design a mathematical model.

In the present manuscript, a nonlinear epidemic model for swine flu infection along early treatment programs with sensitivity analysis and optimal controls is framed in section 2. In section 3, basic traits of the model are mentioned and also basic reproduction number is calculated. Then sensitivity analysis of the basic reproduction number is argued with regard to various constraints. Further, stability analysis of the model is discussed in section 4. In section 5, optimal controls are measured. Finally, numerical simulations are performed to compare the theoretical results and relevant graphs are illustrated in section 6.

2. Formulation of the Model

To outline a SEIR mathematical model with early treatment programs for Swine flu disease, the total population (P) is categorized into subclasses namely, Susceptible(S), Exposed(E), Infected (I) and Recovered (R). if the individuals are not aware about the status of disease and they do not avail initial medical treatment, it may precede to the growth of infected patients. In the assistance of health care agencies many antiretroviral drugs are approved by government bodies to reduce the

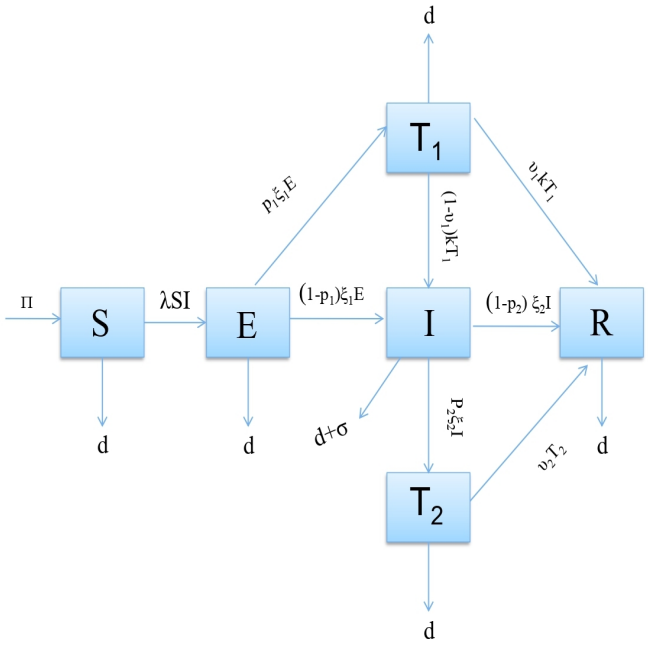

Figure 1: **Transfer Diagram**

risk of infection, now which are made available into the population P.

On the basis of above-mentioned hypothesis, the transmission dynamics of Swine flu can be described by system of nonlinear differential equations as follows:

$$\frac{dS}{dt} = \Pi - \lambda SI - dS \tag{2.1}$$

$$\frac{dE}{dt} = \lambda SI - \xi_1 E - dE \tag{2.2}$$

$$\frac{dT_1}{dt} = p_1\xi_1 E - kT_1 - dT_1 \tag{2.3}$$

$$\frac{dI}{dt} = (1-p_1)\,\xi_1 E + (1-\vartheta_1)kT_1 - \xi_2 I - (d+\sigma)\,I \tag{2.4}$$

$$\frac{dT_2}{dt} = p_2\xi_2 I - \vartheta_2 T_2 - dT_2 \tag{2.5}$$

$$\frac{dR}{dt} = \vartheta_1 kT_1 + (1-p_2)\,\xi_2 I + \vartheta_2 T_2 - dR \tag{2.6}$$

Subject to the initial conditions,
$S(0) = S_0 > 0$, $E(0) = E_0 > 0$,$T_1(0) = T_{10} > 0$,$I(0) = I_0 > 0$, $T_2(0) = T_{20} > 0$ and $R(0) = R_0 > 0$
The total population at any time $'t'$ is given as

$$P(t) = S(t) + E(t) + T_1(t) + I(t) + T_2(t) + R(t)$$

The transfer diagram of designed model is illustrated in Figure 1.

In this model, the classes of individuals are associated as follows:
Π denotes the constant recruitment rate of susceptible class. λ be the transmission rate of infection from infected population to susceptible population and d be the mortality rate of population.

Contact between susceptible and infected pigs or swine flu infected individual can increase risk of infection. Swine flu has latent period of 2-3 days so firstly susceptible population join the exposed class then after some time, they catch infection properly and move to infected class. After proceeding the initial treatment for infection, let ξ_1 be the conversion rate from exposed to infected class; p_1 be the fraction of ξ_1 joining treated class I while some individuals directly join the infection class with a rate $(1-p_1)$ .Now let k be the development of full-blown infected of treated class I; $(1-\upsilon_1)$ be the fraction of k joining infection class while some individuals directly recover with a rate υ_1.Again availing further special medical treatment and hospitalization for infection, let ξ_2 be the conversion rate from infected to recovered class; p_2 be the fraction of ξ_2 which joins treated class II while some individuals directly joining the recover class with a rate $(1-p_2)$. Further, υ_2 be the recovery rate of treated class II and σ be the disease associated death rate. In this manuscript, it is also assumed that the Swine flu patients never recover. The detail about variables and parameters are mentioned in Table 1.

Table 1: Details of Variables and Parameters

Symbols	**Variables and Parameters**
$S(t)$	Susceptible population at time t.
$E(t)$	Exposed population at time t.
$T_1(t)$	Treated population availing initial treatment after being exposed from swine flu at time t.
$I(t)$	Infected population at time t.
$T_2(t)$	Treated population availing special medical treatment and hospitalization after being infected from swine at time t.
$R(t)$	Recovered population at time t.
Π	Recruitment rate of susceptible population.
λ	Transmission rate of swine flu.
d	Natural death rate.
ξ_1	Conversion rate from exposed to either treated class I or infection class.
ξ_2	Conversion rate from infected to either treated class II or recovered class.
σ	Disease induced death rate.
υ_1	Recovery rate after availing initial treatment.
υ_2	Recovery rate after availing special medical treatment and hospitalization.
k	Development of full blown infected of treated class I.
p_1	Fraction of ξ_1 joining initial treatment.
p_2	Fraction of ξ_2 joining special medical treatment and hospitalization.

t The scheme for the analysis of the designed model is given in Table 2.

Table 2: Scheme for analysis of model

Step			Tools used
1.	Title	Stability Analysis of Swine flu Epidemics and Its Control by early Treatment Programs	Swine flu transmission and treatment
2.	Formulation of model	Classification of population	Swine flu transmission and treatment
		Model formulation	Ordinary differential equation
3.	Basic Traits of model	Disease free equilibrium point	Disease free and steady state for differential equation
		Basic reproduction number	Next generation method
		Sensitivity analysis	Normalized forward sensitivity index method
		Endemic equilibrium point	Steady state for differential equation
4.	Stability analysis	Linear stability analysis of Disease free equilibrium point	Descartes' rule of signs
		Non linear stability analysis of Disease free equilibrium point	Lyapunov stability theory
		Linear stability analysis of endemic equilibrium point	Descartes' rule of signs
		Non linear stability analysis of endemic equilibrium point	Lyapunov stability theory
5.	Optimal control problem	p_1 and $\xi_2$are measured as controls for swine flu transmission	Pontryagin's Minimum Principle, Hamiltonian function and Lagrangian function
6.	Numerical simulation	Figure 2 to Figure 7	MATLAB R2014a (32-bit)

3. Basic traits of the model

3.1. ***Bounds of the solutions***

Lemma 3.1. *For all time* $t \geq 0$, *all the solutions of the system* (2.1) - (2.6) *are finally restricted in the bounded region* $\Omega = \left\{(S, E, T_1, I, T_2, R) \in R_+^6 : P(t) = (S(t) + E(t) + T_1(t) + I(t) + T_2(t) + R(t)) \leq \frac{\Pi}{d}\right\}$.

Proof . Let $(S(t), E(t), T_1(t), I(t), T_2(t), R(t))$be the solution of system (2.1) to (2.6) with the initial conditions.
Now suppose, $P(t) = S(t) + E(t) + T_1(t) + I(t) + T_2(t) + R(t)$
Taking time derivative of population $P(t)$,which is given by

$$\frac{dP(t)}{dt} = \frac{dS(t)}{dt} + \frac{dE(t)}{dt} + \frac{dT_1(t)}{dt} + \frac{dI(t)}{dt} + \frac{dT_2(t)}{dt} + \frac{dR(t)}{dt} \tag{3.1}$$

Substituting the values from system (2.1) to (2.6) in equation (3.1), it gives

$$\frac{dP(t)}{dt} = \Pi - d\left(S(t) + E(t) + T_1(t) + I(t) + T_2(t) + R(t)\right) - \sigma I(t)$$

$$\frac{dP(t)}{dt} + dP(t) = \Pi - \sigma I(t)$$

$$\frac{dP(t)}{dt} + dP(t) \leq \Pi$$

On solving the above ODE we have

$$P(t) \leq \frac{\Pi}{d}\left(1 - e^{-dt}\right) + P_0 e^{-dt}$$

Thus for $t \to \infty$ we have $\lim_{t\to\infty} \mathrm{Sup} P(t) \leq \frac{\Pi}{d}$. Consequently, it is proved that all the solutions of system (2.1) to (2.6) with initial conditions are confined in the region Ω, hence all the solutions are bounded in the interval $[0, \infty)$. □

3.2. ***Disease-free equilibrium and Basic reproduction number***

We put each of the equations (2.1) to (2.6) equal to zero to evaluate the disease free equilibrium points. Thus, the disease-free equilibrium E_{df} of the designed model is given by; $E_{df} = (S,\, E,\, T_1,\, I,\, T_2,\, R) = \left(\frac{\Pi}{d},\, 0,\, 0,\, 0,\, 0,\, 0\right)$.

