Mathematical Modelling and Analysis
Volume 14 Number 3, 2009, pages 291–312
Doi:10.3846/1392-6292.2009.14.291-312

ISSN 1392-6292 print
ISSN 1648-3510 online
www.vgtu.lt/mma/

A Two Strain Tuberculosis Transmission Model with Therapy and Quarantine

C. P. Bhunu[1] **and W. Garira**[2]

[1,2] *Modelling Biomedical Systems Research Group, Department of Applied Mathematics, National University of Science and Technology*
[1] P. O. Box AC 939 Ascot, Bulawayo, Zimbabwe
[2] *Department of Mathematics and Applied Mathematics, University of Venda, South Africa*
E-mail(*corresp.*): cpbhunu1762@nust.ac.zw; cpbhunu@gmail.com

Received May 12, 2008; revised January 23, 2009; published online July 15, 2009

Abstract. A two strain tuberculosis model with treatment which allows TB patients with the drug sensitive of strain *Mycobacterium tuberculosis* to be cured is presented. The model is further extended to incorporate quarantine for active TB cases with multi-drug resistant TB strains. The model assumes that latently infected individuals develop active disease as a result of endogenous activation and exogenous reinfection. Qualitative analysis of the model including positivity, boundedness and persistence of solutions are presented. The thresholds and equilibria quantities for the models are determined and stability of the solution is analyzed. From the study we conclude that quarantine of the multi-drug resistant tuberculosis cases reduces the multi-drug resistant tuberculosis induced reproduction number to values below unit, thus this intervention strategy can control the development of multi-drug resistant tuberculosis epidemic. Also effective chemoprophylaxis and treatment of infectives result in a reduction of multi-drug resistant tuberculosis cases since most multi-drug resistant tuberculosis cases are a result of inappropriate treatment.

Key words: Tuberculosis model, chemoprophylaxis, treatment, quarantine, exogenous re-infection, multi-drug resistant.

1 Introduction

Tuberculosis (TB) is second common cause of death after HIV/AIDS (Frieden et al., [17]) in the world. There were an estimated 8-9 million new cases of TB in 2000, fewer than half of which were reported, 3-4 million cases were sputum-smear positive, the most infectious form of the disease (Corbet et al. [11]). Tuberculosis is a bacterial disease with an estimated one third of the world population as its reservoir (Castillo-Chavez and Feng, [8]). It is caused by *Mycobacterium tuberculosis* bacteria (Mtb). The disease is most commonly transmitted from a person suffering of infectious tuberculosis to susceptible and

possibly latently infected individuals by infected droplets produced by an individual with active TB coughs, sneezes or talks (Castillo-Chavez and Feng, [8]). Individuals with latent forms of TB are not clinically ill and cannot transmit TB (Miller, [20]). Sub-Saharan Africa remains the epicenter of the epidemic, but India, China, Indonesia, Bangladesh and Pakistan together account for more than half of the cases in the world (Frieden et al., [17]). TB has declined in the developed world, but has increased in the former Soviet Union due to general failure of TB control programs (Shilov and Dye, [24]). Periodic surveys have shown that over 10% of new TB cases in Latvia, Estonia and some parts of Russia are multi-drug resistant (WHO, 2003). Multi-drug resistant TB (MDRTB) is defined as resistance to isoniazid and rifampicin whether there is resistance to other first line drugs or not (Davies, [12]). It is therefore incorrect to classify a patient as having MDRTB if one is infected with a bacterium susceptible to rifampicin but resistant to many other drugs. Resistance to isoniazid and streptomycin only is the most common form of resistance to more than one drug. This is not strictly MDRTB, perhaps another separate term is needed to define this combination of resistances (Davies, [12]). The success of the drug treatment of TB has catalyzed the emergence of a new wave drug resistant TB. Early single use of streptomycin has taught us that taking one drug on its own for TB would lead to drug resistance (Davies, [12]). A combination of poor compliance and poor medical supervision can result n multi-drug resistance. However some acquire MDRTB by being infected with a multi-drug resistant strain. MDRTB is transmitted in the same way as the normal drug sensitive strain. Current estimates are at least 2000 newly active MDRTB cases in South Africa each year (National Tuberculosis Research Programme, [23]). Cure rates for MDRTB are under 50%, over 30% of MDRTB are fatal within two years. The remainder are chronic and continue to be infectious, posing a threat to communities (National Tuberculosis Research Programme, [23]).

