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A Mathematical Modelling of Tuberculosis infection Dynamics with Effects of Case Detection and Drug Resistance

Yusuf Zubair[1] , Gbolahan Bolarin[2], and Abdulhakeem Yusuf[3]

[1,2,3]Mathematics Department, Federal University of Technology, Minna, Nigeria,
E-mail(s): [2]g..bolarin@futminna.edu.ng, [1]zubairoyereyi@gmail.com [3]a.yusuf@futminna.edu.ng

Abstract

A deterministic mathematical model of tuberculosis incorporating case detection and drug resistance with constant recruitment rate was developed. The population was subdivided into six compartments according to their disease status. The basic reproduction number of the model was obtained using the next generation matrix. The existence of disease free and endemics equilibrium points were shown and the conditions for their stability was also esterblished. The results show that the disease free equilibrium points are locally asymptotically stable if $R_0 < 1$ and globally stable if $R_0 \leq 1$. Also the results further show that the endemic equilibrium points are locally asymptotically stable if $R_0 > 1$ and globally stable if $R_0 \geq 1$. We obtain the approximate solution of the model using Homotopy Perturbation Methods. The graphical summaries of the solution were carried out and the result show that increase in case detection and sustained treatment can help to reduce transmission of tuberculosis disease.

Key words: Tuberculosis, Reproduction Number, Homotopy Perturbation Method, Next Generation Matrix

1. Introduction

Tuberculosis is a bacterial disease which attacks some part of the human body such as lungs, bones, lymph nodes and brain. This disease is caused by a known mycobacterium tuberculosis that looks like rod-shape bacterium. Some of the symptoms are in the form of cough, chest pains, shortness of breath, loss of appetite, weight loss, fever, chills and fatigue.

Tuberculosis is the second leading cause of death from infectious disease worldwide after those caused by Human Immune Deficiency Virus (HIV) [4]**.** This disease affect over 2 billion of the world population. Approximately over nine million people develop active tuberculosis and up to 2 million death cases is recorded from tuberculosis every year. Also over 480 thousand people developed drug resistance to tuberculosis with 210 thousand of those who developed multi drug resistance tuberculosis result to death [6].

Tuberculosis (TB) infection is of two type, namely, latent infection and active infection. The latent infection in the body system is a condition in which a patient holds dormant (sleeping) Tuberculosis bacteria in the

body and they do not cause TB disease to the patient's body. However, in a certain period, the sleeping bacteria would be awake and become active. People infected latently are called latent TB patients and are unable to infect those vulnerable to TB disease. Actively infected is a state in which the bacteria causing tuberculosis in the patient's body are actively multiplying and the disease symptoms becomes very visible in the body system. Those patients that are infected actively are called active tuberculosis and they can transmit the disease to vulnerable people [17].

Patients of latent and active TB can be treated but they are not totally protected from the disease. Within a certain time, those who recovered can be re-infected again in case contact with TB infectious patient. Based upon the chain of actions of TB bacteria infection, the associated population can be grouped into several different sub-populations which are susceptible to the TB disease. The sub-population groups are latent infectious, active infectious and recovered infectious groups.

About one-third of the world population has latent TB, which means people have been infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease. People infected with TB bacteria have a 10 % lifetime risk of falling ill with Tuberculosis disease. Latent Tuberculosis infection can progress to active tuberculosis when the immunity of the host decreases due to aging, stress, over use of immunosuppressant or co-infection with HIV [16].

The spread of tuberculosis diseases can be analysed through mathematical models. The models can help to predict and control the spread of tuberculosis outbreak in the future. The spread of tuberculosis disease can be modelled with some types of epidemics models which can come in different variance of SIR models; see [1,2,5,11,12,13,14]. Also, some author studied the effects of vaccination or otherwise on the overall dynamics of tuberculosis in the population,[7, 9,10].

In this current study, we are going to develop and analyze a model with six compartements and solve the model with a semi-analytuc method known as homotopy perturbation method.

2. Material and Methods

In this section, we are going to formulate the proposed model and conduct standard epidemiological analysis on it.

2.1 Model formulation

We first divide the human population at time $t \geq 0$, into six classes they are Susceptible $S(t)$, Expossed $E(t)$, Infected $I(t)$, Resistance to first line of treatment $R_1(t)$, Resistance to second line of treatmet $R_2(t)$, and the recorvered humans $R(t)$. The size of the human population is given by

$$N(t) = S(t) + E(t) + I(t) + R_1(t) + R_2(t) + R.$$

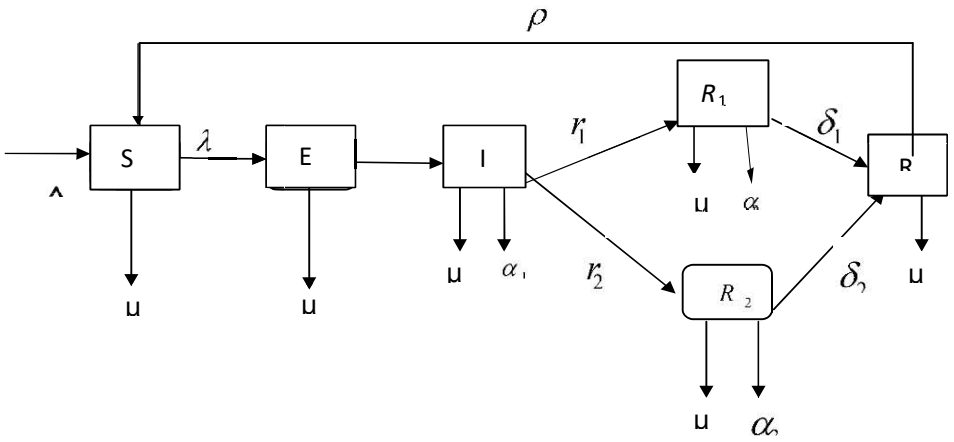

Figure 1 Schematic Diagram Showing the Flow of Tuberculosis Transmission Model

Table 1: Description of Parameters/Variables of the model

Parameter/Variables	Description
Λ	Recruitment rate
$S(t)$	Susceptible humans at time t
$E(t)$	Exposed human at time t
$I(t)$	Infected humans at time t
$R_1(t)$	Resistance class of individual to first line of treatment
$R_2(t)$	Resistance class of individual to second line of treatment
$R(t)$	Recovered humans at time t
η	Case detection rate
λ_1	Rate of transmission (detection)
λ_2	Rate of transmission (undetected)
μ	Natural death rate
γ	The rate at which the infected becomes infectious
ρ	Rate at which recovered individual loss their immunity
r_1	Resistance rate to first line of treatment
r_2	Resistance rate to second line of treatment

α_1	Diseases induced death rate
δ_1	Recovery rate after first line of treatment
δ_2	Recovery rate after second line of treatment
α_2	Diseases induced death rate after first line of treatment
α_3	Diseases induced death rate after second line of treatment

2.2 Basic assumptions of the model

1. The population is varying and homogenously mixed i.e. All people are equally likely to be infected by the infectious individual in case of contact.
2. Both detected and undetected case of individual transmit Tuberculosis at the different rate i.e. it is higher in undetected cases.
3. It is assumed that no permanent immunity to Tuberculosis.
4. Some infected individual delay treatment and moved to resistance classes.
5. Natural death occur in all the classes.