The basic reproduction number is necessary requirement for the assessment of the local stability of the equilibrium points. Computation of the basic reproduction number can be obtained by applying next generation method on the system (2.1) to (2.6). The basic reproduction number is defined as the average number of secondary infections produced by an infected individual during the entire infection period. Suppose F is the rate of growth of new infection in infected class and V is the shifting of individuals out of infected class by all other means then the dominating Eigen value of the matrix FV^{-1} is known as basic reproduction number [17].

$F_1(E, T_1, I, T_2) = \lambda SI,\ F_2(E, T_1, I, T_2) = 0,\ F_3(E, T_1, I, T_2) = 0$ and $F_4(E, T_1, I, T_2) = 0$
$V_1(E, T_1, I, T_2) = (\xi_1 + d)\, E,\ V_2(E, T_1, I, T_2) = -p_1\xi_1 E + (k + d)\, T_1,$
$V_3(E, T_1, I, T_2) = -(1 - p_1)\,\xi_1 E - (1 - \vartheta_1)\, k T_1 + (\xi_2 + d + \sigma)\, I,\ V_4(E, T_1, I, T_2) = -p_2\xi_2 I + (\vartheta_2 + d)\, T_2.$

Therefore

$$F = \begin{bmatrix} 0 & 0 & \lambda S & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} (\xi_1 + d) & 0 & 0 & 0 \\ -p_1\xi_1 & (k + d) & 0 & 0 \\ -(1 - p_1)\,\xi_1 & -(1 - \vartheta_1)\, k & (\xi_2 + d + \sigma) & 0 \\ 0 & 0 & -p_2\xi_2 & (\vartheta_2 + d) \end{bmatrix}$$

$$V^{-1} = \frac{1}{(\xi_1 + d)(k + d)(\xi_2 + d + \sigma)(\vartheta_2 + d)} \begin{bmatrix} (k + d)(\xi_2 + d + \sigma)(\vartheta_2 + d) \\ p_1\xi_1 (\xi_2 + d + \sigma)(\vartheta_2 + d) \\ (p_1(1 - \vartheta_1)\, k + (1 - p_1)(k + d))\,\xi_1 (\vartheta_2 + d) \\ (p_1(1 - \vartheta_1)\, k + (1 - p_1)(k + d))\,\xi_1 p_2\xi_2 \end{bmatrix}$$

$$\begin{bmatrix} 0 & 0 & 0 \\ (\xi_1 + d)(\xi_2 + d + \sigma)(\vartheta_2 + d) & 0 & 0 \\ (1 - \vartheta_1)\, k\,(\xi_1 + d)(\vartheta_2 + d) & (\xi_1 + d)(k + d)(\vartheta_2 + d) & 0 \\ (1 - \vartheta_1)\, p_2 k\xi_2 (\xi_1 + d) & p_2\xi_2 (\xi_1 + d)(k + d) & (\xi_1 + d)(k + d)(\xi_2 + d + \sigma) \end{bmatrix}$$

$$FV^{-1} = \frac{1}{(\xi_1 + d)(k + d)(\xi_2 + d + \sigma)(\vartheta_2 + d)} \begin{bmatrix} (p_1(1 - \vartheta_1)\, k + (1 - p_1)(k + d))\,\xi_1 (\vartheta_2 + d)\,\lambda S \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

$$\begin{bmatrix} (\xi_1+d)(1-\vartheta_1)(\vartheta_2+d)k\lambda S & (\xi_1+d)(k+d)(\vartheta_2+d)\lambda S & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

The characteristic equation of FV^{-1} is as follows:

$$\psi^3\left(\psi - \frac{(p_1(1-\vartheta_1)k+(1-p_1)(k+d))}{(\xi_1+d)(k+d)(\xi_2+d+\sigma)}\xi_1\lambda S\right) = 0$$

The largest positive eigen value of FV^{-1} is $\frac{(p_1(1-\vartheta_1)k+(1-p_1)(k+d))}{(\xi_1+d)(k+d)(\xi_2+d+\sigma)}\xi_1\lambda S$.
There fore

$$R_0 = \frac{(p_1(1-\vartheta_1)k+(1-p_1)(k+d))}{d(\xi_1+d)(k+d)(\xi_2+d+\sigma)}\xi_1\lambda\Pi.$$

The basic reproduction number R_0 manipulates the function of the model and status of the disease i.e. whether an infection will be spread in a susceptible population.

3.3. ***Sensitivity analysis of the Basic reproduction number***

To determine the significance of parameters in disease transmission and prevalence, we introduce the sensitivity analysis of the basic reproduction number. Sensitivity indices permit us to measure the relative change in a state variable. These indices indicate us the importance of each parameter that leads to disease transmission. Sensitivity indices of a variable with respect to a parameter can be evaluated by normalized forward sensitivity index method. As we have explicit formula

$$R_0 = \frac{(p_1(1-\vartheta_1)k+(1-p_1)(k+d))}{d(\xi_1+d)(k+d)(\xi_2+d+\sigma)}\xi_1\lambda\Pi.$$

The parameter values and normalized sensitivity indices of R_0 with respect to various parameters are illustrated in Table 3.

Table 3: Sensitivity indices of R_0 with respect to parameter x_i

$R_0 = 1.91$		
Parameters x_i	**Parameter values**	**Sensitivity indices $i_{x_i}^{R_0} = \frac{\partial R_0}{\partial x_i}\cdot\frac{x_i}{R_0}$**
Π	1.5	+1.00
λ	0.0035	+1.00
p_1	0.1	-0.02
ϑ_1	0.01	-0.0008
k	0.08	+0.02
ξ_1	0.6	+0.03
ξ_2	0.1	-0.77
σ	0.01	-0.08
d	0.02	-1.20

From Table 3, we can conclude that the positive sensitivity indices show that Π, λ, ξ_1 and k have positive impact on the value of basic reproduction number i.e. $i_{\xi_1}^{R_0}$ =+0.03 indicates, if value of ξ_1 is increased by 10%, value of R_0 will be increased by 0.32%. While the negative sensitivity indices

show that p_1, υ_1, ξ_2, σ and d have negative impact on the value of basic reproduction number i.e. $i_{\xi_2}^{R_0}$ =-0.77 indicates, if value of ξ_2 is increased by 10%, value of R_0 will be decreased by 7.69%.

3.4. ***Existence of Endemic equilibrium***

To find the conditions for the existence endemic equilibrium points, the nonlinear system of equations (2.1) to (2.6) is equated to zero. Thus endemic equilibrium point $E_e = \left(\overline{S},\, \overline{E},\, \overline{T_1},\, \overline{I},\, \overline{T_2},\, \overline{R}\right)$ is given by

$$\overline{S} = \frac{\Pi}{\lambda\overline{I} + d},$$

$$\overline{E} = \frac{\Pi\lambda\overline{I}}{\left(\lambda\overline{I} + d\right)(\xi_1 + d)},$$

$$\overline{T_1} = \frac{p_1\xi_1\Pi\lambda\overline{I}}{(k+d)(\xi_1+d)\left(\lambda\overline{I}+d\right)},$$

$$\overline{T_2} = \frac{p_2\xi_2\overline{I}}{(\vartheta_2 + d)},$$

$$\overline{R} = \left(\frac{\frac{\vartheta_1 k p_1\xi_1\Pi\lambda}{(k+d)(\xi_1+d)\left(\lambda\overline{I}+d\right)} + \frac{(\vartheta_2+d(1-p_2))\xi_2}{(\vartheta_2+d)}}{d}\right).\overline{I},$$

$$\overline{I} = \frac{1}{\lambda}\left(\frac{\left(p_1\left(1-\vartheta_1\right)k + \left(1-p_1\right)(k+d)\right)}{(\xi_1+d)(k+d)(\xi_2+d+\sigma)}\xi_1\lambda\Pi - d\right) = \frac{d}{\lambda}\left(R_0 - 1\right).$$

Hence, each of $\overline{S}$, $\overline{E}$, $\overline{T_1}$, $\overline{T_2}$ and $\overline{R}$ is positive if $\overline{I} > 0$ and $\overline{I}$ is positive only when $R_0 > 1$. so, endemic equilibrium point $E_e\left(\overline{S},\, \overline{E},\, \overline{T_1},\, \overline{I},\, \overline{T_2},\, \overline{R}\right)$ is positive and exists if $R_0 > 1$.

4. Stability Analysis

Lemma 4.1. *The disease-free equilibrium E_{df} of the model* (2.1) *to* (2.6) *is linearly stable when $R_0 < 1$ and unstable otherwise.*

Proof . The Disease free equilibrium point is given by $E_{df} = \left(\frac{\Pi}{d},\, 0,\, 0,\, 0, 0, 0\right)$.
Now taking small perturbation around it, $S\left(t\right) = \frac{\Pi}{d} + x_1$, $E\left(t\right) = x_2$, $T_1\left(t\right) = x_3$, $I\left(t\right) = x_4$, $T_2\left(t\right) = x_5$ and $R\left(t\right) = x_6$ then linearized system of model equations (2.1) to (2.6) is given as follows,

$$\frac{dx_1}{dt} = -\frac{\lambda\Pi}{d}x_4 - dx_1$$

$$\frac{dx_2}{dt} = \frac{\lambda\Pi}{d}x_4 - \left(\xi_1 + d\right)x_2$$

$$\frac{dx_3}{dt} = p_1\xi_1 x_2 - \left(k+d\right)x_3$$

$$\frac{dx_4}{dt} = \left(1-p_1\right)\xi_1 x_2 + (1-\vartheta_1)kx_3 - \left(\xi_2 + d + \sigma\right)x_4$$

$$\frac{dx_5}{dt} = p_2\xi_2 x_4 - \left(\vartheta_2 + d\right)x_5$$

$$\frac{dx_6}{dt} = \vartheta_1 k x_3 + \left(1-p_2\right)\xi_2 x_4 + \vartheta_2 x_5 - dx_6$$