Except South Africa, most developing countries in Sub-Saharan Africa such as Zimbabwe lack second line drugs because they are poor. Second line drugs are drugs used to treat MDRTB. Preventing the outbreak of MDRTB remains the effective key in controlling this epidemic. The spread of MDRTB bacteria depends on factors such as the total number and concentration of infectious people in any place and time of exposure, along with the presence of people with a higher risk of being infected such as those with HIV/AIDS. Failure to control MDRTB leads to the creation of extensively drug resistant TB (XDRTB) which is resistant to first and second line drugs. Treatment options for XDRTB are limited, and in May 2007 an individual with XDRTB was quarantined in the USA to prevent the spread of the disease (Singh, [25]).

Coexistence of different pathogens (strains) in the same host were studied (Ackleh and Allan, [1]; Allen et al., [2]; Blower and Gerberding, [4]; Blyuss and Kyrychko, [5]; Castillo-Chavez and Feng, [7, 8]; Dye and William, [15]; Martcheva et al., [18]; May and Nowak, [19]; Nowak and Sigmund, [22]; Naresh and Tripath, [21]). Castillo-Chavez and Feng [7, 8]) studied a two strain TB model in the context of treatment. Our work differs from all these studies that, in addition to treatment, we consider the possible benefits to the community if MDRTB cases are quarantined. We have also added a scenario where an

individual sick from the drug sensitive TB can be infected with multi-drug resistant TB and move to MDRTB stage. We have also incorporated a scenario where an individual in the latent stage of drug sensitive TB can become sick with MDRTB after being infected with drug resistant strain.

2 Model

We subdivide the population into susceptible individuals (S), those exposed to drug sensitive TB only (E_{T_1}), individuals with symptoms of TB and drug sensitive, (I_{T_1}), those who have recovered (R_T), those exposed to multi-drug resistant TB (E_{T_2}) and those displaying symptoms of TB and multi-drug resistant, (I_{T_2}). Susceptible humans are recruited into the population at per capita rate Λ. Susceptible individuals acquire Mtb infection following contact with an active TB case at a rate $\lambda_i,\ i = 1,\ 2$ where $i = 1$ and $i = 2$ represent rates of infection by drug sensitive strain and multi-drug resistant strain, respectively. The large population size $N(t)$ is