2.3 The model equation

$$\frac{dS}{dt} = \Lambda - \mu S - \left(\lambda_1\eta + \lambda_2(1-\eta)\right)IS + \rho R \tag{1}$$

$$\frac{dE}{dt} = \left(\lambda_1\eta + \lambda_2(1-\eta)\right)IS - \left(\mu + \gamma\right)E \tag{2}$$

$$\frac{dI}{dt} = \gamma E - \left(\mu + \alpha_1 + r_1 + r_2\right)I \tag{3}$$

$$\frac{dR_1}{dt} = r_1 I - \left(\mu + \alpha_2 + \delta_1\right)R_1 \tag{4}$$

$$\frac{dR_2}{dt} = r_2 I - \left(\mu + \alpha_3 + \delta_2\right)R_2 \tag{5}$$

$$\frac{dR}{dt} = \delta_1 R_1 + \delta_2 R_2 - \left(\mu + \rho\right)R \tag{6}$$

2.4 Analysis of the Model

We present standard epidemiological analysis of the model in the following subsections.

2.4.1 Invariant Region of the Model

The rate of total population is given by

$$\frac{dN}{dt}=\frac{dS}{dt}+\frac{dE}{dt}+\frac{dI}{dt}+\frac{dR_1}{dt}+\frac{dR_2}{dt}+\frac{dR}{dt} \tag{7}$$

$$\frac{dN}{dt}=\Lambda-\mu\left(S+E+I+R_1+R_2+R\right)-\left(\alpha_1 I+\alpha_2 R_1+\alpha_3 R_2\right) \tag{8}$$

$$\frac{dN}{dt}\le\Lambda-\mu\left(S+E+I+R_1+R_2+R\right) \tag{9}$$

$$\frac{dN}{dt}\le\Lambda-\mu N \tag{10}$$

Where

$$N=S+E+I+R_1+R_2+R \tag{11}$$

Theorem 1: Model equations (1)-(6) has solutions which contain in the feasible region Ω for all $t\ge 0$.

Proof:

Let $\Omega=\left(S,E,I,R_1,R_2,R\right)\in\Re^6$ be any solution of the model 1-6 with non-negative initial conditions then from equation (10) we have

$$\frac{dN}{dt}\le\Lambda-\mu N \tag{12}$$

$$0\le N\le\frac{\Lambda}{\mu} \tag{13}$$

We seek solution of the form

$$IF=e^{\int\mu dt}=e^{\mu t} \tag{14}$$

By multiplying through our equation (12) with the integrating factor we obtain

$$\left[Ne^{\mu t}\right]'\le\Lambda e^{\mu t} \tag{15}$$

$\Rightarrow$

$$\Lambda - \mu N \geq Ce^{\mu t} \tag{16}$$

Therefore, all feasible solution of the human population of the model is in the region

$$\Omega = \left\{ \left(S, E, I, R_1, R_{2,} R\right) \in \Re^6 : \left(S, E, I, R_1, R_{2,} R\right) \geq 0, N \leq \frac{\Lambda}{\mu} \right\} \tag{17}$$

2.4.2 Positivity of the solutions

Lemma 1: Let the initial solutions be $\{S(0), E(0), I(0), R_1(0), R_2(0), R(0) \geq 0\} \in \Omega$ then the solution $\{S(t), E(t), I(t), R_1(t), R_2(t), R(t)\}$ of the model equations (1)-(6) is positive for all time $t \geq 0$.

Proof:

From equation (1) we have

$$\frac{dS}{dt} \geq -\mu S \tag{18}$$

By separating the variable and integrating equation (18) we have

$$\int \frac{dS}{S} \geq -\int \mu dt \tag{19}$$

$\Rightarrow$

$$S(t) \geq S(0)e^{-\mu t} \tag{20}$$

Similarly we can show that

$$E(t) \geq E(0)e^{-(\mu+\gamma)t} \tag{21}$$

$$I(t) \geq I(0)e^{-(\mu+\alpha_1+r_1+r_2)t} \tag{22}$$

$$R_1(t) \geq R_1(0)e^{-(\mu+\alpha_2+\delta_1)t} \tag{23}$$

$$R_2(t) \geq R_2(0)e^{-(\mu+\alpha_3+\delta_2)t} \tag{24}$$

$$R(t) \geq R(0)e^{-(\mu+\rho)t} \tag{25}$$

Therefore all the solution of the equations (1) –(6) are positive for all time $t \geq 0$.

2.5 Basic Reproduction Number R_0

The basic reproduction number (R_0) is the average number of new infections that one infected case will generate during their entire infection life time. It is an important tool in determining whether the diseases persist or die out in population.

We use the next generation matrix approach an in [15] to compute the basic reproduction number.

Basic reproduction number is the spectral radius $\rho\left(F_1V_1^{-1}\right)$ where the matrix F_i and V_i are the new infection terms and the remaining transfer terms respectively. The basic reproduction number is obtained as follow

Consider the following differential equations for the diseases compartment

$$\frac{dE}{dt} = \lambda IS - (\mu+\gamma)E \tag{26}$$

$$\frac{dI}{dt} = \gamma E - (\mu+\alpha_1+r_1+r_2)I \tag{27}$$

$$\frac{dR_1}{dt} = r_1 I - (\mu+\alpha_2+\delta_1)R_1 \tag{28}$$

$$\frac{dR_2}{dt} = r_2 I - (\mu+\alpha_3+\delta_2)R_2 \tag{29}$$

Where $\lambda = \lambda_1\eta + \lambda_2(1-\eta)$

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

$$\frac{dX_i}{dt} = F_i(X) - V_i(X) \tag{30}$$

$$\text{Where } F(X)_i = \begin{pmatrix} \lambda SI \\ 0 \\ 0 \\ 0 \end{pmatrix}, \qquad V_i(X) = \begin{pmatrix} (\mu+\gamma)E \\ -\gamma E + (\mu+\alpha_1+r_1+r_2)I \\ -r_1 I + (\mu+\alpha_2+\delta_1)R_1 \\ -r_2 I + (\mu+\alpha_3+\delta_2)R_2 \end{pmatrix} \tag{31}$$

The Jacobian matrix of $F_i(X)$ and $V_i(X)$ at the diseases free equilibrium X_0 are,

$$\frac{dF_i(X_0)}{d(X)} = F_1 = \begin{pmatrix} 0 & \frac{\beta\Lambda}{\mu} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{32}$$

$$\frac{dV_i(X)}{d(X)} = V_1 = \begin{pmatrix} \mu+\gamma & 0 & 0 & 0 \\ -\gamma & \mu+\alpha_1+r_1+r_2 & 0 & 0 \\ 0 & -r_1 & \mu+\alpha_2+\delta_1 & 0 \\ 0 & 0 & 0 & -r_2 \end{pmatrix} \tag{33}$$