To examine linear stability of the disease free equilibrium point E_{df} we calculate variational matrix J_1.
The variational matrix of the above system around E_{df} is given by,

$$J_1 = \begin{bmatrix} -d & 0 & 0 & -\frac{\lambda\Pi}{d} & 0 & 0 \\ 0 & -(\xi_1+d) & 0 & \frac{\lambda\Pi}{d} & 0 & 0 \\ 0 & p_1\xi_1 & -(k+d) & 0 & 0 & 0 \\ 0 & (1-p_1)\xi_1 & (1-\vartheta_1)k & -(\xi_2+d+\sigma) & 0 & 0 \\ 0 & 0 & 0 & p_2\xi_2 & -(\vartheta_2+d) & 0 \\ 0 & 0 & \vartheta_1 k & (1-p_2)\xi_2 & \vartheta_2 & -d \end{bmatrix}$$

The characteristic equation of J_1 is obtained as,

$$(\psi+d)^2(\psi+(\vartheta_2+d))\left(\psi^3+C_1\psi^2+C_2\psi+C_3\right)=0. \tag{4.1}$$

where
$C_1 = ((\xi_1+d)+(k+d)+(\xi_2+d+\sigma))$,
$C_2 = (k+d)(\xi_2+d+\sigma)+(\xi_1+d)(k+d)+(\xi_1+d)(\xi_2+d+\sigma)-\frac{(1-p_1)\xi_1\lambda\Pi}{d}$

$$= \frac{p_1(1-\vartheta_1)k\xi_1\lambda\Pi}{d(k+d)}+(k+d)(\xi_2+d+\sigma)+(\xi_1+d)(k+d)+(\xi_1+d)(\xi_2+d+\sigma)(1-R_0),$$

$C_3 = (\xi_1+d)(k+d)(\xi_2+d+\sigma)-\frac{(p_1(1-\vartheta_1)k+(k+d)(1-p_1))\xi_1\lambda\Pi}{d}$

$$= (\xi_1+d)(k+d)(\xi_2+d+\sigma)(1-R_0).$$

Clearly three roots of equation (4.1) are negative and also $C_1>0, C_2>0$ and $C_3>0$ when $R_0<1$, Then by using Descartes' rule of signs, remaining three characteristic roots will be negative.
Hence, all the six roots of equation (4.1) are negative if $R_0<1$.
Thus we conclude that the disease free equilibrium point E_{df} of the model (2.1) to (2.6) is linearly stable if $R_0<1$. However, it is unstable if $R_0>1$. □

Lemma 4.2. *The disease-free equilibrium point E_{df} of the model (2.1) to (2.6) is non linearly stable if following three conditions are satisfied.*
$(\xi_1+d)>\frac{\lambda\Pi}{2d}$,$(\xi_2+d+\sigma)>\frac{\lambda\Pi}{d}$,$\frac{1}{2}\left((\xi_1+d)-\frac{\lambda\Pi}{2d}\right)\left((\xi_2+d+\sigma)-\frac{\lambda\Pi}{d}\right)>((1-p_1)\xi_1)^2$ *otherwise unstable.*

Proof . The Disease free equilibrium point is given by $E_{df}=\left(\frac{\Pi}{d},0,0,0,0,0\right)$.
Now taking small perturbation around it as follows,
$S(t)=\frac{\Pi}{d}+x_1$, $E(t)=x_2$, $T_1(t)=x_3$, $I(t)=x_4$, $T_2(t)=x_5$ and $R(t)=x_6$.
Now consider a positive definite function

$$U=\frac{1}{2}(A_1x_1^2+A_2x_2^2+A_3x_3^2+A_4x_4^2+A_5x_5^2+A_6x_6^2)$$

Differentiating U w.r.to time t and using the model (2.1) to (2.6), we get
$\frac{dU}{dt}=A_1\left[-\lambda\left(\frac{\Pi}{d}+x_1\right)x_1x_4-d{x_1}^2\right]+A_2\left[\lambda\left(\frac{\Pi}{d}+x_1\right)x_2x_4-(\xi_1+d){x_2}^2\right]$

$$+A_3\left[p_1\xi_1x_2x_3-(k+d){x_3}^2\right]+A_4\left[(1-p_1)\xi_1x_2x_4+(1-\vartheta_1)kx_3x_4-(\xi_2+d+\sigma){x_4}^2\right]$$

$$+A_5\left[p_2\xi_2x_4x_5-(\vartheta_2+d){x_5}^2\right]+A_6\left[\vartheta_1kx_3x_6+(1-p_2)\xi_2x_4x_6+\vartheta_2x_5x_6-d{x_6}^2\right].$$

Now using the inequality, $\pm 2\,x\,y \leq x^2 + y^2$ on the right hand side of $\frac{dU}{dt}$, we find that

$$\begin{aligned}\frac{dU}{dt} \leq\ & A_1\left[\tfrac{\lambda}{2}\left(\tfrac{\Pi}{d}+x_1\right)\left(x_1{}^2+x_4{}^2\right)-dx_1{}^2\right]+A_2\left[\tfrac{\lambda}{2}\left(\tfrac{\Pi}{d}+x_1\right)\left(x_2{}^2+x_4{}^2\right)-(\xi_1+d)\,x_2{}^2\right]\\ &+A_3\left[p_1\xi_1x_2x_3-(k+d)\,x_3{}^2\right]+A_4\left[(1-p_1)\,\xi_1x_2x_4+(1-\vartheta_1)kx_3x_4-(\xi_2+d+\sigma)\,x_4{}^2\right]\\ &+A_5\left[p_2\xi_2x_4x_5-(\vartheta_2+d)\,x_5{}^2\right]+A_6\left[\vartheta_1kx_3x_6+(1-p_2)\,\xi_2x_4x_6+\vartheta_2x_5x_6-dx_6{}^2\right].\end{aligned}$$

Again on rearranging the above inequality, we get,

$$\begin{aligned}\frac{dU}{dt} \leq -\big[&\left(d-\tfrac{\lambda\Pi}{2d}\right)A_1x_1{}^2+\left((\xi_1+d)-\tfrac{\lambda\Pi}{2d}\right)A_2x_2{}^2+(k+d)\,A_3x_3{}^2+\left((\xi_2+d+\sigma)\,A_4-\tfrac{\lambda\Pi}{2d}\,(A_1+A_2)\right)x_4{}^2\\ &+(\vartheta_2+d)\,A_5x_5{}^2+dx_6{}^2-p_1\xi_1A_3x_2x_3-(1-p_1)\,\xi_1A_4x_2x_4-(1-\vartheta_1)kA_4x_3x_4-\vartheta_1kA_6x_3x_6\\ &-(1-p_2)\,\xi_2A_6x_4x_6-\vartheta_2A_6x_5\,x_6\big].\end{aligned}$$

$$\begin{aligned}\frac{dU}{dt} \leq -\big[&\left(d-\tfrac{\lambda\Pi}{2d}\right)\big]A_1x_1{}^2+\left(\tfrac{1}{2}\left((\xi_1+d)-\tfrac{\lambda\Pi}{2d}\right)A_2x_2{}^2-p_1\xi_1A_3x_2x_3+\tfrac{1}{3}\,(k+d)\,A_3x_3{}^2\right)\\ &+\left(\frac{1}{2}\left((\xi_1+d)-\frac{\lambda\Pi}{2d}\right)A_2x_2{}^2-(1-p_1)\,\xi_1A_4x_2x_4+\frac{1}{4}\left((\xi_2+d+\sigma)\,A_4-\frac{\lambda\Pi}{2d}\,(A_1+A_2)\right)x_4{}^2\right)\\ &+\left(\frac{1}{3}\,(k+d)\,A_3x_3{}^2-(1-\vartheta_1)kA_4x_3x_4+\frac{1}{4}\left((\xi_2+d+\sigma)\,A_4-\frac{\lambda\Pi}{2d}\,(A_1+A_2)\right)x_4{}^2\right)\\ &+\left(\frac{1}{3}\,(k+d)\,A_3x_3{}^2-\vartheta_1kA_6x_3x_6+\frac{1}{3}dA_6x_6{}^2\right)\\ &+\left(\frac{1}{4}\left((\xi_2+d+\sigma)\,A_4-\frac{\lambda\Pi}{2d}\,(A_1+A_2)\right)x_4{}^2-p_2\xi_2A_5x_4x_5+\frac{1}{2}\,(\vartheta_2+d)\,A_5x_5{}^2\right)\\ &+\left(\frac{1}{4}\left((\xi_2+d+\sigma)\,A_4-\frac{\lambda\Pi}{2d}\,(A_1+A_2)\right)x_4{}^2-(1-p_2)\,\xi_2A_6x_4x_6+\frac{1}{3}dA_6x_6{}^2\right)\\ &+\left(\frac{1}{2}\,(\vartheta_2+d)\,A_5x_5{}^2-\vartheta_2A_6x_5x_6+\frac{1}{3}dA_6x_6{}^2\right)\Bigg].\end{aligned}$$

Hence by Lyapunov's direct method of stability we find that the disease free equilibrium point is non-linearly stable if following conditions are satisfied.