$$N(t) = S(t) + E_{T_1}(t) + I_{T_1}(t) + R_T(t) + E_{T_2}(t) + I_{T_2}(t).$$

Individuals in different human subgroups suffer from natural death at a constant rate μ. The force of infection (λ_i), associated with Mtb infection is $\lambda_i = (\beta_i c I_{T_i})/N$, where β_i is the probability that an individual is infected with one infectious individual and c is per capita contact rate. Susceptible are infected with drug sensitive Mtb at rate λ_1 and multi-drug resistant strain at rate λ_2 entering classes E_{T_1} and E_{T_2}, respectively. Individuals in E_{T_1} enter the infectious class I_{T_1} from endogenous reactivation progression and exogenous reinfection at rates k_1 and $\delta_1\lambda_1$, with $\delta_1 \in (0, 1)$ since primary infection offers some degree of immunity. Active forms of tuberculosis are treated using first line drugs (rifampicin, isoniazid, pyrazinamide, ethambutol) taken daily for two months and followed by a daily intake of rifampicin and isoniazid for a period of four months. Exposed individuals are treated with isoniazid. Twelve months isoniazid daily intake gives 70% to 90% protection against development of active TB, six months of therapy provides 50% to 60% protection (Coleman and Slutkin, [10]). However for suspected isoniazid-resistant Mtb infection it is safest to treat with rifampicin (with or without isoniazid). Individuals in E_{T_1} receive chemoprophylaxis at a rate of r_1 and move to the recovered class R_T. Individuals infected with Mtb in E_{T_1} can acquire TB resistance following infection with the drug resistant strain at rate and λ_2 and enter E_{T_2}. Individuals sick with drug sensitive strain of TB receive treatment at rate r_2 and a proportion pr_2 respond to treatment and move into R_T, a proportion qr_2 partially respond and move back to the exposed class E_{T_1} and in the remaining proportion $(1 - (p + q))r_2$ failure of treatment results in the development of multi-drug resistant strains and the individuals move into E_{T_2}.

There is an additional disease induced-death d_1 for those in I_{T_1}. Individuals in this class acquire drug resistance from being infected with the drug resistant strain at rate λ_2 and this process is referred to as super-infection. Those in R_T are not fully immune to Mtb, are infected with drug sensitive strain at rate λ_1 to move into E_{T_1}, and are infected with drug resistant strain at rate λ_2 to move

into E_{T_2}. Individuals in E_{T_2} enter the drug resistant active TB class, I_{T_2} from endogenous reactivation at rates k_2, and exogenous reinfection at rates λ_1 and $\delta_2\lambda_2$ with $\delta_2 \in (0,1)$ since primary infection confers some degree of immunity. Individuals in the infectious class I_{T_2} suffer an additional disease induced death at rate d_2. As it is difficult to treat MDRTB in developing countries such as Zimbabwe due to the unavailability of second line drugs, we ignore treatment of the multi-drug resistant strain. This makes our model more appropriate for resource-poor settings. The model flow diagram is shown in Figure 1. The following system of differential equations describe the interaction of the two strains:

$$\begin{cases} S'(t)=\Lambda-(\lambda_1+\lambda_2)S-\mu S, \\ E'_{T_1}(t)=\lambda_1(S+R_T)-\delta_1\lambda_1 E_{T_1}-\lambda_2 E_{T_1}-(k_1+\mu+r_1)E_{T_1}+qr_2 I_{T_1}, \\ I'_{T_1}(t)=\delta_1\lambda_1 E_{T_1}+k_1 E_{T_1}-\lambda_2 I_{T_1}-(r_2+\mu+d_1)I_{T_1}, \\ R'_T(t)=pr_2 I_{T_1}+r_1 E_{T_1}-(\lambda_1+\lambda_2)R_T-\mu R_T, \\ E'_{T_2}(t)=\lambda_2 S+(1-(p+q))r_2 I_{T_1}+\lambda_2 R_T-\lambda_1 E_{T_2}-\delta_2\lambda_2 E_{T_2}-(\mu+k_2)E_{T_2}, \\ I'_{T_2}(t)=\lambda_1 E_{T_2}+\delta_2\lambda_2 E_{T_2}+k_2 E_{T_2}+\lambda_2 E_{T_1}+\lambda_2 I_{T_1}-(\mu+d_2)I_{T_2}. \end{cases} \tag{2.1}$$

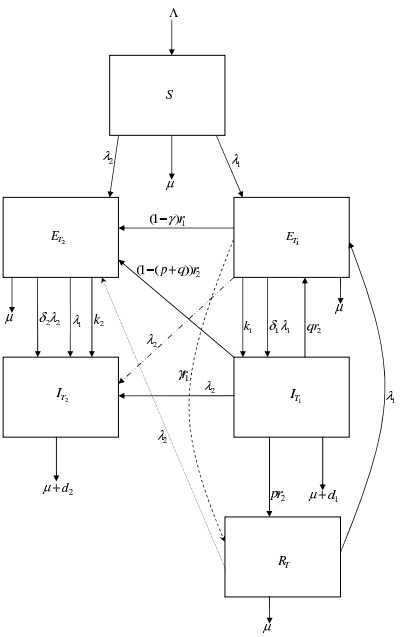

Figure 1. Structure of model. In this case $\gamma = 1$.