Now

$$V_1^{-1} = \begin{pmatrix} \frac{1}{\mu+\gamma} & 0 & 0 & 0 \\ \frac{\gamma}{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)} & \frac{1}{\mu+\alpha_1+r_1+r_2} & 0 & 0 \\ \frac{r_1\gamma}{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)(\mu+\alpha_2+\delta_1)} & \frac{r_1}{(\mu+\alpha_1+r_1+r_2)(\mu+\alpha_2+\delta_1)} & \frac{1}{\mu+\alpha_2+\delta_1} & 0 \\ 0 & & & \\ \frac{r_2\gamma}{(\mu+\alpha_1+r_1+r_2)(\mu+\alpha_2+\delta_1)(\mu+\alpha_3+\delta_2)} & \frac{r_2}{(\mu+\alpha_1+r_1+r_2)(\mu+\alpha_3+\delta_2)} & 0 & \frac{1}{\mu+\alpha_3+\delta_2} \end{pmatrix} \quad (34)$$

The next generation matrix of the system is given by

$$F_1V_1^{-1} = \begin{pmatrix} \frac{\lambda\gamma\Lambda}{\mu(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)} & \frac{\lambda\Lambda}{\mu(\mu+\alpha_1+r_1+r_2)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad (35)$$

Thus our basic reproduction number is:

$$R_0 = \frac{\lambda\gamma\Lambda}{\mu(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)} \quad (36)$$

2.6 Equilibrium points of the model

We obtained two equilibrium point for our model, these are the Disease free Equilibrium point and Endemic Equilibrium point.

2.6.1 Disease Free Equilibrium of the Model

Let $X_0 = (S^0, E^0, I^0, R_1^0, R_2^0, R^0)$ be the diseases free equilibrium points on equations (1) − (6) then the equation (1)- (6) above becomes

$$\Lambda - \mu S^0 - \left(\lambda_1\eta + \lambda_2(1-\eta)\right) I^0 S^0 + \rho R^0 = 0 \quad (37)$$

$$\left(\lambda_1\eta + \lambda_2(1-\eta)\right) I^0 S^0 - \left(\mu + \gamma\right) E^0 = 0 \quad (38)$$

$$\gamma E^0 - \left(\mu + \alpha_1 + r_1 + r_2\right) I^0 = 0 \quad (39)$$

$$r_1 I^0 - \left(\mu + \alpha_2 + \delta_1\right) R_1 = 0 \quad (40)$$

$$r_2 I^0 - \left(\mu + \alpha_3 + \delta_2\right) R^0{}_2 = 0 \quad (41)$$

$$\delta_1 R_1{}^0 + \delta_2 R^0{}_2 - \left(\mu + \rho\right) R^0 = 0 \quad (42)$$

From equation (38) we have

$$E^0 = \frac{\left(\lambda_1\eta + \lambda_2(1-\eta)\right) I^0 S^0}{\left(\mu + \gamma\right)} \quad (43)$$

Substituting (43) into (39) we have

$$\left(\frac{\gamma\left(\lambda_1\eta + \lambda_2(1-\eta)\right) S^0}{\left(\mu + \gamma\right)} - \left(\mu + \alpha_1 + r_1 + r_2\right) \right) I^0 = 0 \quad (44)$$

Which implies that

$$I^0 = 0 \quad (45)$$

or,

$$\left(\frac{\gamma\left(\lambda_1\eta + \lambda_2(1-\eta)\right) S^0}{\left(\mu + \gamma\right)} - \left(\mu + \alpha_1 + r_1 + r_2\right) \right) = 0 \quad (46)$$

Thus if $I^0 \neq 0$ we have

$$S^0 = \frac{\left(\mu + \gamma\right)\left(\mu + \alpha_1 + r_1 + r_2\right)}{\gamma\left(\lambda_1\eta + \lambda_2(1-\eta)\right)} \quad (47)$$

Putting equation (45) into (40) and (41) gives

$$R_1^0 = 0 \tag{48}$$

$$R_2^0 = 0 \tag{49}$$

Substituting equation (45) into (42)

$$R^0 = 0 \tag{50}$$

Putting (45) and (50) into (37) result in

$$S^0 = \frac{\Lambda}{\mu} \tag{51}$$

Thus diseases free equilibrium of the model is given by

$$X_0 = \left(S^0, E^0, I^0, R_1^0, R_2^0, R^0\right) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0\right) \tag{52}$$

2.6.2 Endemic equilibrium $\left(S^*, E^*, I^*, R_1^*, R_2^*, R^*\right)$

We have $I \neq 0,\ E \neq 0, R_1 \neq 0 \ \ and \ \ R_2 \neq 0$

Thus from equation (47) we have

$$S^* = \frac{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}{\gamma\left(\lambda_1\eta + \lambda_2(1-\eta)\right)} \tag{53}$$

From equation (1) we have

$$I^* = \frac{\Lambda - \mu S^* + \rho R^*}{\left(\lambda_1\eta + \lambda_2(1-\eta)\right)S^*} \tag{54}$$

From (2)

$$E^* = \frac{\left(\lambda_1\eta + \lambda_2\left(1-\eta\right)\right)S^*I^*}{\left(\mu+\gamma\right)} \tag{55}$$

From equation (4)

$$R_1^* = \frac{r_1 I^*}{\mu+\alpha_2+\delta_1} \tag{56}$$

From (5) we have

$$R_2^* = \frac{r_2 I^*}{\mu+\alpha_3+\delta_2} \tag{57}$$

From (6) we have

$$R^* = \frac{\delta_1 R^*_1 + \delta_2 R^*_2}{\mu+\rho} \tag{58}$$

On solving equations (53) to (58) we have the endemic equilibrium pointof the model as

$$S^* = \frac{\left(\mu+\gamma\right)\left(\mu+\alpha_1+r_1+r_2\right)}{\lambda\gamma} = \frac{\Lambda}{\mu R_0} \tag{59}$$

$$E^* = \frac{\lambda K\mu\left(\mu+\alpha_1+r_1+r_2\right)\left(R_0-1\right)}{\left(\lambda K-b\right)} \tag{60}$$

$$I^* = \frac{K\mu}{\lambda K - b}(R_0 - 1) \tag{61}$$

$$R_1^* = \frac{r_1 K(R_0 - 1)}{(\mu + \alpha_2 + \delta_1)(\lambda K - b)} \tag{62}$$

$$R_2^* = \frac{r_2 K(R_0 - 1)}{(\mu + \alpha_3 + \delta_2)(\lambda K - b)} \tag{63}$$

$$R^* = \frac{bK(R_0 - 1)}{\rho(\lambda K - b)} \tag{64}$$

Where $K = \dfrac{(\mu + \gamma)(\mu + \alpha_1 + r_1 + r_2)(\mu + \rho)}{\lambda\gamma}$ (65)

$$b = \rho\left(\frac{\delta_1 r_1}{\mu + \alpha_2 + \delta_1} + \frac{\delta_2 r_2}{\mu + \alpha_3 + \delta_2}\right) \tag{66}$$

$$\lambda = \lambda_1\eta + \lambda_2(1 - \eta) \tag{67}$$

2.6.3 Condition of existence and positivity of endemic equilibrium

The system will remain positive provided we have:

$$\frac{\Lambda-\mu\left(\frac{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}{\lambda\gamma}\right)}{\lambda\left(\frac{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}{\lambda\gamma}\right)(\mu+\rho)-b}>0 \tag{68}$$

$$\Leftrightarrow \Lambda-\mu\left(\frac{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}{\lambda\gamma}\right)>0 \quad and \quad \lambda\left(\frac{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}{\lambda\gamma}\right)(\mu+\rho)-b>0$$

$$\Leftrightarrow \lambda\gamma\Lambda>\mu(\mu+\gamma)(\mu+\alpha_1+r_1+r_2) \quad and \quad \lambda K-b>0$$

$$\Leftrightarrow \frac{\lambda\gamma\Lambda}{\mu(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}>1 \quad and \quad \lambda K-b>0$$

$$\Leftrightarrow R_0 \succ 1 \quad and \quad \lambda K>b \tag{69}$$

This expression in equation (69) is the condition for existence and positivity of the endemic equilibrium solution.