$$\frac{2}{3}\left((\xi_1+d)-\frac{\lambda\Pi}{2d}\right)(k+d)\,A_2>\left(p_1\xi_1\right)^2A_3,$$

$$\frac{1}{2}\left((\xi_1+d)-\frac{\lambda\Pi}{2d}\right)\left((\xi_2+d+\sigma)\,A_4-\frac{\lambda\Pi}{2d}\,(A_1+A_2)\right)A_2>\left((1-p_1)\,\xi_1A_4\right)^2,$$

$$\frac{1}{3}\,(k+d)\left((\xi_2+d+\sigma)\,A_4-\frac{\lambda\Pi}{2d}\,(A_1+A_2)\right)A_3>\left((1-\vartheta_1)kA_4\right)^2,$$

$$\frac{4}{9}\,(k+d)\,dA_3>\left(\vartheta_1k\right)^2A_6,$$

$$\frac{1}{2}\left((\xi_2+d+\sigma)\,A_4-\frac{\lambda\Pi}{2d}\,(A_1+A_2)\right)(\vartheta_2+d)\ >\left(p_2\xi_2\right)^2A_5,$$

$$\frac{1}{3}\left(\left(\xi_2+d+\sigma\right)A_4-\frac{\lambda\Pi}{2d}\left(A_1+A_2\right)\right)d>\left(\left(1-p_2\right)\xi_2\right)^2A_6,$$

$$\frac{2}{3}\left(\vartheta_2+d\right)dA_5>{\vartheta_2}^2A_6.$$

Again choosing $A_1=A_2=A_4=1$, we get

$$A_3<\frac{\frac{2}{3}\left(\left(\xi_1+d\right)-\frac{\lambda\Pi}{2d}\right)\left(k+d\right)}{\left(p_1\xi_1\right)^2},$$

$$A_5<\frac{\frac{1}{2}\left(\left(\xi_2+d+\sigma\right)-\frac{\lambda\Pi}{d}\right)\left(\vartheta_2+d\right)}{\left(p_2\xi_2\right)^2},$$

$$A_6<\frac{\frac{1}{3}\left(\left(\xi_2+d+\sigma\right)-\frac{\lambda\Pi}{d}\right)d}{\left(\left(1-p_2\right)\xi_2\right)^2}.$$

Finally, disease free equilibrium point E_{df} is nonlinear stable if,

$$\left(\xi_1+d\right)>\frac{\lambda\Pi}{2d},$$

$$\left(\xi_2+d+\sigma\right)>\frac{\lambda\Pi}{d},$$

$$\frac{1}{2}\left(\left(\xi_1+d\right)-\frac{\lambda\Pi}{2d}\right)\left(\left(\xi_2+d+\sigma\right)-\frac{\lambda\Pi}{d}\right)>\left(\left(1-p_1\right)\xi_1\right)^2$$

otherwise unstable. □

Lemma 4.3. *The endemic equilibrium point* $E_e=\left(\overline{S},\,\overline{E},\,\overline{T_1},\,\overline{I},\,\overline{T_2},\,\overline{R}\right)$ *of the model* (2.1) *to* (2.6) *is linearly stable when* $R_0>1$ *and unstable otherwise.*

Proof . The endemic equilibrium point is given by $E_e=\left(\overline{S},\overline{E},\overline{T_1},\overline{I},\overline{T_2},\overline{R}\right)$
Now taking small perturbation around it,
$S=\overline{S}+y_1$, $E=\overline{E}+y_2$, $T_1=\overline{T_1}+y_3$, $I=\overline{I}+y_4$, $T_2=\overline{T_2}+y_5$ and $R=\overline{R}+y_6$ then linearized system of model equations (2.1) to (2.6) is given by,

$$\frac{dy_1}{dt}=-\lambda\left(y_4\overline{S}+y_1\overline{I}\right)-dy_1$$

$$\frac{dy_2}{dt}=\lambda\left(y_4\overline{S}+y_1\overline{I}\right)-\left(\xi_1+d\right)y_2$$

$$\frac{dy_3}{dt}=p_1\xi_1y_2-ky_3-dy_3$$

$$\frac{dy_4}{dt}=\left(1-p_1\right)\xi_1y_2+(1-\vartheta_1)ky_3-\left(\xi_2+d+\sigma\right)y_4$$

$$\frac{dy_5}{dt}=p_2\xi_2y_4-\left(\vartheta_2+d\right)y_5$$

$$\frac{dy_6}{dt}=\vartheta_1ky_3+\left(1-p_2\right)\xi_2y_4+\vartheta_2y_5-dy_6$$

The variational matrix of the above system around E_e is given by,

$$J_2 = \begin{bmatrix} -\left(\lambda\overline{I}+d\right) & 0 & 0 & -\lambda\overline{S} & 0 & 0 \\ \lambda\overline{I} & -\left(\xi_1+d\right) & 0 & \lambda\overline{S} & 0 & 0 \\ 0 & p_1\xi_1 & -\left(k+d\right) & 0 & 0 & 0 \\ 0 & \left(1-p_1\right)\xi_1 & \left(1-\vartheta_1\right)k & -\left(\xi_2+d+\sigma\right) & 0 & 0 \\ 0 & 0 & 0 & p_2\xi_2 & -\left(\vartheta_2+d\right) & 0 \\ 0 & 0 & \vartheta_1 k & \left(1-p_2\right)\xi_2 & \vartheta_2 & -d \end{bmatrix}$$

The characteristic equation of J_2 is as follows:

$$\left(\psi+d\right)\left(\psi+\left(\vartheta_2+d\right)\right)\left(\psi^4+D_1\psi^3+D_2\psi^2+D_3\psi+D_4\right)=0. \tag{4.2}$$

where,

$$D_1 = \left(\left(\lambda\overline{I}+d\right)+\left(\xi_1+d\right)+\left(k+d\right)+\left(\xi_2+d+\sigma\right)\right),$$

$$\begin{aligned} D_2 &= \left(\lambda\overline{I}+d\right)\left(\left(\xi_1+d\right)+\left(k+d\right)+\left(\xi_2+d+\sigma\right)\right)+\left(\xi_1+d\right)\left(k+d\right)+\left(\xi_1+d\right)\left(\xi_2+d+\sigma\right) \\ &\quad +\left(k+d\right)\left(\xi_2+d+\sigma\right)-\left(1-p_1\right)\xi_1\lambda\overline{S} \\ &= \left(\left(\xi_1+d\right)+\left(k+d\right)+\left(\xi_2+d+\sigma\right)\right)dR_0+\left(\xi_1+d\right)\left(k+d\right)+\left(k+d\right)\left(\xi_2+d+\sigma\right)+\frac{p_1\left(1-\vartheta_1\right)k\xi_1\lambda\Pi}{\left(k+d\right)dR_0}, \end{aligned}$$

$$\begin{aligned} D_3 &= -d\left(1-p_1\right)\xi_1\lambda\overline{S}+\left(\lambda\overline{I}+d\right)\left(\left(\xi_1+d\right)\left(k+d\right)+\left(k+d\right)\left(\xi_2+d+\sigma\right)+\left(\xi_1+d\right)\left(\xi_2+d+\sigma\right)\right) \\ &\quad +\left(\xi_1+d\right)\left(k+d\right)\left(\xi_2+d+\sigma\right)-\left(\left(k+d\right)\left(1-p_1\right)+p_1\left(1-\vartheta_1\right)k\right)\xi_1\lambda\overline{S} \\ &= \frac{p_1 d\left(1-\vartheta_1\right)k\xi_1\lambda\Pi}{\left(k+d\right)dR_0}+\left(\left(\xi_1+d\right)\left(k+d\right)+\left(k+d\right)\left(\xi_2+d+\sigma\right)+\left(\xi_1+d\right)\left(\xi_2+d+\sigma\right)\right)d\left(R_0-1\right) \\ &\quad +d\left(\left(\xi_1+d\right)\left(k+d\right)+\left(k+d\right)\left(\xi_2+d+\sigma\right)\right), \end{aligned}$$

$$D_4 = \left(\xi_1+d\right)\left(k+d\right)\left(\xi_2+d+\sigma\right)\lambda\overline{I} = \left(\xi_1+d\right)\left(k+d\right)\left(\xi_2+d+\sigma\right)d\left(R_0-1\right).$$

It is clear that,
$D_1>0$, $D_2>0$, $D_3>0$and $D_4>0$ when $R_0>1$.
Clearly two roots of equation (4.2) are negative and using Descartes' rule of signs remaining four characteristic roots of characteristic equation (4.2) will be negative if $R_0>1$.Hence all the six roots of equation (4.2) are negative if $R_0>1$. Consequently, the endemic equilibrium point E_e is linearly stable if $R_0>1$. However, it is unstable if $R_0<1$. □

Lemma 4.4. *The endemic equilibrium point E_e of model (2.1) to (2.6) is non-linearly stable under following conditions -*

$$\frac{4}{3}\left(\lambda\overline{I}+d+\frac{\Pi\lambda}{2d}\right)\left(\xi_1+d+\frac{\Pi\lambda}{2d}\right)B_1>\left(\lambda\overline{I}\right)^2B_2,$$

$$\frac{4}{9}\left(\xi_1+d+\frac{\Pi\lambda}{2d}\right)\left(k+d\right)B_2>\left(p_1\xi_1\right)^2B_3,$$

$$\frac{1}{3}\left(\xi_1+d+\frac{\Pi\lambda}{2d}\right)\left(\left(\xi_2+d+\sigma\right)B_4+\frac{\Pi\lambda B_1}{2d}+\frac{\Pi\lambda B_2}{2d}\right)B_2>\left(\left(1-p_1\right)\xi_1B_4\right)^2,$$

$$\frac{1}{3}(k+d)\left((\xi_2+d+\sigma)B_4+\frac{\Pi\lambda B_1}{2d}+\frac{\Pi\lambda B_2}{2d}\right)B_3>\left((1-\vartheta_1)kB_4\right)^2,$$

$$\frac{4}{9}(k+d)dB_3>(\vartheta_1 k)^2B_6,$$

$$\frac{1}{2}\left((\xi_2+d+\sigma)B_4+\frac{\Pi\lambda B_1}{2d}+\frac{\Pi\lambda B_2}{2d}\right)(\vartheta_2+d)>(p_2\xi_2)^2B_5,$$

$$\frac{1}{3}\left((\xi_2+d+\sigma)B_4+\frac{\Pi\lambda B_1}{2d}+\frac{\Pi\lambda B_2}{2d}\right)d>\left((1-p_2)\xi_2\right)^2B_6,$$

$$\frac{2}{3}(\vartheta_2+d)dB_5>{\vartheta_2}^2B_6 \textit{ otherwise unstable.}$$