2.1 Invariant region

The two strain TB transmission model (2.1) will be analyzed in a suitable region as follows. We first show that system (2.1) is dissipative. That is all solutions are uniformly bounded in a proper subset $\mathcal{K} \subset \mathbb{R}^6_+$.

Let, $(S, E_{T_1}, I_{T_1}, R_T, E_{T_2}, I_{T_2}) \in \mathbb{R}^6_+$ be any solution with non-negative initial conditions. Using a theorem by Birkhoff and Rota [3] on differential inequality it follows that

$$\limsup_{t\to\infty} S(t) \leq \frac{\Lambda}{\mu}.$$

Taking the time derivative of $N(t)$ along a solution path of the system gives

$$N'(t) = \Lambda - \mu N(t) - d_1 I_{T_1} - d_2 I_{T_2}.$$

Model system (2.1) has a varying population size ($N' \neq 0$) and therefore a trivial equilibrium is not feasible. Let $\alpha = \min(d_1, d_2)$, then,

$$N' \leq \Lambda - \mu N - \alpha(I_{T_1} + I_{T_2}) < \Lambda - \mu N.$$

So that (following Birkhoff and Rota, [3])

$$0 \leq N \leq \frac{\Lambda}{\mu} + N(0)e^{-\mu t},$$

where $N(0)$ represents the value evaluated at the initial values of the respective variables. Thus $0 \leq N \leq \dfrac{\Lambda}{\mu}$, as $t \to \infty$. Therefore all feasible solutions of system (2.1) enter the region

$$\mathcal{K} = \left\{ (S, E_{T_1}, I_{T_1}, R_T, E_{T_2}, I_{T_2}) \in \mathbb{R}^6_+ : N \leq \frac{\Lambda}{\mu} \right\}.$$

Thus, $\mathcal{K}$ is positively invariant and it is sufficient to consider solutions in $\mathcal{K}$. Existence, uniqueness and continuation results for system (2.1) hold in this region. It can be shown that all solutions of system (2.1) starting in $\mathcal{K}$ remain in $\mathcal{K}$ for all $t \geq 0$. All parameters and state variables for model system (2.1) are assumed to be non-negative for $t \geq 0$ since it monitors human population.

2.2 Disease free equilibrium and stability analysis

The disease free equilibrium is given as

$$\mathcal{U}_0 = \left(S^0,\ E^0_{T_1},\ I^0_{T_1},\ R^0_T,\ E^0_{T_2},\ I^0_{T_2}\right) = \left(\frac{\Lambda}{\mu},\ 0,\ 0,\ 0,\ 0,\ 0\right).$$

The basic reproduction number is defined as the number of secondary infections produced by a single infectious individual during the entire infectious period. In our case the reproduction number defines the number of secondary TB infections produced by a single active TB individual during the entire infectious period. Mathematically it is defined as the spectral radius of the next

generation matrix (van den Driessche and Watmough, [13]). Following van den Driessche and Watmough [13] to determine the reproduction number of the model system (2.1) we have

$$\mathcal{F} = \begin{bmatrix} \lambda_1(S+R_T) \\ 0 \\ 0 \\ \lambda_2(S+R_T) \\ 0 \\ 0 \end{bmatrix} \quad \text{and}$$