2.6.4 Local Stability of Disease Free Equilibrium

Theorem 2. If $R_0<1$ then the diseases free equilibrium of the model is locally asymptotically stable and unstable if $R_0\geq 1$.

Proof: We use the jacobian stability approach to prove the stability of the diseases free equilibrium.

$$J(E)=\begin{pmatrix} -(\mu+\lambda I) & 0 & -\lambda S & 0 & 0 & \rho \\ \lambda I & -(\mu+\gamma) & \lambda S & 0 & 0 & 0 \\ 0 & \gamma & -(\mu+\alpha_1+r_1+r_2) & 0 & 0 & 0 \\ 0 & 0 & r_1 & -(\mu+\alpha_2+\delta_1) & 0 & 0 \\ 0 & 0 & r_2 & 0 & -(\mu+\alpha_3+\delta_2) & 0 \\ 0 & 0 & 0 & \delta_1 & \delta_2 & -(\mu+\rho) \end{pmatrix} \tag{70}$$

At the diseases free equilibrium we have $I=E=R_1=R_2=R=0 \ and \ S=\frac{\Lambda}{\mu}$

Thus the Jacobian matrix at disease free equilibrium is given by:

$$J(E_0)=\begin{pmatrix} -\mu & 0 & -\frac{\lambda\Lambda}{\mu} & 0 & 0 & \rho \\ 0 & -(\mu+\gamma) & \frac{\lambda\Lambda}{\mu} & 0 & 0 & 0 \\ 0 & \gamma & -(\mu+\alpha_1+r_1+r_2) & 0 & 0 & 0 \\ 0 & 0 & r_1 & -(\mu+\alpha_2+\delta_1) & 0 & 0 \\ 0 & 0 & r_2 & 0 & -(\mu+\alpha_3+\delta_2) & 0 \\ 0 & 0 & 0 & \delta_1 & \delta_2 & -(\mu+\rho) \end{pmatrix} \tag{71}$$

Let $K=\mu+\alpha_1+r_1+r_2$

$$J(E_0)=\begin{pmatrix} -\mu & 0 & -\frac{\lambda\Lambda}{\mu} & 0 & 0 & \rho \\ 0 & -(\mu+\gamma) & \frac{\lambda\Lambda}{\mu} & 0 & 0 & 0 \\ 0 & \gamma & -K & 0 & 0 & 0 \\ 0 & 0 & r_1 & -(\mu+\alpha_2+\delta_1) & 0 & 0 \\ 0 & 0 & r_2 & 0 & -(\mu+\alpha_3+\delta_2) & 0 \\ 0 & 0 & 0 & \delta_1 & \delta_2 & -(\mu+\rho) \end{pmatrix} \tag{72}$$

Thus the Eigenvalues of the jacobian matrix is given by

$$\lambda_1=-\mu<0 \tag{73}$$

$$\lambda_2=-(\mu+\alpha_2+\delta_1)<0 \tag{74}$$

$$\lambda_3=-(\mu+\alpha_3+\delta_2)<0 \tag{75}$$

$$\lambda_4=-(\mu+\rho)<0 \tag{76}$$

$$\lambda_5=-\frac{1}{2}\left(K+\mu+\gamma+\sqrt{\frac{4\lambda\gamma\Lambda}{\mu}+K^2-2K\mu-2K\gamma+\mu^2+2\mu\gamma+\gamma^2}\right)<0 \tag{77}$$

and

$$\lambda_6=\frac{1}{2}\left(-(K+\mu+\gamma)+\sqrt{\frac{4\lambda\gamma\Lambda}{\mu}+K^2-2K\mu-2K\gamma+\mu^2+2\mu\gamma+\gamma^2}\right) \tag{78}$$

Now for

$$\lambda_6 = \frac{1}{2}\left(-(K+\mu+\gamma) + \sqrt{\frac{4\lambda\gamma\Lambda}{\mu} + K^2 - 2K\mu - 2K\gamma + \mu^2 + 2\mu\gamma + \gamma^2} \right) < 0$$

implies that

$$(K+\mu+\gamma)^2 > \frac{4\lambda\gamma\Lambda}{\mu} + K\left((K-2(\mu+\gamma)\right) + (\mu+\gamma)^2 \tag{79}$$

Let $Z = \mu + \gamma$ (80)

$$(K+Z)^2 > \frac{4\lambda\gamma\Lambda}{\mu} + K(K-2Z) + Z^2 \tag{81}$$

$\Rightarrow$

$$\frac{4\lambda\gamma\Lambda}{\mu} + K(K-2Z) + Z^2 - (K+Z)^2 < 0 \tag{82}$$

$\Rightarrow$

$$\frac{4\lambda\gamma\Lambda}{\mu} + K^2 + Z^2 - 2KZ - K^2 - 2KZ - Z^2 < 0 \tag{83}$$

$\Rightarrow$

$$\frac{4\beta\gamma\Lambda}{\mu} - 4KZ < 0 \tag{84}$$

Putting $Z = \mu + \gamma$ and $K = \mu + \alpha_1 + r_1 + r_2$ into equation (84) we have

$$\frac{4\lambda\gamma\Lambda}{\mu} - 4(\mu+\alpha_1+r_1+r_2)(\mu+\gamma) < 0 \tag{85}$$

$\Rightarrow$

$$\frac{4}{(\mu+\alpha_1+r_1+r_2)(\mu+\gamma)}\left(\frac{\lambda\gamma\Lambda}{\mu(\mu+\alpha_1+r_1+r_2)(\mu+\gamma)} - 1 \right) < 0 \tag{86}$$

But R_0 is

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

Thus we have

$$\frac{4}{(\mu+\alpha_1+r_1+r_2)(\mu+\gamma)}(R_0 - 1) < 0 \tag{87}$$

Equation (87) will hold if $R_0 < 1$

Thus all eigenvalues of the Jacobian Matrix above has negative real part if $R_0 < 1$

Hence from Routh Hurwitz stability criterion we conclude that the diseases free equilibrium is locally asymptotically stable.

2.6.5 Global stability of the diseases free equilibrium.

Theorem 2: If $R_0 \leq 1$ then the diseases free equilibrium of the system is globally asymptotically stable on Ω.

Proof. By constructing an appropriate Lyapunov function $V = (S, E, I, R_1, R_2, R)$ on the positively invariant compact set Ω.

