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Mathematical Model of Tuberculosis with Drug Resistance to the First and Second Line of Treatment

Virendra Kumar Gupta[3] <vkg61@yahoo.co.in>
Sandeep Kumar Tiwari[1] <skt_tiwari75@yahoo.co.in>
Shivram Sharma[2] <shivramsharmajnu85@gmail.com>
Lakhan Nagar[1,*] <lakhannagar988@gmail.com>

[1]*School of Studies in Mathematics, Vikram University, Ujjain, (M.P.)*
[2]*Department of Mathematics, Medi Caps University, Indore, (M.P.)*
[3]*Govt. Madhav Science P.G., College, Ujjain (M.P.)*

Abstract - This study proposed a mathematical model of tuberculosis with drug resistance to a first and second line of treatment. The basic reproduction number for the model using next generation method is obtained. The equilibrium point of the model was investigated and also found the global stability of the disease free equilibrium and endemic equilibrium for the model. This study shows the effect of resistance rate of the first and second line of treatment to the infected and resistant population. If basic reproduction number is less than one, the disease free equilibrium is globally asymptotically stable and if basic reproduction number is greater than one, then the endemic equilibrium is a globally asymptotically stable.

Keywords *- Tuberculosis, Mycobacterium tuberculosis bacteria [Mtb], developed multi-drug resistant [MDR], Basic reproduction number, Stability.*

1. Introduction

Tuberculosis is an airborne disease caused by Mycobacterium tuberculosis bacteria (Mtb). Ullah et al. [8] discuss a general SIR epidemic model which represents the direct transmission of infectious disease. It is an ancient disease with evidence of its existence being found in relics from ancient Egypt, India and China [1]. Today, this disease ranks as the second leading cause of morbidity and mortality in the world from a single infectious agent, after the human immunodeficiency virus (HIV) according to Daniel. [10] Interestingly, about one third of the world's population is infected with Mycobacterium tuberculosis bacteria with approximately nine million people developing active tuberculosis and up to nearly two million people worldwide die from the disease every year. Approximately 480,000 people

[*]*Corresponding Author.*

developed multidrug resistant (MDR) tuberculosis globally with 210,000 of those who developed MDR tuberculosis succumbing to it. In addition to posing a, major health concern to low and middle income countries, tuberculosis affect economic growth negatively. [3] Psycho-social distress that communities go through is enormous. This involves thinking about the loss of their loved ones and the economic impact of taking care of sick ones especially among the low income individuals. This impacts not only the individuals, but also the economic progress of the country. Zaman [7] gives, another category of people largely at risk of contracting tuberculosis are those who work closely or live close to a person with active tuberculosis and they could include health care workers, people living in crowded living spaces or confined places such as schools or prisons. According to Semenza et al. [5] over the last twenty five years, the mortality rate of tuberculosis has greatly decreased by 45% since and this is largely due to effective diagnosis and treatment. However, the world is still far from defeating the disease. About 8 billion US dollars per year is needed for a full response to the global tuberculosis epidemic in low and middle income countries by the year 2015 with a funding gap of 2 billion US dollars per year. This amount excluded resources required for research and development, which was estimated to be about 2 billion US dollars yearly. Clearly, this reveals that the current investment in tuberculosis falls below the low and middle income country's needs.

Tuberculosis is responsible for more deaths worldwide than any other infectious agent. Waaler and Anderson [4] developed a first tuberculosis model for the transmission dynamics of tuberculosis. The enormous progress in prevention and treatment, tuberculosis disease remains a leading cause of death worldwide and one of the major sources of concern is the drug resistant strain, MDR-TB (multidrug resistant tuberculosis) and XDR-TB (extensively drug resistant tuberculosis). Young et al. [2] studies, tuberculosis is curable provided an early diagnosis is made and one follows the proper treatment regimen which would take six months upto two years for the active tuberculosis to clear. Sharma et al. [9] given that the infected population is similar on the sociological and psychological effect rate. Cohen and Murray [11] modelled epidemics of multi-drug resistant tuberculosis of heterogeneous fitness.