Proof . The endemic equilibrium point is given by $E_e=\left(\overline{S},\overline{E},\overline{T_1},\overline{I},\overline{T_2},\overline{R}\right)$
Now taking small perturbation around it,
$S=\overline{S}+y_1$, $E=\overline{E}+y_2$, $T_1=\overline{T_1}+y_3$, $I=\overline{I}+y_4$, $T_2=\overline{T_2}+y_5$ and $R=\overline{R}+y_6$ then system of model equations (2.1) to (2.6) is given by,

$$\frac{dy_1}{dt}=-\lambda\left(y_4\overline{S}+y_1\overline{I}+y_1y_4\right)-dy_1$$

$$\frac{dy_2}{dt}=\lambda\left(y_4\overline{S}+y_1\overline{I}+y_1y_4\right)-(\xi_1+d)y_2$$

$$\frac{dy_3}{dt}=p_1\xi_1y_2-ky_3-dy_3$$

$$\frac{dy_4}{dt}=(1-p_1)\xi_1y_2+(1-\vartheta_1)ky_3-(\xi_2+d+\sigma)y_4$$

$$\frac{dy_5}{dt}=p_2\xi_2y_4-(\vartheta_2+d)y_5$$

$$\frac{dy_6}{dt}=\vartheta_1ky_3+(1-p_2)\xi_2y_4+\vartheta_2y_5-dy_6$$

Now consider a positive definite function

$$V=\frac{1}{2}(B_1y_1^2+B_2y_2^2+B_3y_3^2+B_4y_4^2+B_5y_5^2+B_6y_6^2)$$

Then using the above system of equations in $\frac{dV}{dt}$, we get
$\frac{dV}{dt}=B_1y_1\left(-\lambda y_4\overline{S}-\lambda y_1\overline{I}-\lambda y_1y_4-dy_1\right)+B_2y_2\left(\lambda y_4\overline{S}+\lambda y_1\overline{I}+\lambda y_1y_4-(\xi_1+d)y_2\right)$

$+B_3y_3\left(p_1\xi_1y_2-ky_3-dy_3\right)+B_4y_4\left((1-p_1)\xi_1y_2+(1-\vartheta_1)ky_3-(\xi_2+d+\sigma)y_4\right)$

$+B_5y_5\left(p_2\xi_2y_4-(\vartheta_2+d)y_5\right)+B_6y_6\left(\vartheta_1ky_3+(1-p_2)\xi_2y_4+\vartheta_2y_5-dy_6\right).$

On solving, we get
$\frac{dV}{dt}=\left[-\lambda B_1\overline{S}y_1y_4-\lambda B_1\overline{I}{y_1}^2-(\lambda B_1y_1)y_1y_4-dB_1{y_1}^2\right]+\left[\lambda B_2\overline{S}y_2y_4+\lambda B_2\overline{I}y_1y_2+(\lambda B_2y_2)y_1y_4\right.$

$\left.-(\xi_1+d)B_2{y_2}^2\right]+\left[p_1\xi_1B_3y_2y_3-(k+d)B_3{y_3}^2\right]+\left[(1-p_1)\xi_1B_4y_2y_4+(1-\vartheta_1)kB_4y_3y_4\right.$

$\left.-(\xi_2+d+\sigma)B_4{y_4}^2\right]+\left[p_2\xi_2B_5y_4y_5-(\vartheta_2+d)B_5{y_5}^2\right]+\left[\vartheta_1kB_6y_3y_6+(1-p_2)\xi_2B_6y_4y_6\right.$

$\left.+\vartheta_2B_6y_5y_6-dB_6{y_6}^2\right].$

On rearranging and using the inequality, $\pm 2\,x\,y \leq x^2 + y^2$ and also using the region Ω on the RHS of $\frac{dV}{dt}$, we obtain;

$$\begin{aligned}\frac{dV}{dt} \leq -\big[&\left(\lambda\overline{I}+d\right)B_1{y_1}^2 + \tfrac{\Pi\lambda B_1}{2d}\left({y_1}^2+{y_4}^2\right) - \lambda\overline{I}B_2y_1y_2 \;+\; \left(\xi_1+d\right)B_2{y_2}^2 + \big(\tfrac{\Pi\lambda B_2}{2d}\left({y_2}^2+{y_4}^2\right)\\ &-\left(1-p_1\right)\xi_1B_4y_2y_4\big) - p_1\xi_1B_3y_2y_3 + \left(k+d\right)B_3{y_3}^2 - \left(1-\vartheta_1\right)kB_4y_3y_4 - \vartheta_1kB_6y_3y_6\\ &+\left(\xi_2+d+\sigma\right)B_4{y_4}^2 - p_2\xi_2B_5y_4y_5 + \left(\vartheta_2+d\right)B_5{y_5}^2 - \left(1-p_2\right)\xi_2B_6y_4y_6 - \vartheta_2B_6y_5y_6\\ &+d\,B_6{y_6}^2\big].\end{aligned}$$

Further, we have

$$\begin{aligned}\frac{dV}{dt} \leq -\big[&\left(\lambda\overline{I}+d+\tfrac{\Pi\lambda}{2d}\right)B_1{y_1}^2 - \lambda\overline{I}B_2y_1y_2 \;+\; \left(\xi_1+d+\tfrac{\Pi\lambda}{2d}\right)B_2{y_2}^2 - \left(1-p_1\right)\xi_1B_4y_2y_4\\ &-p_1\xi_1B_3y_2y_3 + \left(k+d\right)B_3{y_3}^2 - \left(1-\vartheta_1\right)kB_4y_3y_4 - \vartheta_1kB_6y_3y_6 + \left(\left(\xi_2+d+\sigma\right)B_4\right.\\ &\left.+\frac{\Pi\lambda B_1}{2d}+\frac{\Pi\lambda B_2}{2d}\right){y_4}^2 - p_2\xi_2B_5y_4y_5 + \left(\vartheta_2+d\right)B_5{y_5}^2 - \left(1-p_2\right)\xi_2B_6y_4y_6 - \vartheta_2B_6y_5y_6\\ &+d\,B_6{y_6}^2\big].\end{aligned}$$

This implies,

$$\begin{aligned}\frac{dV}{dt} \leq \big(&-\left[b_{11}{y_1}^2 - b_{12}y_1y_2 \;+\; \tfrac{b_{22}}{3}{y_2}^2\right] + \left[\tfrac{b_{22}}{3}{y_2}^2 - b_{23}y_2y_3 + \tfrac{b_{33}}{3}{y_3}^2\right]\\ &+\left[\frac{b_{22}}{3}{y_2}^2 - b_{24}y_2y_4 + \frac{b_{44}}{4}{y_4}^2\right] + \left[\frac{b_{33}}{3}{y_3}^2 - b_{34}y_3y_4 + \frac{b_{44}}{4}{y_4}^2\right]\\ &+\left[\frac{b_{33}}{3}{y_3}^2 - b_{36}y_3y_6 + \frac{b_{66}}{3}{y_6}^2\right] + \left[\frac{b_{44}}{4}{y_4}^2 - b_{45}y_4y_5 + \frac{b_{55}}{2}{y_5}^2\right]\\ &+\left[\frac{b_{44}}{4}{y_4}^2 - b_{46}y_4y_6 + \frac{b_{66}}{3}{y_6}^2\right] + \left[\frac{b_{55}}{2}{y_5}^2 - b_{56}y_5y_6 + \frac{b_{66}}{3}{y_6}^2\right]\end{aligned}$$

$b_{11} = \left(\lambda\overline{I}+d+\frac{\Pi\lambda}{2d}\right)B_1$, $b_{12} = \lambda\overline{I}B_2$, $b_{22} = \left(\xi_1+d+\frac{\Pi\lambda}{2d}\right)B_2$, $b_{23} = p_1\xi_1B_3$, $b_{24} = \left(1-p_1\right)\xi_1B_4$,
$b_{33} = \left(k+d\right)B_3, b_{34} = \left(1-\vartheta_1\right)kB_4, b_{36} = \vartheta_1kB_6, b_{44} = \left(\left(\xi_2+d+\sigma\right)B_4 + \frac{\Pi\lambda B_1}{2d} + \frac{\Pi\lambda B_2}{2d}\right)$,
$b_{45} = p_2\xi_2B_5, b_{55} = \left(\vartheta_2+d\right)B_5$, $b_{46} = \left(1-p_2\right)\xi_2B_6, b_{56} = \vartheta_2B_6, b_{66} = dB_6$.