Defined

$$V = (S, E, I, R_1, R_2, R) = \gamma E + (\mu + \gamma) I \tag{88}$$

Differentiate equation (88) by t we have

$$\frac{dV}{dt} = \gamma \frac{dE}{dt} + (\mu + \gamma) \frac{dI}{dt} \tag{89}$$

Substitute equation (2) and (3) into (89) we have

$$\frac{dV}{dt} = \gamma \left(\lambda IS - (\mu + \gamma) E \right) + (\mu + \gamma) \left(\gamma E - (\mu + \alpha_1 + r_1 + r_2) \right) I \tag{90}$$

which gives

$$\frac{dV}{dt} = (\mu + \gamma)(\mu + \alpha_1 + r_1 + r_2) \left(\frac{\lambda \gamma \Lambda}{\mu (\mu + \gamma)(\mu + \alpha_1 + r_1 + r_2)} - 1 \right) I \tag{91}$$

therefore

$$\frac{dV}{dt} = (\mu + \gamma)(\mu + \alpha_1 + r_1 + r_2)(R_0 - 1) I \tag{92}$$

Which is strictly decreasing when $R_0 < 1$

i.e

$$\frac{dV}{dt} < 0 \ \ if \ \ R_0 < 1 \tag{93}$$

and

$\frac{dV}{dt} = 0$ If and only if $E = 0, I = 0, R_1 = 0, R_2 = 0 \ and \ R_0 = 1$

Defining the set $E_0 = \left\{ (E, I, R_1, R_2) \in \Omega : \frac{dL}{dt} = 0 \right\}$ the largest invariant set E_0 is contained in the set thus by LaSalle invariant principle [8] the diseases free equilibrium is globally asymptotically stable.

Hence the proof is complete.

2.6.6 Local stability of the endemic equilibrium

Theorem 4 The endemic equilibrium state of the system (1-6) is locally asymptotically stable if $R_0 > 1$.

Proof:
Using jacobian stability approach we consider the Jacobian matrix of (1-6) at endemic equilibrium points

$$J(E) = \begin{pmatrix} -(\mu+\lambda I^*) & 0 & -\lambda S^* & 0 & 0 & \rho \\ \lambda I^* & -(\mu+\gamma) & \lambda S^* & 0 & 0 & 0 \\ 0 & \gamma & -(\mu+\alpha_1+r_1+r_2) & 0 & 0 & 0 \\ 0 & 0 & r_1 & -(\mu+\alpha_2+\delta_1) & 0 & 0 \\ 0 & 0 & r_2 & 0 & -(\mu+\alpha_3+\delta_2) & 0 \\ 0 & 0 & 0 & \delta_1 & \delta_2 & -(\mu+\rho) \end{pmatrix} \quad (94)$$

Let K1= $\mu+\alpha_1+r_1+r_2$, K2= $\mu+\alpha_2+\delta_1$, K3= $\mu+\alpha_3+\delta_2$, K4= $\mu+\rho$, K5= $\mu+\gamma$ Also at the endemic equilibrium we have

$$S^* = \frac{(\mu+\gamma)(\mu+\alpha_1+r_1+r_2)}{\lambda\gamma} = \frac{\Lambda}{\mu R_0} \quad (95)$$

$$I^* = \frac{K\mu}{\lambda K - b}(R_0 - 1) = A(R_0 - 1) \quad (96)$$

Where $A = \frac{K\mu}{\lambda K - b}$

We are sure that A is always positive since both K and μ are positive parameter and from equation (69)

We have that $R_0 > 1$ implies $\lambda K - b > 0$

Putting equation (95) and (96) into (94) we obtain

$$J(E)=\begin{pmatrix} -(\mu+\lambda A(R_0-1)) & 0 & \frac{-\lambda\Lambda}{\mu R_0} & 0 & 0 & \rho \\ \lambda A(R_0-1) & -K_5 & \frac{\lambda\Lambda}{\mu R_0} & 0 & 0 & 0 \\ 0 & \gamma & -K_1 & 0 & 0 & 0 \\ 0 & 0 & r_1 & -K_2 & 0 & 0 \\ 0 & 0 & r_2 & 0 & -K_3 & 0 \\ 0 & 0 & 0 & \delta_1 & \delta_2 & -K_4 \end{pmatrix} \tag{97}$$

By reducing equation (97) to upper triangular matrix using Gaussian elimination method we have

$$J(E)=\begin{pmatrix} -(\mu+\lambda A(R_0-1)) & 0 & \frac{-\lambda\Lambda}{\mu R_0} & 0 & 0 & \rho \\ 0 & -K_5 & \frac{\lambda\Lambda}{(A\lambda(R_0-1)+\mu)R_0} & 0 & 0 & \frac{\lambda A(R_0-1)\rho}{(A\lambda(R_0-1)+\mu)} \\ 0 & 0 & -\frac{ZR_0(R_0-1)}{K_5(A\lambda(R_0-1)+\mu)R_0} & 0 & 0 & \frac{\lambda A\gamma(R_0-1)\rho}{K_5(A\lambda(R_0-1)+\mu)} \\ 0 & 0 & 0 & -K_2 & 0 & \frac{\lambda AR_0r_1\gamma(R_0-1)\rho}{ZR_0(R_0-1)} \\ 0 & 0 & 0 & 0 & -K_3 & \frac{\lambda AR_0r_2\gamma(R_0-1)\rho}{Z(R_0-1)} \\ 0 & 0 & 0 & 0 & 0 & -\frac{R_0(K_3K_4K_2Z-(M_1+M_2))(R_0-1)}{K_2K_3(Z(R_0-1))} \end{pmatrix} \tag{98}$$

Where $Z = AK_1K_5\lambda$ *and* $M_1 + M_2 = (K_3\delta_1r_1 + K_2\delta_2r_2)\gamma\lambda A\rho$

Thus the Eigenvalues of the reduced Jacobian matrix is

$$\lambda_1 = -K_5 < 0 \tag{99}$$

$$\lambda_2 = -K_3 < 0 \tag{100}$$

$$\lambda_3 = -K_2 < 0 \tag{101}$$

$$\lambda_4 = -(\mu+\lambda A(R_0-1) < 0 \tag{102}$$

$If \;\; R_0 > 1$

$$\lambda_5 = -\frac{Z(R_0 - 1)}{K_5\left(A\lambda(R_0 - 1) + \mu\right)R_0} < 0 \tag{103}$$

$$\lambda_6 = -\frac{R_0\left(K_3K_4K_2Z - (M_1 + M_2)\right)(R_0 - 1)}{K_2K_3\left(Z(R_0 - 1)\right)} < 0 \tag{104}$$

$if \;\; R_0 > 1 \quad and \quad K_3K_4K_5Z > M_1 + M_2$

Which verified the local stability of the endemic equilibrium $if \;\; R_0 > 1$.

The epidemiological implication of this is that the diseases persist in the population $if \;\; R_0 > 1$

2.6.7 Global Stability of Diseases Endemic Equilibrium

Theorem 5 The endemic equilibrium $\Phi = \left(S^*, E^*, I^*, R_1^*, R_1^*, R^*\right)$ is globally asymptotically stable Ω $If \;\; R_0 > 1$.