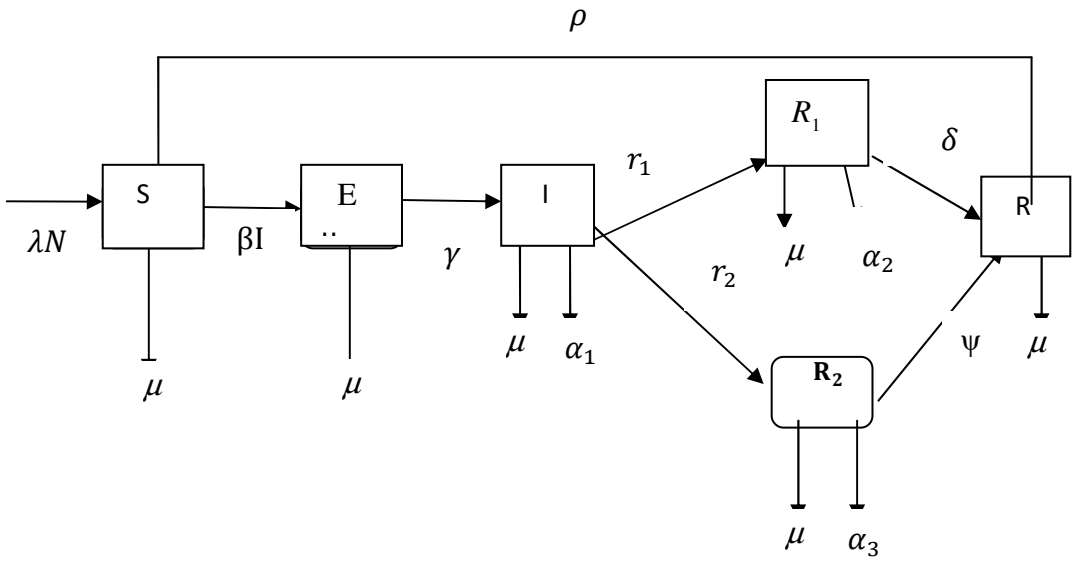
2. Model Analysis

This study will first extend the standard SEIRS mathematical model for the transmission of tuberculosis which will demonstrate the transmission of the Mycobacterium tuberculosis in human hosts taking into account the multidrug resistant (MDR) tuberculosis.

2.1. The Model Equations

This study presents a simple model that can easily be analysed so as to properly understand the dynamics of this disease. Humans can contract MTB tuberculosis through contact with individuals who are infected with the disease after which they enter the exposed phase where a proportion of this class develop active tuberculosis thus moving into the infectious class. If treatment is administered promptly, those who recover from the disease will move to the recovered class and those who delay treatment and develop MDR tuberculosis will move to the resistant class. Those who recover from MDR tuberculosis will move to the recovered class. Given that there is no permanent immunity to tuberculosis, the recovered can lose their immunity and become susceptible again. Figure represent the flow of individuals into the different compartments and it has been constructed with these assumptions: recruitment is by

birth only, a variable population, a constant mortality rate, no permanent immunity to tuberculosis, no immediate infectively.



The human population is categorized into six cl ıch that at time $t \geq 0$ there are S, susceptible humans, E, exposed humans to tuberculosis, I, infected humans with active tuberculosis, R_1, resistant humans to the first line of treatment , R_2, resistant humans to the second line of treatment, R, recovered humans. Thus the size of the human population is given as $N = S + E + I + R_{ES} + R$. In our model, the recruitment into the susceptible human population is by birth λ. The size of the human population is further increased by the partial immune humans in R after they lose their immunity at the rate ρ. The size of human population is decreased by natural deaths (μ) and exposure to Mtb. The exposed susceptible to Mtb move to the exposed classes E with the force of infection being β resulting in an increase in the exposed class. The exposed class is further decreased by natural death(μ) and the proportion who move to the infected class I after developing active tuberculosis. The infected class I is also reduced by natural deaths (μ), disease induced death (α_1), those who recover (δ) and also by those resistance rate to the first and second line of treatment $r_1$and r_2 respectively. Thus the infected class (I), and the resistant classes ($R_1 and\ R_2$) gain partial immunity at the rates (δ) and (ψ) respectively thus moving to the recovered class R thus reducing their respective classes and also increasing the recovered class. The resistant classes R_1, R_2 also reduced by natural deaths (μ) and disease induced deaths while the recovered class is reduced by natural deaths (μ) and those who lose their partial immunity at the rate ρ.