$$\mathcal{V} = \begin{bmatrix} (\delta_1\lambda_1+\lambda_2)E_{T_1} + (\mu+k_1+r_1)E_{T_1} - qr_2I_{T_1} \\ (\mu+d_1+r_2)I_{T_1} + \lambda_2 I_{T_1} - k_1E_{T1} - \delta_1\lambda_1E_{T_1} \\ \mu R_T + (\lambda_1+\lambda_2)R_T - r_1E_{T_1} - pr_2I_{T_1} \\ (\mu+k_2)E_{T_2} + (\lambda_1+\delta_2\lambda_2)E_{T_2} - \big(1-(p+q)\big)r_2I_{T_1} \\ (\mu+d_2)I_{T_2} - \lambda_2(I_{T_1}+E_{T_1}) - k_2E_{T_2} - (\lambda_1+\delta_2\lambda_2)E_{T_2} \\ \mu S + (\lambda_1+\lambda_2)S - \Lambda \end{bmatrix}.$$

The infected compartments are $E_{T_1},\ I_{T_1},\ E_{T_2}$ and I_{T_2}. Thus

$$F = \begin{bmatrix} 0 & \beta_1 c & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_2 c \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad \text{and}$$

$$V = \begin{bmatrix} \mu+k_1+r_1 & -qr_2 & 0 & 0 \\ -k_1 & \mu+d_1+r_2 & 0 & 0 \\ 0 & -\big(1-(p+q)\big)r_2 & \mu+k_2 & 0 \\ 0 & 0 & -k_2 & \mu+d_2 \end{bmatrix}.$$

The dominant eigenvalues of FV^{-1} are given by

$$\mathcal{R}_1 = \frac{\beta_1 c k_1}{(k_1+r_1+\mu)(d_1+\mu)+r_2(r_1+\mu+k_1(1-q))}, \quad \mathcal{R}_2 = \frac{\beta_2 c k_2}{(\mu+k_2)(\mu+d_2)}.$$

The reproduction number is given as $\mathcal{R}_{rs} = \max\{\mathcal{R}_1, \mathcal{R}_2\}$, where $\mathcal{R}_1$ and $\mathcal{R}_2$ are reproduction numbers for drug sensitive TB strain only and drug resistant TB strain only respectively. Theorem 1 follows from van den Driessche and Watmough [13] (Theorem 2).

Theorem 1. *The disease free equilibrium point $\mathcal{U}_0$ is locally asymptotically stable if $\mathcal{R}_{rs} < 1$, that is $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$, and unstable otherwise.*

2.3 Endemic equilibria and invasion reproduction numbers

There are three possible endemic equilibria for model system (2.1): two boundary equilibria $\mathcal{U}_1$ (when only the first strain is present) and $\mathcal{U}_2$ (when only the

second strain is p resent), and the interior equilibrium point $\mathcal{U}_3$ (when both strains exist).

2.3.1 The drug sensitive TB-strain only equilibrium

This is obtained by setting $E_{T_2} = I_{T_2} = 0$ and $p + q = 1$. The drug sensitive TB only equilibrium in terms of the equilibrium value of the force of infection λ_1^* is given as

$$\mathcal{U}_1 = (S^*, E_{T_1}^*, I_{T_1}^*, R_T^*, 0, 0), \tag{2.2}$$

where $S^* = \Lambda/\mu + \lambda_1^*$,

$$E_{T_1}^* = \frac{(r_2 + \mu + d_1)\Lambda}{(\lambda_1^* + \mu)(A_1\lambda_1^{2*} + B_1\lambda_1^* + C_1)}, \quad I_{T_1}^* = \frac{\Lambda(\delta_1\lambda_1^* + k_1)}{A_1\lambda_1^{2*} + B_1\lambda_1^* + C_1}$$

$$R_T^* = \frac{(1-q)r_2\Lambda(\delta_1\lambda_1^* + k_1)r2}{(\lambda_1^* + \mu)(A_1\lambda_1^{2*} + B_1\lambda_1^* + C_1)} + \frac{\Lambda r_1(r_2 + \mu + d_1)}{(\lambda_1^* + \mu)(A_1\lambda_1^{2*} + B_1\lambda_1^* + C_1)},$$