Hence by Lyapunov's direct method of stability, we conclude that the endemic equilibrium point E_e is non-linearly stable if following conditions are satisfied.

$$\frac{4}{3}\left(\lambda\overline{I}+d+\frac{\Pi\lambda}{2d}\right)\left(\xi_1+d+\frac{\Pi\lambda}{2d}\right)B_1 > \left(\lambda\overline{I}\right)^2B_2,$$

$$\frac{4}{9}\left(\xi_1+d+\frac{\Pi\lambda}{2d}\right)\left(k+d\right)B_2 > \left(p_1\xi_1\right)^2B_3,$$

$$\frac{1}{3}\left(\xi_1+d+\frac{\Pi\lambda}{2d}\right)\left(\left(\xi_2+d+\sigma\right)B_4+\frac{\Pi\lambda B_1}{2d}+\frac{\Pi\lambda B_2}{2d}\right)B_2 > \left(\left(1-p_1\right)\xi_1B_4\right)^2,$$

$$\frac{1}{3}\left(k+d\right)\left(\left(\xi_2+d+\sigma\right)B_4+\frac{\Pi\lambda B_1}{2d}+\frac{\Pi\lambda B_2}{2d}\right)B_3 > \left(\left(1-\vartheta_1\right)kB_4\right)^2,$$

$$\frac{4}{9}\left(k+d\right)dB_3 > \left(\vartheta_1k\right)^2B_6\,,$$

$$\frac{1}{2}\left(\left(\xi_2+d+\sigma\right)B_4+\frac{\Pi\lambda B_1}{2d}+\frac{\Pi\lambda B_2}{2d}\right)\left(\vartheta_2+d\right)>\left(p_2\xi_2\right)^2B_5,$$

$$\frac{1}{3}\left(\left(\xi_2+d+\sigma\right)B_4+\frac{\Pi\lambda B_1}{2d}+\frac{\Pi\lambda B_2}{2d}\right)d>\left(\left(1-p_2\right)\xi_2\right)^2B_6,$$

$$\frac{2}{3}\left(\vartheta_2+d\right)dB_5>{\vartheta_2}^2B_6.$$

Consequently, the endemic equilibrium point E_e is non-linearly stable under the above mentioned conditions otherwise unstable. □

5. Optimal Control Problem

In this section, we propose an optimal control problem, which influences to swine flu transmission demonstrated in the model (2.1) to (2.6). Here, our purpose is to find the optimal control $U\left(t\right)=\left(p_1\left(t\right),\xi_2\left(t\right)\right)^T\in R^2$. In the present manuscript, p_1 fraction of exposed population availing initial treatment and ξ_2 conversion rate from infected to either treated class II or recovered class are the parameters, that can minimize the number of exposed and infected population. We are using Pontryagin's Minimum Principle to study the optimal values of parameters that would be required to control the swine flu transmission. Now suppose the objective functional J, which minimizes the number of exposed and infected population and the cost to control p_1 and ξ_2. here, we approach to values of p_1 and ξ_2 both that are used to optimize the objective function J. Thus, the objective function to be minimized is given by-

$$J\left(p_1\left(t\right),\xi_2\left(t\right)\right)=\int_o^{t_f}\left[A_1E\left(t\right)+A_2I\left(t\right)+\frac{A_3}{2}\left(p_1\right)^2+\frac{A_4}{2}\left(\xi_2\right)^2\right]dt \tag{5.1}$$

The parameters $A_1>0,\ A_2>0,\ A_3>0$ and $A_4>0$ are dimensionless weight constants. We obtain an optimal control parameters ${p_1}^*$ and ${\xi_2}^*$ such that

$$J\left({p_1}^*,{\xi_2}^*\right)=\min_{p_1,\xi_2}\left[J\left(p_1,\xi_2\right)|p_1,\xi_2\in U\right]$$

Where $U=\{p_1,\ \xi_2|\ 0\le p_1,\ \xi_2\le 1\,and\,t\in[0,t_f]\}$
Using Pontryagin's Minimum Principle, model system (2.1)-(2.6) and (5.1) are changed to a problem of minimizing point-wise a Hamiltonian function $H$with respect to p_1 and ξ_2. For this, we introduce Lagrangian function for the problem is defined by,

$$L\left(E,I,p_1,\xi_2\right)=A_1E\left(t\right)+A_2I\left(t\right)+\frac{A_3}{2}\left(p_1\right)^2+\frac{A_4}{2}\left(\xi_2\right)^2$$

and also we determine the Hamiltonian function as follow,

$$H=A_1E\left(t\right)+A_2I\left(t\right)+\tfrac{A_3}{2}\left(p_1\right)^2+\tfrac{A_4}{2}\left(\xi_2\right)^2+\lambda_1\left[\Pi-\lambda SI-dS\right]+\lambda_2\left[\lambda SI-\xi_1E-dE\right]$$

$$+\lambda_3\left[p_1\xi_1E-kT_1-dT_1\right]+\lambda_4\left[\left(1-p_1\right)\xi_1E+\left(1-\vartheta_1\right)kT_1-\xi_2I-\left(d+\sigma\right)I\right]$$

$$+\lambda_5\left[p_2\xi_2I-\vartheta_2T_2-dT_2\right]+\lambda_6\left[\vartheta_1kT_1+\left(1-p_2\right)\xi_2I+\vartheta_2T_2-dR\right].$$

Where $\lambda_1,\ \lambda_2,\ \lambda_3,\ \lambda_4,\ \lambda_5,\ \lambda_6$ are the adjoint variables or co-state variables.

Lemma 5.1. *There exists optimal controls p_1^* and ξ_2^* in U such that $J\left({p_1}^*,{\xi_2}^*\right)=\min_{p_1,\xi_2}\left[J\left(p_1,\xi_2\right)|p_1,\xi_2\in U\right]$ subject to the model system (2.1) to (2.6) and for all $t\in[0,t_f]$.*

Proof . To find the system of differential equations with respect to the associated adjoint variables, we differentiate the Hamiltonian with respect to each of the state variables and obtain the following,

$$\frac{d\lambda_1}{dt} = \lambda_1(\lambda I + S) - \lambda_2(\lambda I) \tag{5.2}$$

$$\frac{d\lambda_2}{dt} = -A_1 - \lambda_2(\xi_1 + d)\xi_1 - \lambda_3(p_1\xi_1) - \lambda_4((1-p_1)\xi_1) \tag{5.3}$$

$$\frac{d\lambda_3}{dt} = \lambda_3(k+d) - \lambda_4((1-\vartheta_1)k) - \lambda_6(\vartheta_1 k) \tag{5.4}$$

$$\frac{d\lambda_4}{dt} = -A_2 + \lambda_1(\lambda S) - \lambda_2(\lambda S) + \lambda_4(\xi_2 + d + \sigma) - \lambda_5(p_2\xi_2) - \lambda_6((1-p_2)\xi_2) \tag{5.5}$$

$$\frac{d\lambda_5}{dt} = \lambda_5(\vartheta_2 + d) - \lambda_6(\vartheta_2) \tag{5.6}$$

$$\frac{d\lambda_6}{dt} = \lambda_6(d) \tag{5.7}$$

with transversality condition,

$$\lambda_1(T) = \lambda_2(T) = \lambda_3,(T) = \lambda_4,(T) = \lambda_5(T) = \lambda_6,(T) = 0 \tag{5.8}$$

For above mentioned transversality condition (5.8), the following hold-

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S}, \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial E}, \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial T_1}, \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial I}, \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial T_2}, \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial R} \tag{5.9}$$

The optimal controls can be distinguished by the following expressions-

$$p_1{}^*(t) = \max\left\{0, \min\left(\hat{p_1}(t), 1\right)\right\},\ \xi_2{}^*(t) = \max\left\{0, \min\left(\hat{\xi_2}(t), 1\right)\right\}.$$

Further, upper and lower bounds of the controls p_1 and ξ_2 are 0 and 1 respectively, on this basis we can conclude the following:

$$p_1{}^* = \begin{cases} 0 & if\, \hat{p_1} \le 0, \\ \hat{p_1} & if\ 0 < \hat{p_1} < 1, \\ 1 & \text{if } \hat{p_1} \ge 1, \end{cases} \quad \xi_2{}^* = \begin{cases} 0 & if\, \hat{\xi_2} \le 0, \\ \hat{\xi_2} & if\ 0 < \hat{\xi_2} < 1, \\ 1 & \text{if } \hat{\xi_2} \ge 1, \end{cases}$$

The control parameter $p_1^* = 1$ indicates that there is highest reduction in exposed population, i.e. They should go for initial treatment of swine flu moreover $\xi_2^* = 1$ highlight the highest decline in infected population, i.e. either they will go for special treatment and hospitalized or get recover from swine flu. It is also pointed out that ξ_2^* most effective control parameter for protecting society from swine flu infection

differentiating H with respect to each of the permissible controls p_1 and ξ_2 , we have

$$\frac{\partial H}{\partial p_1} = A_3(p_1) + \lambda_3(\xi_1 E) - \lambda_4(\xi_1 E)$$

$$\frac{\partial H}{\partial \xi_2} = A_4(\xi_2) - \lambda_4(I) + \lambda_5(p_2 I) + \lambda_6((1-p_2)I).$$

The control categorization, $\hat{p_1}$ and $\hat{\xi_2}$ of the optimal controls $p_1{}^*$ and $\xi_2{}^*$ are obtained by substituting $\frac{\partial H}{\partial p_1} = \frac{\partial H}{\partial \xi_2} = 0$ which gives,

$$\hat{p_1} = \frac{(\lambda_4 - \lambda_3)(\xi_1 E)}{A_3}, \quad \hat{\xi_2} = \frac{(\lambda_4 - \lambda_5(p_2) - \lambda_6(1-p_2))I}{A_4}.$$

□

6. Numerical simulation

Numerical facts are established for the existence and stability properties of the equilibrium points. Using MATLAB R2014a (32-bit) software, the model system (2.1) to (2.6) is simulated for the set of parameters values to review the effect of the control measures on infected population.