Following Table (1) and (2) gives the description of variables and parameters

Table 1

Description of variables
$S(t)$ = Susceptible humans
$E(t)$ = exposed humans
$I(t)$ = infected humans
$R_1(t)$ = resistant to the first line of treatment
$R_2(t)$ = resistant to the second line of treatment
R(t) = Recovered humans

Table 2

Description of Parameters
$\beta =$ Rate at which the susceptible become exposed to Mtb
$\gamma =$ Infection rate
$\alpha_1 =$ Disease induced death rate
$\mu =$ Rate of natural death
$r_1 =$ Resistance rate of first line treatment
$r_2 =$ Resistance rate of second line treatment
$\delta =$ Recovery after first line of treatment
$\psi =$ Recovery after second line of treatment
$\rho =$ Rate at which recovered loss their immunity
$\alpha_2, \alpha_3 =$ Disease induced death rate after first and second resistance respectively

2.2. Differential Equations

From the above discussion, we get the following system of ordinary differential equations

$$\left.\begin{aligned} \frac{dS}{dt} &= \lambda N - \mu S - \beta SI + \rho R, \\ \frac{dE}{dt} &= \beta SI - (\mu + \gamma)E, \\ \frac{dI}{dt} &= \gamma E - (\mu + \alpha_1 + r_1 + r_2)I, \\ \frac{dR_1}{dt} &= r_1 I - (\mu + \alpha_2 + \delta)R_1, \\ \frac{dR_2}{dt} &= r_2 I - (\mu + \alpha_3 + \psi)R_2, \\ \frac{dR}{dt} &= \delta R_1 + \pi R_2 - (\mu + \rho)R \end{aligned}\right\} \quad (1)$$

2.3. Equilibrium Points

To obtain the equilibrium points for the system of differential equation (1) by equating each of the equations to 0 as shown in below

$$\left.\begin{aligned} \frac{dS}{dt} &= \lambda N - \mu S - \beta SI + \rho R = 0, \\ \frac{dE}{dt} &= \beta SI - (\mu + \gamma)E = 0, \\ \frac{dI}{dt} &= \gamma E - (\mu + \alpha_1 + r_1 + r_2)I = 0, \\ \frac{dR_1}{dt} &= r_1 I - (\mu + \alpha_2 + \delta)R_1 = 0, \\ \frac{dR_2}{dt} &= r_2 I - (\mu + \alpha_3 + \psi)R_2 = 0, \\ \frac{dR}{dt} &= \delta R_1 + \psi R_2 - (\mu + \rho)R = 0, \end{aligned}\right\} \quad (2)$$

Solving system (2), to get two equilibrium points, one being the diseases free equilibrium while the other being the endemic equilibrium. Disease free equilibrium Point (S, E, I, R_1, R_2, R) is expressed as follows: $X_0 = (S, E, I, R_1, R_2, R) = \left(\frac{\lambda N}{\mu}, 0,0,0,0,0\right)$ and endemic equilibrium point $(S^*, E^*, I^*, R_1^*, R_2^*\ R^*)$ is expressed as follows:

$$S^* = \frac{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}{\beta\gamma}, \qquad E^* = \frac{\beta x(\mu+\rho)(\lambda N-\mu x)}{(\mu+\gamma)(\beta x(\mu+\rho)-p)},$$

$$I^* = \frac{(\mu+\rho)(\lambda N-\mu x)}{\beta x(\mu+\rho)-p}, \qquad R_1^* = \frac{r_1(\mu+\rho)(\lambda N-\mu x)}{(\mu+\alpha_2+\delta)(\beta x(\mu+\rho)-p)} \tag{3}$$
$$R_2^* = \frac{r_2(\mu+\rho)(\lambda N-\mu x)}{(\mu+\alpha_3+\psi)(\beta x(\mu+\rho)-p)}, \quad R^* = \frac{(\lambda N-\mu x)p}{(\beta x(\mu+\rho)-p)\rho}$$

where $x = S^*$ and $p = \rho\left(\frac{\delta r_1}{\mu+\alpha_2+\delta} + \frac{\psi r_2}{\mu+\alpha_3+\psi}\right)$.

2.4. Condition of Existence/Positivity of Equilibrium

The system will remain positive provided this condition holds:

$$\frac{\lambda N - \mu x}{\beta x(\mu+\rho) - p} > 0$$
$$\Leftrightarrow \lambda N - \mu x > 0$$
$$\Leftrightarrow \lambda N > \mu x$$

Substituting for x

$$\Leftrightarrow \lambda N > \mu \frac{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}{\beta\gamma}$$

$$\Leftrightarrow \lambda N\beta\gamma > \mu(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)$$

$$\frac{\lambda N\beta\gamma}{\mu(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)} > 1$$

This expression is the condition of existence.