Proof:

We establish the stability of endemic equilibrium by constructing Lyapunuv function

$$V\left(S, E, I, R_1, R_2, R\right) = \begin{bmatrix} \lambda_1\left[S - S^* - S^* \ln\left(\frac{S}{S^*}\right)\right] + \lambda_2\left[E - E^* - E^* \ln\left(\frac{E}{E^*}\right)\right] + \\ \lambda_3\left[I - I^* - I^* \ln\left(\frac{I}{I^*}\right)\right] + \lambda_4\left[R_1 - R_1^* - R_1^* \ln\left(\frac{R_1}{R_1^*}\right)\right] + \\ \lambda_5\left[R_2 - R_2^* - R_2^* \ln\left(\frac{R_2}{R_2^*}\right)\right] + \lambda_6\left[R - R^* - R^* \ln\left(\frac{R}{R^*}\right)\right] \end{bmatrix} \tag{105}$$

Where $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6$ are positive constant.

Taking the derivative of the Lyapunov function V above we have

$$\frac{dV}{dt} = \left[\begin{array}{l} \lambda_1\left(1-\frac{S^*}{S}\right)\frac{dS}{dt} + \lambda_2\left(1-\frac{E^*}{E}\right)\frac{dE}{dt} + \lambda_3\left(1-\frac{I^*}{I}\right)\frac{dE}{dt} + \\ \lambda_4\left(1-\frac{R_1^*}{R_1}\right)\frac{dR_1}{dt} + \lambda_5\left(1-\frac{R_2^*}{R_2}\right)\frac{dR_2}{dt} + \lambda_6\left(1-\frac{R^*}{R}\right)\frac{dR}{dt} \end{array} \right] \tag{106}$$

By substituting equation 1-6 into (98) and using the relation obtain from (1-6) as

$$\Lambda + \rho R^* = \left(\lambda I^* + \mu\right)S^* \tag{107}$$

$$\lambda I^* S^* = \left(\mu + \gamma\right)E^* \tag{108}$$

$$\gamma E^* = \left(\mu + \alpha_1 + r_1 + r_2\right)I^* \tag{109}$$

$$r_1 I^* = \left(\mu + \alpha_2 + \delta_1\right)R_1^* \tag{110}$$

$$r_2 I^* = \left(\mu + \alpha_3 + \delta_2\right)R_2^* \tag{111}$$

$$\delta_1 R_1^* + \delta_2 R_2^* = \left(\mu + \rho\right)R^* \tag{112}$$

We obtain

$$\frac{dV}{dt} = -\left[\begin{array}{l} \frac{\lambda_1\left(S-S^*\right)^2\left(\lambda I^* + \mu\right)}{S} + \frac{\lambda_2\left(E-E^*\right)^2\left(\mu+\gamma\right)}{E} + \frac{\lambda_3\left(I-I^*\right)^2\left(\mu+\alpha_1+r_1+r_2\right)}{I} + \\ \frac{\lambda_4\left(R_1-R_1^*\right)^2\left(\mu+\alpha_2+\delta_1\right)}{R_1} + \frac{\lambda_5\left(R_2-R_2^*\right)^2\left(\mu+\alpha_3+\delta_2\right)}{R_2} + \frac{\lambda_6\left(R-R^*\right)^2\left(\mu+\rho\right)}{R} \end{array} \right] \tag{113}$$

But $I^* = A(R_0 - 1)$, thus equation (113) becomes

$$\frac{dV}{dt} = -\left[\begin{array}{l} \frac{\lambda_1\left(S-S^*\right)^2\left(\lambda A(R_0-1) + \mu\right)}{S} + \frac{\lambda_2\left(E-E^*\right)^2\left(\mu+\gamma\right)}{E} + \frac{\lambda_3\left(I-I^*\right)^2\left(\mu+\alpha_1+r_1+r_2\right)}{I} + \\ \frac{\lambda_4\left(R_1-R_1^*\right)^2\left(\mu+\alpha_2+\delta_1\right)}{R_1} + \frac{\lambda_5\left(R_2-R_2^*\right)^2\left(\mu+\alpha_3+\delta_2\right)}{R_2} + \frac{\lambda_6\left(R-R^*\right)^2\left(\mu+\rho\right)}{R} \end{array} \right] \tag{114}$$

$\Rightarrow$

$\frac{dV}{dt} < 0 \;\; if \;\; R_0 > 1$

and

$\frac{dV}{dt} = 0 \;\; iff \;\; S = S^*, \; E = E^*, \; I = I^*, \;\; R_1 = R_1^*, \; R_2 = R_2^*, \; and \;\; R = R^*$

Thus the largest compact invariant set in $\Phi = \left(S^*, E^*, I^*, R_1^*, R_1^*, R^*\right) \in \Omega : \frac{dV}{dt} = 0$ is the singleton set Φ where Φ is the endemic equilibrium. Thus Φ is globally asymptotically stable in the interior of the region Ω.

Hence the proof is complete.

3.0 Results and Discussion

3.1 Solutions of the model

We solve the model using homotopy perturbation method; see [3] for details on applications of homotopy perturbation method.

The solutions to equations 1-6 are

$$S(t) = S_0 + (\Lambda + \rho z_0 - \lambda I_0 S_0 - \mu S_0)t + \left[\begin{array}{r} \rho\left(\delta_1 (R_1)_0 + \delta_2 (R_2)_0 - (\mu + \rho) R_0\right) - \lambda I_0 (\Lambda + \rho z_0 - \lambda I_0 S_0 - \mu S_0) \\ - \lambda\left(\gamma E_0 - K_1 I_0\right) S_0 - \mu\left(\Lambda + \rho z_0 - \lambda I_0 S_0 - \mu S_0\right) \end{array}\right] \frac{t^2}{2} \quad (115)$$

$$E(t) = E_0 + \left(\lambda I_0 S_0 - (\mu + \gamma) E_0\right)t + \left[\begin{array}{r} \lambda w_0 \left(\Lambda + \rho z_0 - \lambda I_0 S_0 - \mu S\right) - (\mu + \gamma)\left(\lambda I_0 S_0 - (\mu + \gamma) E_0\right) \\ - S_0 \left(\gamma E_0 - K_1 I_0\right) \end{array}\right] \frac{t^2}{2} \quad (116)$$

$$I(t) = I_0 + \left(\gamma E_0 - K_1 I_0\right)t + \left[\gamma\left(\lambda I_0 S_0 - (\mu + \gamma) E_0\right) - K_1\left(\gamma E_0 - K_1 I_0\right)\right] \frac{t^2}{2} \quad (117)$$

$$R_1(t) = (R_1)_0 + (r_1 I_0 - K_2(R_1)_0)t + \left[r_1(\gamma E_0 - K_1 I_0) - K_2(r_1 I_0 - K_2(R_1)_0)\right]\frac{t^2}{2} \quad (118)$$

$$R_2(t) = (R_2)_0 + (r_2 I_0 - K_3(R_2)_0)t + \left[r_2(\gamma E_0 - K_1 I_0) - K_3(r_2 I_0 - K_3(R_2)_0)\right]\frac{t^2}{2} \quad (119)$$

$$R(t) = R_0 + \left(\delta_1(R_1)_0 + \delta_2(R_2)_0 - (\mu+\rho)R_0\right)t + \begin{bmatrix} \delta_1(r_2 I_0 - K_3(R_2)_0) + \delta_2(r_2 I_0 - K_3(R_2)_0) \\ -(\mu+\rho)(\delta_1(R_1)_0 + \delta_2(R_2)_0) \end{bmatrix}\frac{t^2}{2} \quad (120)$$

3.2 Numerical Simulation

The parameter and variable values of six compartments model are assumed and estimated from the population of interest and also on Tuberculosis disease epidemiology. The description of the parameters of the model is show in the table below.