For the analysis of swine flu transmission with early treatment programs in this section, we choose set-1 for values of parameters given below-
$\Pi = 1.5$, $\lambda = 0.0035$, $p_1 = 0.1$, $p_2 = 0.2$, $\xi_1 = 0.6$, $\xi_2 = 0.25$, $k = 0.008$, $\vartheta_1 = 0.01$, $\vartheta_2 = 0.01$, $d = 0.02$ and $\sigma = 0.01$. These numerical values of these parameters are selected only for illustrative purpose, for set-1 the value of $R_0 = 0.888387 < 1$ and the disease free equilibrium point is $E_{df} = (75, 0, 0, 0, 0, 0)$. Figure 2 depicts all species versus time, it is cleared that all the trajectories tends towards the disease free condition, which exhibit that the disease free equilibrium is locally asymptotically stable. Moreover, we take all parameters are same as mentioned in set-1 except $\xi_2 = 0.05$.Then for these values of parameters, the value of $R_0 = 3.10935 > 1$ and the endemic equilibrium point is $E_e = (24.1208, 1.64127, 0.984759, 12.0535, 4.01782, 26.1552)$ .In Figure 3, it is pointed out that endemic equilibrium is stable under these values of parameters. Further, we take set-2 for these values of parameters;
$\Pi = 1.5$, $\lambda = 0.0035$, $p_1 = 0.1$, $p_2 = 0.2$, $\xi_1 = 0.6$, $\xi_2 = 0.1$, $k = 0.008$, $\vartheta_1 = 0.01$, $\vartheta_2 = 0.01$, $d = 0.02$ and $\sigma = 0.01$. In Figure 4, it is shown that as the transmission rate of disease (λ) increases then the value of R_0 increases and also infected population increases. Infection does not persist in the environment. Consequentially, it does not spread in the population. Corresponding equilibrium points are stated in Table 4 given below-

Table 4: Value of R_0 and equilibrium point for various values of ($\boldsymbol{\lambda}$)

Transmission rate of disease($\boldsymbol{\lambda}$)	**Basic reproduction number(R_0)**	**Equilibrium point**
0.001	0.5467	$E_{df} = (75, 0, 0, 0, 0, 0)$
0.0035	1.91345	$E_e = (39.1962, 1.15496, 0.69297, 5.21971, 3.47981, 22.6465)$
0.007	3.8269	$E_e = (19.5981, 1.78716, 1.07229, 8.07685, 5.38457, 35.0426)$
0.03	16.401	$E_e = (4.57289, 2.27184, 1.36311, 10.2673, 6.84489, 44.5463)$

Again, for the same values of parameters; it is shown that as (p_1) increases then the value of R_0 decreases and also infection population decreases, see Figure 5. Related values of R_0 and equilibrium points are mentioned in Table 5 as follows-

Table 5: Value of R_0 and equilibrium point for various values of ($\mathbf{p_1}$)

Fraction of exposed availing initial treatment ($\mathbf{p_1}$)	**Basic reproduction number(R_0)**	**Equilibrium point**
0.2	1.8728	$E_e = (40.0469, 1.12752, 1.35302, 4.98745, 3.32497, 21.6664)$
0.4	1.79151	$E_e = (41.864, 1.0689, 2.56536, 4.52294, 3.01529, 19.702)$
0.6	1.71022	$E_e = (43.8539, 1.00471, 3.61696, 4.05842, 2.70561, 17.7312)$
0.8	1.62893	$E_e = (46.0424, 0.934116, 4.48376, 3.5939, 2.39594, 15.7529)$

Similarly, for the same values of parameters; it is shown that as (ξ_2) increases then the value of R_0 decreases and also infection population decreases, see Figure 6. Related values of R_0 and equilibrium points are given in Table 6 given below-

Table 6: Value of R_0 and equilibrium point for various values of ($\boldsymbol{\xi_2}$)

Conversion rate from infected to treated II or recovered ($\boldsymbol{\xi_2}$)	**Basic reproduction number (R_0)**	**Equilibrium point**
0.05	3.10935	E_e = (24.1208, 1.64127, 0.984759, 12.0535, 4.01782, 26.1552)
0.1	1.91345	E_e = (39.1962, 1.15496, 0.69297, 5.21971, 3.47981, 22.6465)
0.15	1.38194	E_e = (54.2717, 0.668655, 0.401193, 2.18249, 2.18249, 14.2022)
0.25	0.888387	E_{df} = (75, 0, 0, 0, 0, 0)

Numerical simulation for optimal controls is also performed. The impact of the optimal control strategies on swine flu transmission is depicted in Figure 7.To urge on the lower and upper bounds for the controls, we assumed that it is realistically impossible to have 100% effective controls. Consequently the upper bounds for p_1 and ξ_2 will lie between 0 and 1 respectively. We choose the following parametric values-
$\Pi = 1.5$, $\lambda = 0.0035$, $p_2 = 0.2$, $\xi_1 = 0.6$, $k = 0.008$, $\vartheta_1 = 0.01$, $\vartheta_2 = 0.01$, $d = 0.02$ and $\sigma = 0.01$.

Associated values of R_0 and equilibrium points are given in Table 7 also a plot for time versus infected population is illustrated without control, with any one control and both the controls in Figure 7.

Table 7: Value of R_0 and equilibrium point for controls ($\mathbf{p_1}$)and ($\boldsymbol{\xi_2}$)

Controls ($\mathbf{p_1}$)and ($\boldsymbol{\xi_2}$)	**Basic reproduction number(R_0)**	**Equilibrium point**
$p_1 = 0$and $\xi_2 = 0$	8.46774	E_e = (8.85714, 2.13364, 0, 42.6728, 0, 0)
$p_1 = 0$and $\xi_2 = 1$	0.246633	E_{df} = (75, 0, 0, 0, 0, 0)
$p_1 = 1$and $\xi_2 = 0$	6.70645	E_e = (11.1833, 2.0586, 12.3516, 32.6083, 0, 0.494065)
$p_1 = 1$and $\xi_2 = 1$	0.195334	E_{df} = (75, 0, 0, 0, 0, 0)

Numerical simulation for sensitivity indices is indicated in Table 3. The sensitivity indices for the values of Π, λ, ξ_1 and k are positive in sign whereas the sensitivity indices for the values of p_1, υ_1 and ξ_2 are negative in sign. We can easily notice on the basis of indices sign that how these parameters should be managed to control swine flu epidemic as follows:
1. Reduce the recruitment rate Π of susceptible.
2. Reduce the transmission rate of disease λ by using mask or availing appropriate treatment.
3. Reduce the conversion rate ξ_1 from exposed to treated class I or infected class so that disease could not move further.
4. Reduce the development of full blown infected of treated class I, k i.e. efficiency of initial treatment should be enhanced.
5. Increase the fraction p_1 of exposed population joining initial treatment for swine flu by proper awareness.
6. Increase the recovery rate υ_1 by maintaining good physical condition and having proper diet.

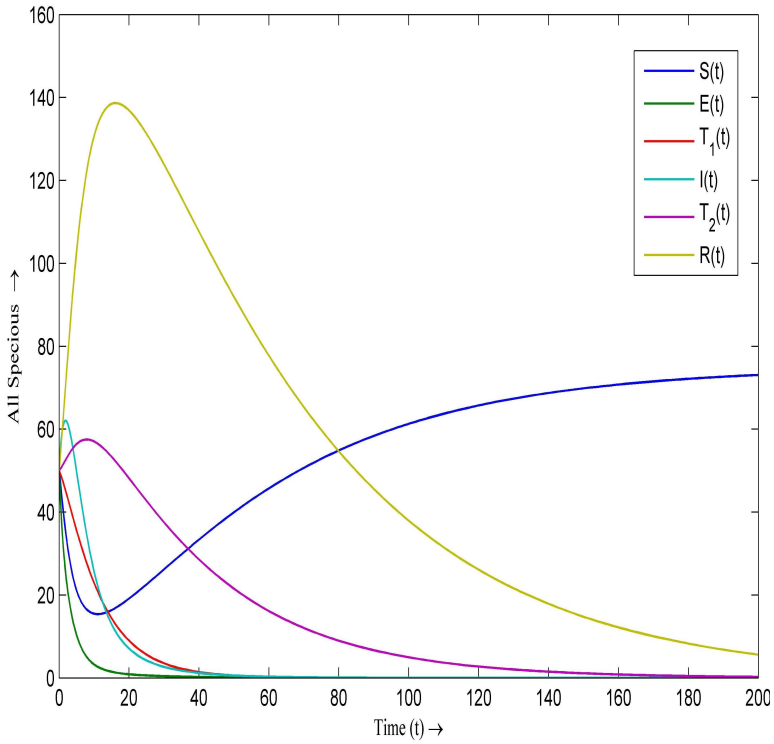

Figure 2: Time (t) versus all species for $R_0 = 0.888387 < 1$

7. Increase the conversion rate from infected to treated class II or recovery ξ_2 by improving the treatment i.e. special care or hospitalization.

These numerical simulations are performed to support the theoretical results. Relevant figures are given below to assist the numerical simulations.

7. Conclusion

In present manuscript, we have analyzed a mathematical model on the transmission dynamics of swine flu with early treatment programs. The model consists of nonlinear ordinary differential equations for six different interacting populations. It is assumed that swine flu spreads due to direct or indirect interaction between susceptible and infectious and by availing early treatment programs, risk of infection can be minimized. The behavior of the suggested swine flu model with early treatment programs can be determined by calculating the basic reproduction number (R_0) and it has been derived that for $R_0 < 1$ the disease-free equilibrium point E_{df} is locally asymptotically stable otherwise unstable. It is also observed that swine flu will be perished from the community if the basic reproduction number is less than unity. We have also noticed that for $R_0 > 1$ unique endemic equilibrium point E_e exists and is stable otherwise unstable. Awareness about the status of swine flu and treatment policies may reduce the risk of infection in the individuals. From the sensitivity analysis it is cleared that the recruitment rate, transmission rate, conversion rate of exposed and development rate of full blown infected of treated class I i.e. Π, λ, ξ_1 and k are directly proportional to R_0 whereas fraction of population joining treatment I, recovery rate, conversion rate of infected and mortality rates i.e. p_1, υ_1 and ξ_2 are inversely proportional to R_0, see Table 3. Optimal control values for fraction of exposed population joining treatment I and infected populations joining treatment II or