2.5. The Basic Reproduction Number R_0

Let us look at the following system of differential equations.

$$\frac{dE}{dt} = \beta SI - (\mu+\gamma)E,$$

$$\frac{dI}{dt} = \gamma E - (\mu+\alpha_1+r_1+r_2)I,$$

$$\frac{dR_1}{dt} = r_1 I - (\mu+\alpha_2+\delta)R_1,$$

$$\frac{dR_2}{dt} = r_2 I - (\mu+\alpha_3+\psi)R_2,$$

Let $X = (E, I, R_1, R_2)^T$ then above system can be represented in matrix form as shown below:

$$\frac{dX}{dt} = F(X) - V(X)$$

where

$$F(X)=\begin{pmatrix}\beta SI\\0\\0\\0\end{pmatrix},\quad V(X)=\begin{pmatrix}-\gamma E+(\mu+\alpha_1+r_1+r_2)I\\(\mu+\gamma)E\\-r_1+(\mu+\alpha_2+\delta)R_1\\r_2-(\mu+\alpha_3+\pi)R_2\end{pmatrix}$$

The Jacobian matrix of $F(X)$ and $V(X)$ at the disease free equilibrium X_0 are,

$$DF(X_o)=\begin{pmatrix}F_1 & 0\\0 & 0\end{pmatrix},\ DV(X_o)=\begin{pmatrix}V_1 & 0\\0 & 0\end{pmatrix}\text{ respectively,}$$

where

$$F_1=\begin{pmatrix}0 & \dfrac{\beta\lambda N}{\mu} & 0 & 0\\0 & 0 & 0 & 0\\0 & 0 & 0 & 0\\0 & 0 & 0 & 0\end{pmatrix}$$

and

$$V_1=\begin{pmatrix}\mu+\gamma & 0 & 0 & 0\\-\gamma & \mu+\alpha_1+r_1+r_2 & 0 & 0\\0 & -r_1 & \mu+\alpha_2+\delta & 0\\0 & r_2 & 0 & -(\mu+\alpha_3+\pi)\end{pmatrix}.$$

Now

$$V_1^{-1}=\begin{pmatrix}\dfrac{1}{\mu+\gamma} & 0 & 0 & 0\\ \dfrac{\gamma}{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)} & \dfrac{1}{(\mu+\alpha_1+r_1+r_2)} & 0 & 0\\ \dfrac{\gamma r_1}{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)(\mu+\alpha_2+\delta)} & \dfrac{r_1}{(\mu+\alpha_1+r_1+r_2)(\mu+\alpha_2+\delta)} & \dfrac{1}{\mu+\alpha_2+\delta} & 0\\ \dfrac{\gamma r_2}{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)(\mu+\alpha_3+\pi)} & \dfrac{r_2}{(\mu+\alpha_1+r_1+r_2)(\mu+\alpha_3+\pi)} & 0 & -\dfrac{1}{\mu+\alpha_3+\pi}\end{pmatrix}.$$

The next generation matrix of the system is given by

$$F_1V_1^{-1}=\begin{pmatrix}\dfrac{\beta\gamma\lambda N}{\mu(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)} & \dfrac{\beta\lambda N}{\mu(\mu+\alpha_1+r_1+r_2)} & 0 & 0\\0 & 0 & 0 & 0\\0 & 0 & 0 & 0\\0 & 0 & 0 & 0\end{pmatrix}$$

Now, to obtain the spectral radius of $F_1V_1^{-1}$, which is defined as the largest eigen value of $F_1V_1^{-1}$ and the spectral radius for the above system is the basic reproduction number and its expression is given by

$$R_0 = \frac{\beta\gamma\lambda N}{\mu(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}$$

2.6. Stability Analysis

In this section this study will determine the stability of the diseases free equilibrium point. This study can easily establish the local stability of the equilibriums by Routh Hurwitz criteria, so left it. This study will discuss only on the global stability of the disease free and endemic equilibrium.