Table 2 Variable and Parameter Values and Estimations

Parameters	Descriptions	Values (yr^{-1})	References
Λ	Recruitment rate	15 .00	Estimated
η	Case detection rate	0.570	Arthitian (2013)
r_1	Resistance to first line of treatment rate	0.400	Kumar Gupta et al (2018)
r_2	Resistance to second line of treatment rate	0.500	Kumar Gupta et al (2018)
δ_1	Recovery due to first line of treatment rate	0.800	Estimated
δ_2	Recovery due to second line of treatment rate	0.300	Estimated
ρ	Rate at which individual losses their immunity	0.400	Kumar Gupta et al (2018)

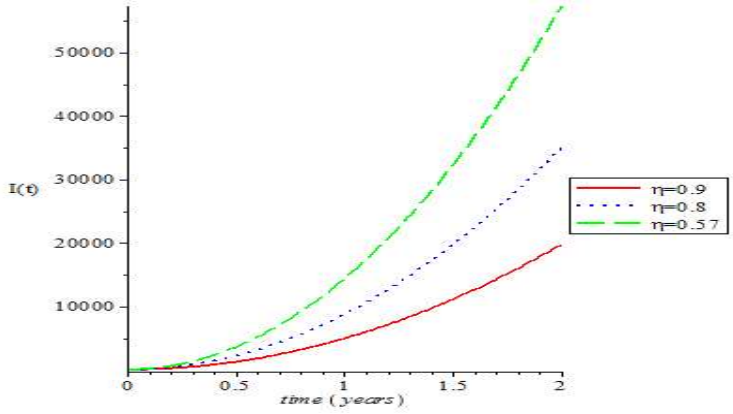

Figure 2 Graph of Infected Individuals against time for different case detection Rate η.

It was observed that the population of infected individuals decreases as case detection rate increases. This means that if early case detection is high then fewer people will be infected compare to when the case detection rate is low as we will have high contact rate between the susceptible and infected individuals as a results of unidentified cases of Tuberculosis.

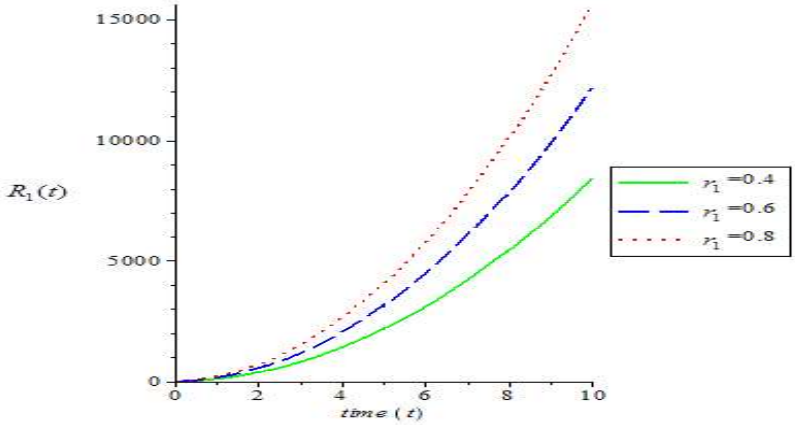

Figure 3 Graph of Individuals who are resistance to first line of treatment against time for different resistance rate to first line of treatment r_1 .

We see from the graph that the population of resistant individuals increases as the resistance rate of first line of treatment increases. This shows that more people will move from infected class to resistance class of first line of treatment as resistance rate due to first line of treatment increases.

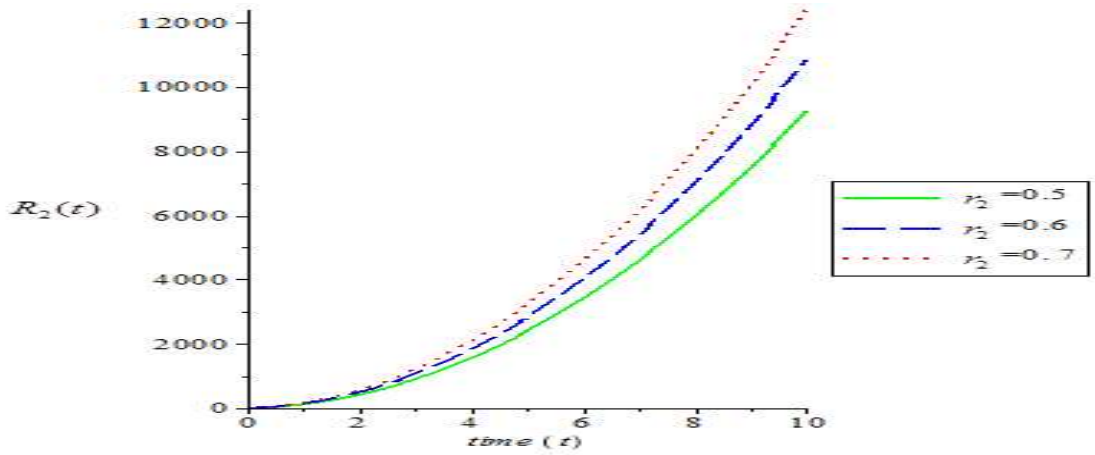

Figure 4 Graph of Individuals who are resistance to second line of treatment against time for different resistance rate to second line of treatment r_2 .

We see from the graph that the population of resistant individuals of second line of treatment class increases as the resistance rate of second line of treatment increases. This shows that more people will move from resistance class of first line of treatment to resistance class of second line of treatment as resistance rate due to second line of treatment increases.

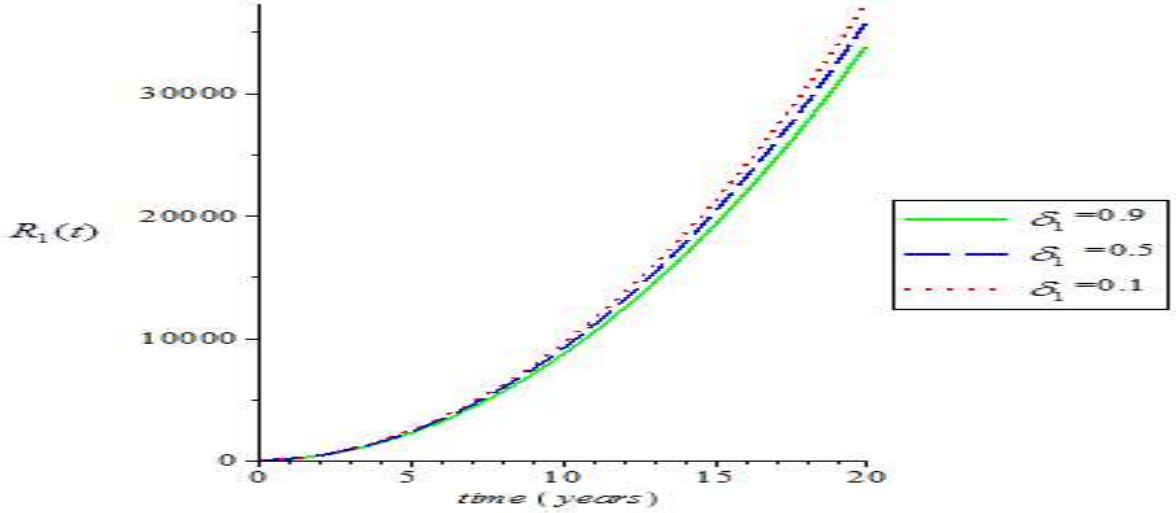

Figure 5 Graph of Individuals who are resistance to first line of treatment against time for different recovery rate due to first line treatment δ_1 .