$$A_1{=}\delta_1(\mu{+}d_1), \; B_1{=}\delta_1\mu(\mu{+}r_2{-}qr_2{+}\mu + d_1){+}(\mu{+}d_1)(\mu{+}k_1){+}\mu r_2,$$

$$C_1 = \mu(\mu + k_1 + r_1)(\mu + d_1) + r_2(k_1 - k_1q + r_1 + \mu).$$

Substituting equation (2.2) into the equation for λ_1^*, we obtain

$$\lambda_1^* g(\lambda_1^*) = \lambda_1^*(A_2\lambda_1^{*2} + B_2\lambda_1^* + C_2) = 0,$$

where $\lambda_1^* = 0$ corresponds to the disease free equilibrium and $g(\lambda_1^*) = 0$ corresponds to the existence of endemic equilibria where

$$A_2 = \frac{1}{(\mu + k_1 + r_1)(\mu + d_{T_1} + r_2) - qr_2k_1},$$

$$B_2 = \frac{\mu + k_1 + d_1 + r_2 - \beta_1 c}{(\mu + k_1 + r_1)(\mu + d_1 + r_2) - qr_2k_1}, \quad C_2 = 1 - \mathcal{R}_1.$$

By examining the quadratic equation we see that there is a unique endemic equilibrium if $B_2 < 0$ and $C_2 = 0$ or $B_2^2 - 4A_2C_2 = 0$, there are two if $C_2 > 0$, $B_2 < 0$ and $B_2^2 - 4A_2C_2 > 0$, and there is non-otherwise. The coefficient A_2 is always positive and C_2 is positive or negative if $\mathcal{R}_1$ is less than or greater than one respectively. We therefore rewrite these conditions in Lemma 1.

Lemma 1. *Model system* (2.1) *has* (i) *precisely one unique endemic equilibrium if* $C_2 < 0 \Leftrightarrow \mathcal{R}_1 > 1$, (ii) *precisely one unique endemic equilibrium if* $B_2 < 0$ *and* $C_2 = 0$ *or* $B_2^2 - 4A_2C_2 = 0$, (iii) *precisely two endemic equilibria if* $C_2 > 0$, $B_2 < 0$ *and* $B_2^2 - 4A_2C_2 > 0$, (iv) *otherwise there are none.*

To find the backward bifurcation point, we set the discriminant $B_2^2 - 4A_2C_2 = 0$ and make $\mathcal{R}_1$ the subject of the formulae to obtain

$$\mathcal{R}_1^c = 1 - \frac{B_2^2}{4A_2},$$

from which it can be shown that backward bifurcation occurs for values of $\mathcal{R}_1$ in the range $\mathcal{R}_1^c < \mathcal{R}_1 < 1$. We now state Theorem 2 to show the existence of the endemic equilibrium point $\mathcal{U}_1$.

Theorem 2. *The endemic equilibrium point $\mathcal{U}_1$ exists for $\mathcal{R}_1 > 1$.*

Proof. Analyzing the equation $g(\lambda_1^*) = 0$ we get $\lambda_1^* = \frac{-B_2+(B_2^2-4A_2C_2)^{(1/2)}}{2A_2}$ from which it is clear that the disease is endemic when

$$\lambda_1 > 0 \Rightarrow B_2^2 - 4A_2C_2 > B_2^2 \Rightarrow 4A_2(1-\mathcal{R}_1) < 0 \Rightarrow \mathcal{R}_1 > 1.$$

Thus the endemic equilibrium point $\mathcal{U}_1$ exists whenever $\mathcal{R}_1 > 1$. □