Global Stability of the Disease Free Equilibrium

The local dynamics of a general SEIRS model is determined by the reproduction number R_0. If $R_0 \leq 1$, then each infected individual in its entire period of infectiousness will produce less than one infected individual on average. This means that the disease will be wiped out of the population. If $R_0 > 1$, then each infected individual in its entire infectious period having contact with susceptible individuals will produce more than one infected individual implying that the disease persist in the population. If $R_0 = 1$ and this is defined as the disease threshold, then one individual infects one more individual. For $R_0 \leq 1$, the disease free equilibrium is locally asymptotically stable while for $R_0 > 1$ the disease free equilibrium becomes unstable. The disease free equilibrium point is $(S, E, I, R_1, R_2, R) = \left(\frac{\lambda N}{\mu}, 0,0,0,0\right)$.

Theorem 1. If $R_0 \leq 1$, then the disease free equilibrium is of the system $(S, E, I, R_1, R_2, R) = \left(\frac{\lambda N}{\mu}, 0,0,0,0,0\right)$ of the system is globally asymptotically stable on Ω.

Proof. Construct the following Lasalle-Lyapunov function $V(S, E, I, R_1, R_2, R)$ on the positively invariant compact set Ω.

Define

$$V(S, E, I, R_1, R_2, R) = \gamma E + (\mu + \gamma)I. \tag{4}$$

Differentiate (4) and using the second and third equations of the system (1), we get

$$\frac{dV}{dt} = \gamma\frac{dE}{dt} + (\mu+\gamma)\frac{dI}{dt}$$

$$\frac{dV}{dt} = [\beta\gamma S - (\mu+\gamma)(\mu+\alpha_1+r_1+r_2)]I.$$

$$\frac{dV}{dt} = (\mu + \gamma)(\mu + \alpha_1 + r_1 + r_2)(R_o - 1)I,$$

which is strictly decreasing when $R_0 < 1$.

Define the set Define the set $E = \{(E, I, R_1, R_2) \in \Omega \,/\, (E, I, R_1, R_2 = 0)$.The largest invariant set is contained in the set E for which $E = 0$ or $I = 0$ or $R_1 = 0, R_2 = 0$ Thus by Lasalle invariant principal the disease free equilibrium is globally asymptotically stable on Ω.

Global Stability of The Endemic Equilibrium Theorem 2. The endemic equilibrium $\emptyset = (E^*, I^*, {R_1}^*, {R_2}^*)$ given by equation (3) is globally asymptotically stable on Ω.

Proof. To establish the global stability of the endemic equilibrium $\emptyset$, so construct the Lyapunov function $V_1: \Omega \to R$ where $\Omega = \{(E(t), I(t), R_1(t), R_2(t)/E(t) > 0, I(t) > 0, R_1 > 0, R_2 > 0\}$ as described by Ullah, Zaman and Islam[10] and it is given as

$$V_1(E, I, R_1, R_2) = L_1\left[E - E^* \ln\left(\frac{E}{E^*}\right)\right] + L_2\left[I - I^* \ln\left(\frac{I}{I^*}\right)\right] + L_3\left[R_1 - {R_1}^* \ln\left(\frac{R_1}{{R^*}_1}\right)\right] +$$

$$L_4[R_2 - {R^*}_2 \ln\left(\frac{R_2}{{R^*}_2}\right)] \quad (5)$$

Where L_1, L_2, L_3, L_4 are positive constant to be later considered.

Taking the derivative of the Lyapunov function V_1as given in equation (5) yields

$$\frac{dV_1}{dt} =$$

$$L_1\left[E - E^*\left(\frac{\beta SI}{E} - (\mu + \gamma)\right)\right] + L_2\left[I - I^*\left(\frac{\gamma E}{I} - (\mu + \alpha_1 + r_1 + r_2)\right)\right] + L_3\left[R_1 - {R_1}^*\left(\frac{r_1 I}{R_1} - \right.\right.$$

$$\left.\left.(\mu + \alpha_2 + \delta)\right)\right] + L_4[R_2 - {R_2}^*(\frac{r_2 I}{R_2} - (\mu + \alpha_3 + \psi))] \quad (6)$$

Choosing $L_1 = L_2 = L_3 = L_4 = 1$, equation (6) becomes

$$= (E - E^*)(\mu + \gamma)(W_1 R_0 - 1) + (I - I^*)(\mu + \alpha_1 + r_1 + r_2)(W_2 R_0 - 1)$$
$$+ r1(R_1 - {R^*}_1)\left(\frac{{R^*}_1 I - R_1 I^*}{R_1 {R^*}_1}\right) + r_2(R_2 - {R^*}_2)(\frac{{R^*}_2 I - R_2 I^*}{R_2 {R^*}_2})$$