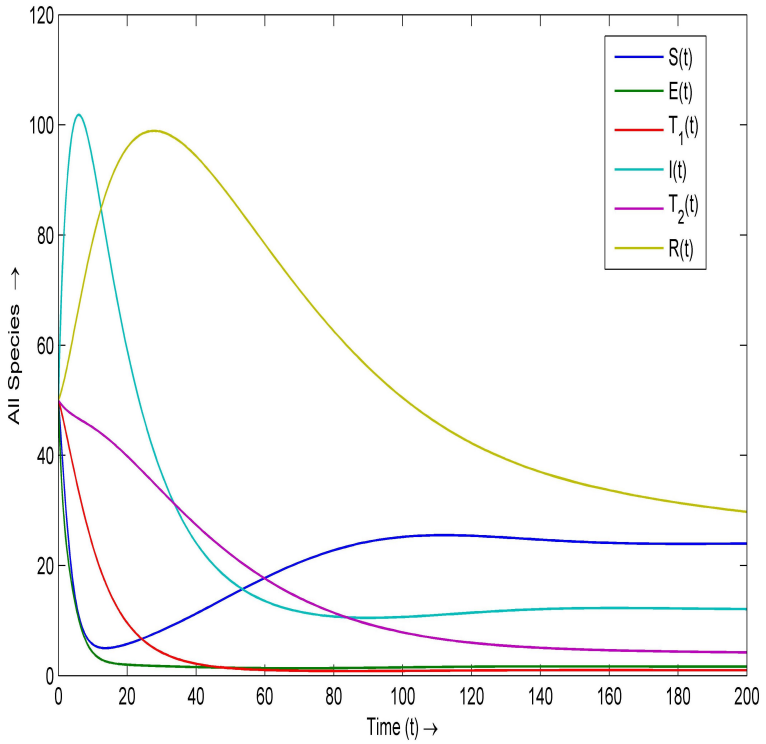

Figure 3: Time (t) versus all species for $R_0 = 3.10935 > 1$

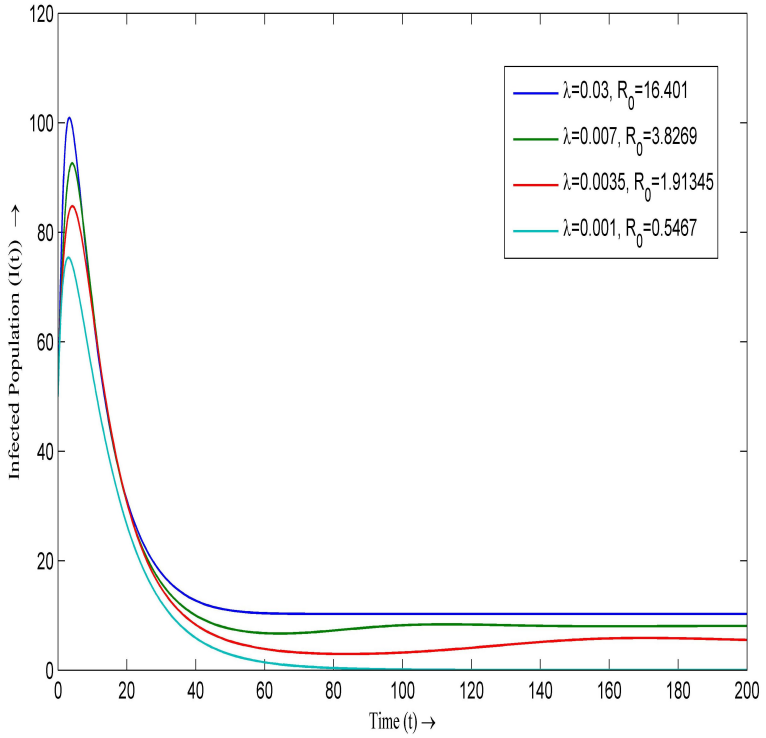

Figure 4: Time (t) versus infected population $I\,(t)$for various values of (λ)

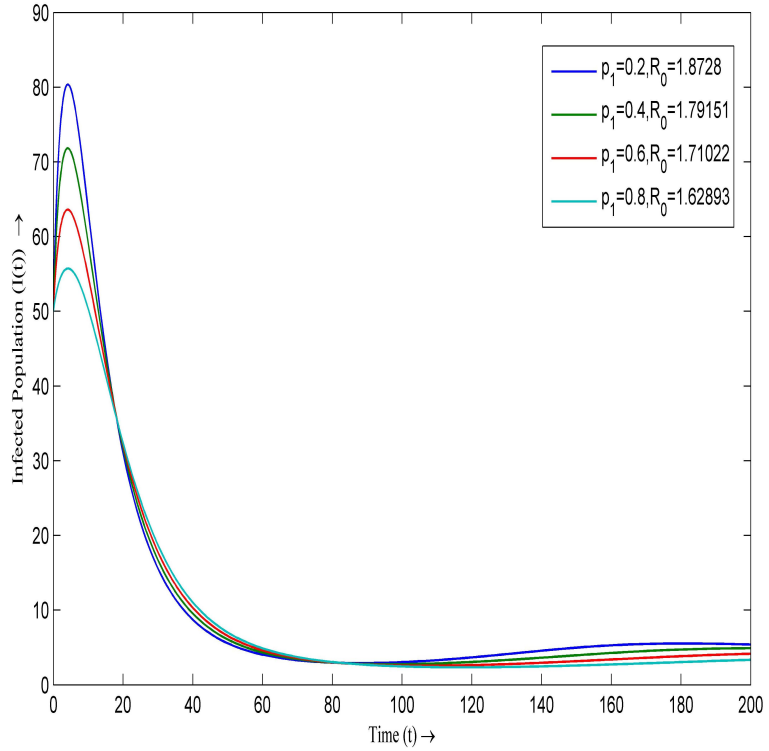

Figure 5: Time (t) versus infected population $I\,(t)$for various values of (ξ_1)

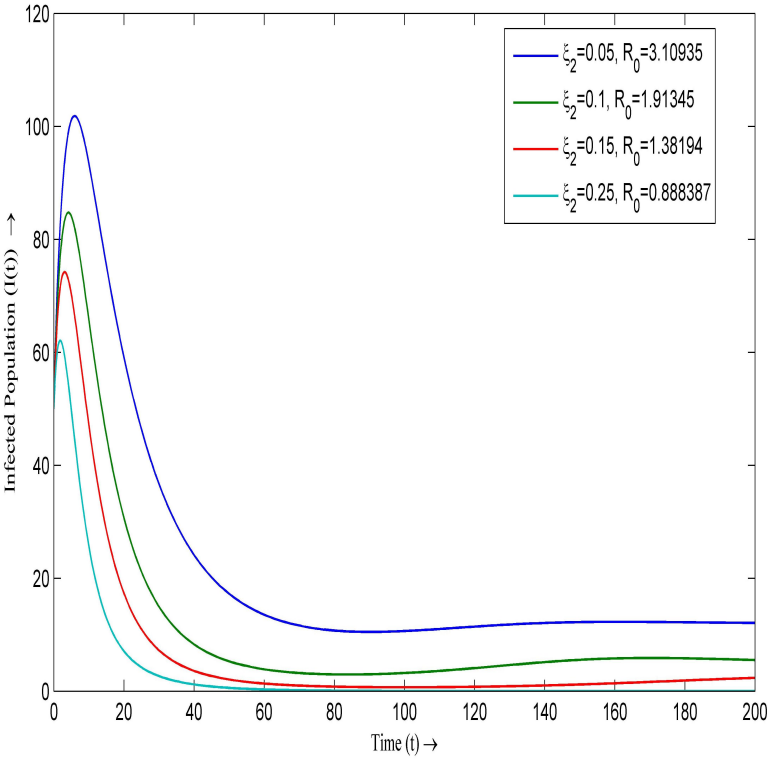

Figure 6: Time (t) versus infected population $I\,(t)$for various values of (ξ_2)

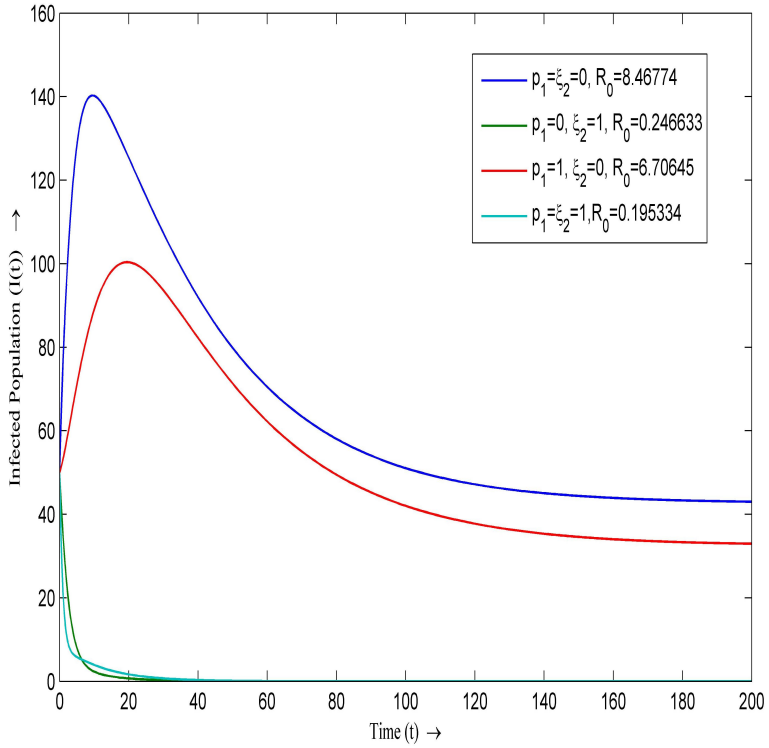

Figure 7: Time (t) versus infected population $I(t)$ for controls $(p_1)$and (ξ_2)

recovery in the outlined swine flu model has also been argued. We have used Pontryagin's Minimum Principle method, to minimize the number of infected human population and cost of the controlling efforts. Thus, we have studied the impact of the controls including their values zero and one on infected population graphically, shown in Figure 7. It is seen that optimal value of ξ_2 is the most effective strategies for swine flu control. Finally, we find that the treatment policies are essential for the reduction of swine flu infection in the outlined model.

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