To determine the asymptotic stability of $\mathcal{U}_1$ we make use of the Centre Manifold theory (Carr, [6]) as described in Theorem 4.1 of Castillo-Chavez and Song [9]. To use the Centre Manifold theory let us make the following change of variables $S = x_1$, $E_{T_1} = x_2$, $I_{T_1} = x_3$, $R_T = x_4$, $E_{T_2} = x_5$ and $I_{T_2} = x_6$, so that $N(t) = \sum_{n=1}^{6} x_n$. Using the vector notation $X = (x_1, x_2, x_3, x_4, x_5, x_6)^T$ model system (2.1) can be written in the form $X'(t) = F = (f_1, f_2, f_3, f_4, f_5, f_6)^T$ as follows

$$\begin{aligned}
x_1'(t) &= f_1 = \Lambda - \frac{\sum_{j=1}^{2}\beta_j c x_{3j} x_1}{\sum_{n=1}^{6} x_n} - \mu x_1,\\
x_2'(t) &= f_2 = \frac{\beta_1 c x_3(x_1+x_4)}{\sum_{n=1}^{6} x_n} - \frac{\delta_1\beta_1 c x_3 x_2}{\sum_{n=1}^{6} x_n} - \frac{\beta_2 c x_6 x_2}{\sum_{n=1}^{6} x_n} - (k_1+\mu+r_1)x_2 + qr_2x_3,\\
x_3'(t) &= f_3 = \frac{\delta_1\beta_1 c x_3 x_2}{\sum_{n=1}^{6} x_n} - \frac{\beta_2 c x_6 x_3}{\sum_{n=1}^{6} x_n} + k_1x_2 - (r_2+\mu+d_1)x_3,\\
x_4'(t) &= f_4 = pr_2x_3 + r_1x_2 - \frac{\sum_{j=1}^{2}\beta_j c x_{3j} x_4}{\sum_{n=1}^{6} x_n} - \mu x_4,\\
x_5'(t) &= f_5 = \frac{\beta_1 c x_6(x_1+x_4)}{\sum_{n=1}^{6} x_n} + (1-(p+q))r_2x_3 - (\mu+k_2)x_5 - \frac{\beta_1 c x_3 x_5}{\sum_{n=1}^{6} x_n} - \frac{\delta_2\beta_2 c x_6 x_5}{\sum_{n=1}^{6} x_n},\\
x_6'(t) &= f_6 = \frac{\beta_1 c x_3 x_5}{\sum_{n=1}^{6} x_n} + \frac{\delta_2\beta_2 c x_6 x_5}{\sum_{n=1}^{6} x_n} + k_2x_5 + \frac{\beta_2 c x_6(x_2+x_3)}{\sum_{n=1}^{6} x_n} - (\mu+d_2)x_6.
\end{aligned} \tag{2.3}$$

The Jacobian matrix of system (2.3) at $\mathcal{U}_0$ is given by

$$J(\mathcal{U}_0) = \begin{bmatrix}
-\mu & 0 & -\beta_1 c & 0 & 0 & -\beta_2 c\\
0 & -(k_1+\mu+r_1) & qr_2+\beta_1 c & 0 & 0 & 0\\
0 & k_1 & -(r_2+\mu+d_1) & 0 & 0 & 0\\
0 & r_1 & pr_2 & -\mu & 0 & 0\\
0 & 0 & (1-(p+q))r_2 & 0 & -(\mu+k_2) & \beta_2 c\\
0 & 0 & 0 & 0 & k_2 & -(\mu+d_2)
\end{bmatrix} \tag{2.4}$$

From (2.4) it can be shown that

$$\begin{aligned}
\mathcal{R}_1 &= \frac{\beta_1 c k_1}{(k_1+r_1+\mu)(d_1+\mu) + r_2(r_1+\mu+k_1(1-q))},\\
\mathcal{R}_2 &= \frac{\beta_2 c k_2}{(\mu+k_2)(\mu+d_2)}.
\end{aligned} \tag{2.5}$$