Thus $\frac{dV_1}{dt} \leq 0 \; iff \; R_0 < 1 \; and \; {R^*}_1 I < R_1 I^*$ and ${R^*}_2 I < R_2 I^*$

To have that $\frac{dV_1}{dt} = 0 \; iff \; E = E^*, I = I^*$

$$R_1 < R^*_1$$

$$R_1 = R^*_1$$

$$R_2 = R^*_2$$

Or when $R_0 = 1 \; and \; R^*_1 I = R_1 I^*$

$$R^*_2 I = R_2 I^*$$

Define the set $\emptyset = \{E^*, I^*, R^*_1, R^*_2\} \in \Omega / \frac{dV_1}{dt} = 0\}$

Therefore the largest compact invariant set is singletone set Φ which is the endemic equilibrium. By Lasalle invariant principle Φ is globally asymptotically stable on Ω.

3. Numerical Simulation

Explain this result through graphically. Consider the parameters as: $\lambda = 0.001, N = 1,000, \beta = 0.398, \gamma = 1, r_1 = 0.4, r_2 = 0.5, \mu = 0.7, \; \alpha_1 = 0.8, \alpha_2 = 0.4, \alpha_3 = 0.3,$ $\delta = 1, \pi = 1.2, \rho = 0.4.$ Then this study give $R_0 = 0.1395 < 1$ and if the initial values of susceptible, exposed, infected, resistant of first and second line treatment population are 1, 2, 1, 1, 1 and 1 respectively. The susceptible population goes to its steady state value while exposed, infected, resistant of first and second line treatment population approach to zero as time increase as shown in Figure 1. So that the disease free equilibrium is globally asymptotically stable.

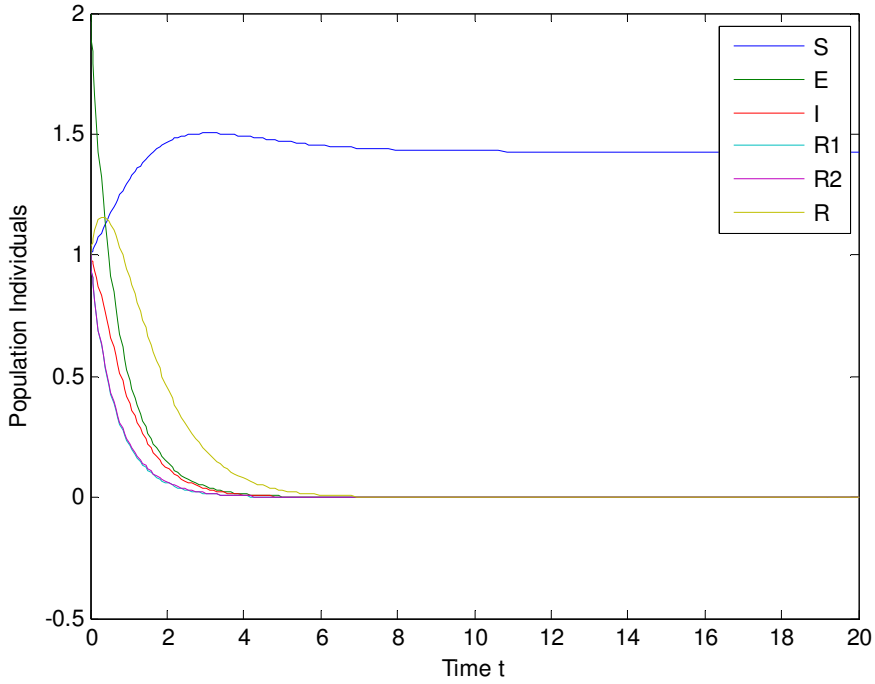


Figure 1. When $R_0 = 0.1395 < 1.$

Again if, we take the parameters of the system as: $\lambda = 0.015, N = 1{,}000, \beta = 0.398, \gamma = 1,$ $r_1 = 0.4,\ r_2 = 0.5, \mu = 0.7, \alpha_1 = 0.8, \alpha_2 = 0.4, \alpha_3 = 0.3,\ \delta = 1, \pi = 1.2, \rho = 0.4.$ Then $E^*(S^*, E^*, I^*, R_1^*, R_2^*, R^*) = (10.25, 4.8, 2, .38, .45, .84)$ and $R_0 = 2.091 > 1.$ If the initial values of susceptible, exposed, infected, resistant of first and second line treatment population are 1, 2, 1, 1, 1 and 1 respectively. Therefore by theorem (2), the endemic equilibrium is a global asymptotically stable as shown in Figure 2.