We observed from the graph that the population of resistant individuals decreases as the recovery rate due to first line of treatment increases. This shows that more people will move from resistance class of first line of treatment to recovered class as recovery rate due to first line of treatment increases.

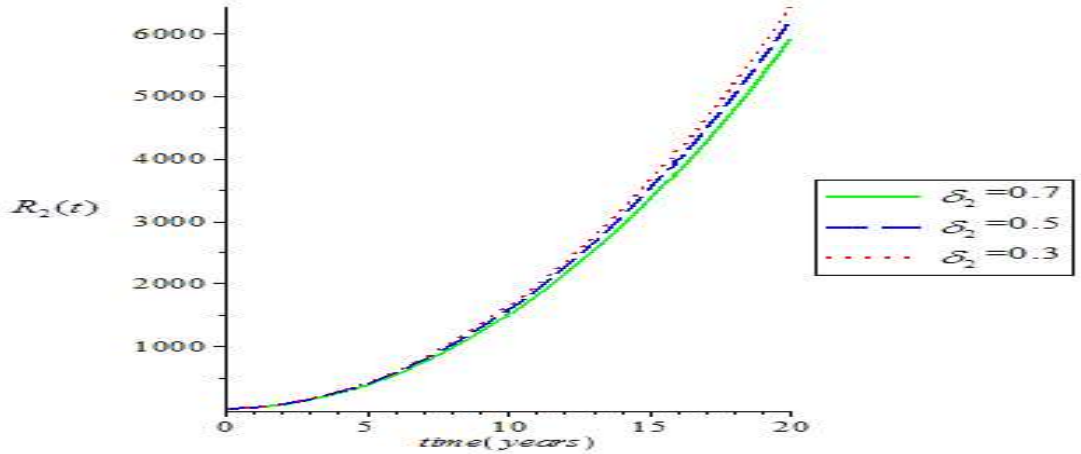

Figure 6 Graph of Individuals who are resistance to second line of treatment against time for different recovery rate due to second line treatment δ_2.

We observed from the graph that the population of resistant individuals decreases as the recovery rate due to second line of treatment increases. This shows that more people will move from resistance class of second line of treatment to recovered class as recovery rate due to second line of treatment increases.

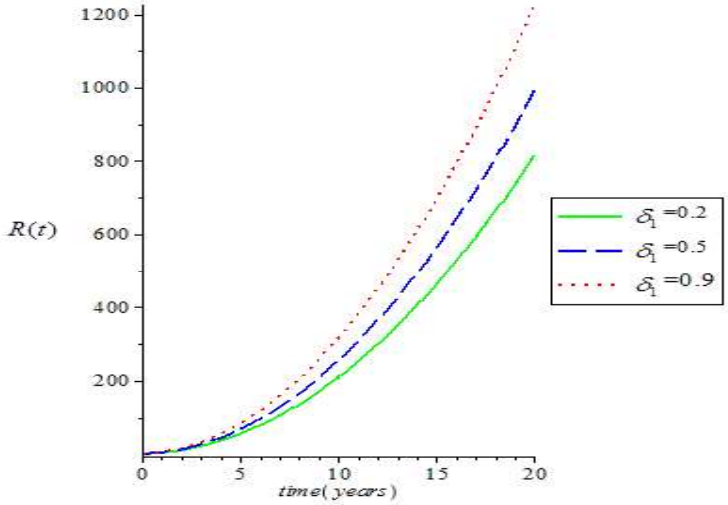

Figure 7 Graph of Recovered Individuals against time for different recovery rate due to first line treatment δ_1.

It was noticed that the population of recovered class increases as the rate of recovery due to first line of treatment increases. This shows that more people will move to recovered class if adequate treatment is administered early.

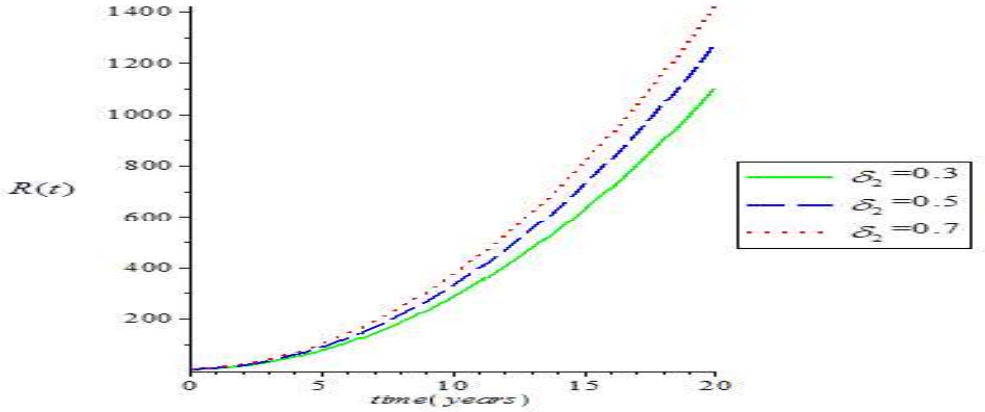

Figure 8 Graph of Recovered Individuals against time for different recovery rate due to second line treatment δ_2 .

It was observed that the population of recovered class increases as the rate of recovery due to second line of treatment increases. This shows that more people will move to recovered class from Resistance class due to second line of treatment.

4. Conclusion

This study presents a deterministic model for the effects of case detection and Resistance to tuberculosis diseases. It was shown that the model is mathematically and epidemiologically meaningful in the feasible region. The positivity of the solution was established, equilibrium points were obtained, and their stability analysis was performed. The conditions for local and global stability of both disease free equilibrium point and endemic equilibrium point were also established. The basic reproduction number using the next generation matrix was obtained was used to form the bases for stability of the equilibrium points. The analysis revealed that diseases free equilibrium is locally asymptotically stable if $R_0 < 1$ and globally stable if $R_0 \leq 1$. Also, the endemic equilibrium point is locally asymptotically stable if $R_0 > 1$ and globally asymptotically stable if $R_0 \geq 1$. Semi-Analytical solutions of the model using Homotopy Perturbation Method (HPM) were obtained graphical profiles of the solutions were presented.

From the results obtained, it was observed that when the case detection rate is high the infected population reduced drastically due to low possibility of contacts between the susceptible population and infectious individuals. Also the result revealed that resistant individuals to first and second line of treatment increase as resistance rate of both classes increases respectively mainly due to treatment failure. The result further revealed that recovered class increases as recovery rate of first and second line of treatment increases.

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