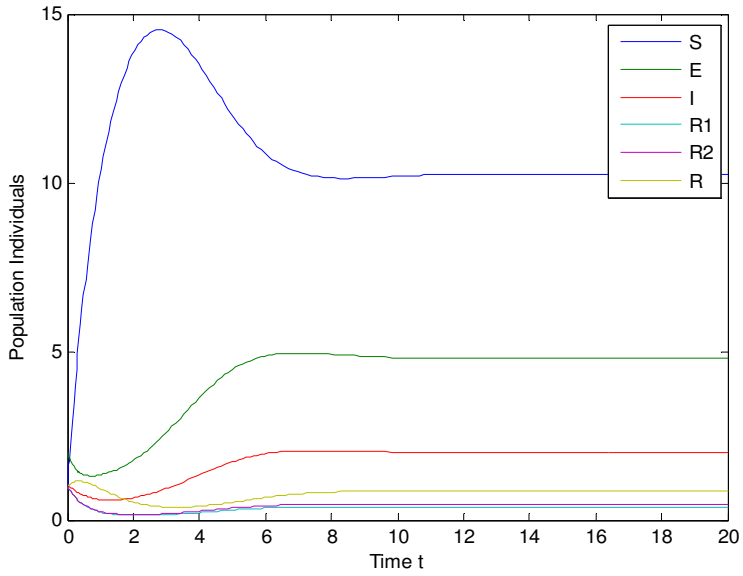


Figure 2. When $R_0 = 2.091 > 1.$

Let us take all the parameters are fixed except the resistance rate of the first and second line of treatments, found that the infected population decreases as the resistance rate of the first and second line of treatment increases which is shown in figure 3(a) and (b). Therefore infected population moves to resistant population of the first line of treatment and to the resistant population of the second line of treatment, as resistant rate increases respectively.

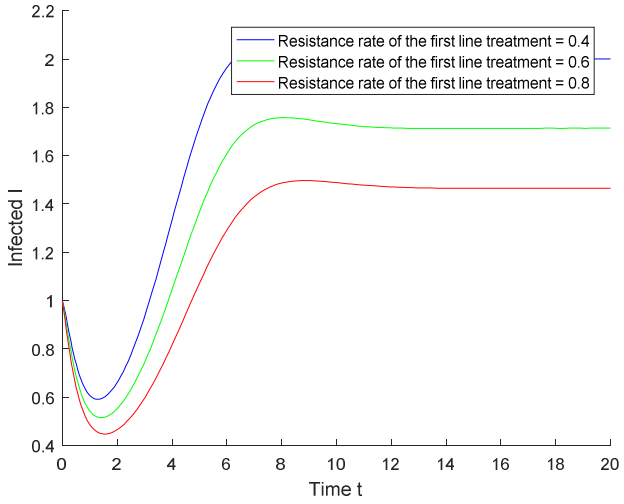


Figure.3(a) Changes in the infected population with respect to resistance rate of the first line treatment, keeping all other parameters are fixed.

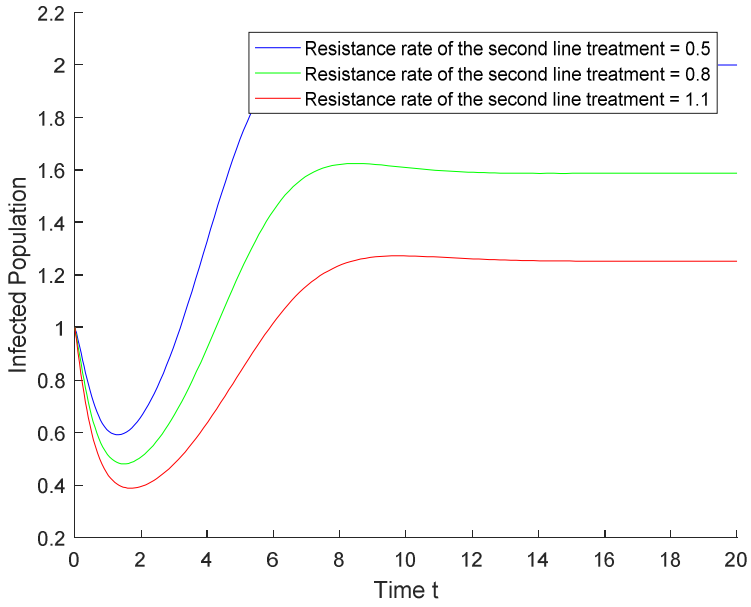


Figure.3(b) Changes in the infected population with respect to resistance rate of the second line treatment, keeping all other parameters are fixed.

Similarly again we take all parameters are fixed except the resistance rate of the first line and the second line of treatment, found that the resistant population of the first line treatment decreases when resistance rate of the first line treatment increases i.e. resistant population $\square_1$ moves to recovered population while the resistant population of the second line treatment increases when the resistance rate of the second line of treatment increases i.e. after the second line treatment, the infected population comes into resistant population which shown in figure 4(a) and 4(b) respectively.

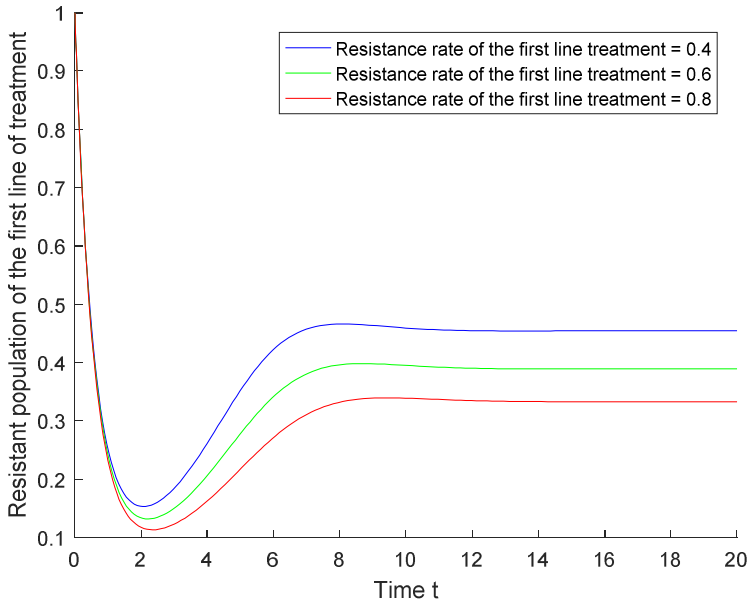


Figure. 4(a) Changes in the resistant population with respect to resistance rate of the first line of treatment, keeping all the other parameters are fixed.

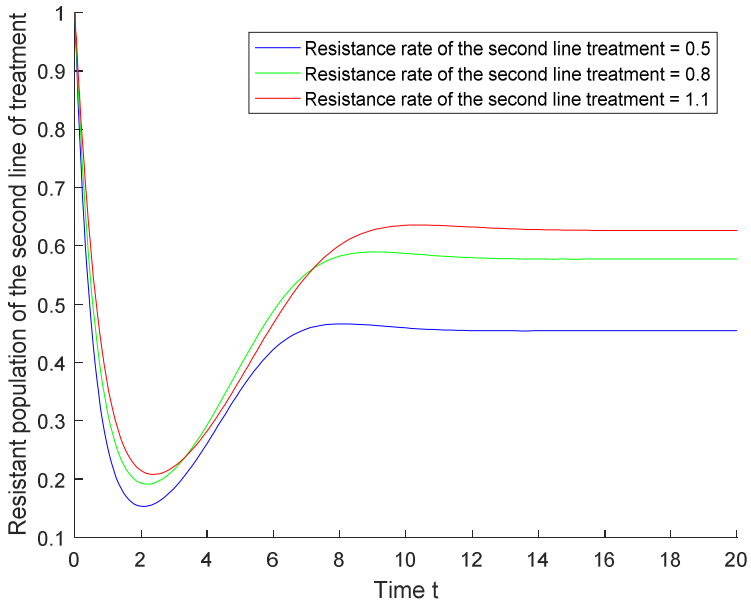


Figure. 4(b) Changes in the resistant population with respect to resistance rate of the second line of treatment, keeping all the other parameters are fixed.

4. Conclusion

This study analyzed the local and global stability of the equilibrium points, found that when the basic reproduction number $R_o < 1$, then disease dies out and when the basic reproduction number $R_o > 1$, then disease persists.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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