If β_1 is taken as a bifurcation point and if we solve $\mathcal{R}_1 = 1$ for β_1 we obtain

$$\beta_1 = \beta_* = \frac{(k_1 + r_1 + \mu)(d_1 + \mu) + r_2(r_1 + \mu + k_1(1-q))}{ck_1} \tag{2.6}$$

The linearized system of the transformed system (2.3) with $\beta_1 = \beta_*$ has a simple zero eigenvalue. Thus the Centre Manifold theory can be applied in the analysis of the dynamics of system (2.3) near $\beta_1 = \beta_*$. The Jacobian of system (2.3) near $\beta_1 = \beta_*$ has a right eigenvector associated with the zero eigenvalue given by $u = [u_1, u_2, u_3, u_4, u_5, u_6]^T$, where

$$\begin{aligned}
u_1 &= -\frac{u_3}{\mu}\left(\beta_* c + \frac{(1-(p+q))r_2k_2\beta_2 c}{(\mu+d_2)(\mu+k_2)(1-\mathcal{R}_2)}\right) < 0 \quad \text{if } 1 > \mathcal{R}_2,\\
u_2 &= \frac{(r_2+\mu+d_1)u_3}{k_1} = \frac{(qr_2+\beta_* c)u_3}{k_1+\mu+r_1} > 0,\ u_3 = u_3 > 0,\\
u_4 &= \frac{((r_2+\mu+d_1)r_1 + pr_2k_1)u_3}{k_1\mu} > 0,\ u_5 = \frac{(1-(p+q))r_2u_3}{(\mu+k_2)(1-\mathcal{R}_2)} > 0 \quad \text{if } 1 > \mathcal{R}_2,\\
u_6 &= \frac{(1-(p+q))r_2k_2u_3}{(\mu+d_2)(\mu+k_2)(1-\mathcal{R}_2)} > 0 \quad \text{if } 1 > \mathcal{R}_2.
\end{aligned} \tag{2.7}$$

The left eigenvector associated with the zero eigenvalue at $\beta_1 = \beta_*$ is given by $v = [v_1, v_2, v_3, v_4, v_5, v_6]^T$ where,

$$\begin{aligned}
&v_1 = 0,\ v_2 = \frac{k_1v_3}{k_1+r_1+\mu},\ v_3 = v_3 > 0,\ v_4 = 0,\\
&v_5 = \frac{((k_1+r_1+\mu)(r_2+\mu+d_1) - (qr_2+\beta_* c)k_1)v_3}{(k_1+r_1+\mu)(1-p-q)r_2} > 0\\
&\text{if } (k_1+r_1+\mu)(r_2+\mu+d_1) - qr_2k_1 > \beta_* ck_1,\\
&v_6 = \frac{\beta_2 cv_5}{\mu+d_2} = \frac{(\mu+k_2)v_5}{k_2} \Leftrightarrow \mathcal{R}_2 = 1.
\end{aligned} \tag{2.8}$$

Further we use Theorem 3 proven by Castillo-Chavez and Song [9].

Theorem 3. *Consider the following general system of ordinary differential equations with a parameter* ϕ

$$\frac{dx}{dt} = f(x,\phi),\ f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}), \tag{2.9}$$

where 0 *is an equilibrium of the system that is* $f(0,\phi) = 0$ *for all* ϕ *and assume*

A1: $A = D_x f(0,0) = (\frac{\partial f_i}{\partial x_j}(0,0))$ *is the linearization of system* (2.9) *around the equilibrium* 0 *with* ϕ *evaluated at* 0. *Zero is a simple eigenvalue of* A *and other eigenvalues of* A *have negative real parts;*

A2: *Matrix* A *has a right eigenvector* u *and a left eigenvector* v *corresponding to the zero eigenvalue.*

Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \quad b = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \tag{2.10}$$

The local dynamics of (2.9) *around* 0 *are totally governed by a and b.*

i. *$a > 0$, $b > 0$. When $\phi < 0$ with $|\phi| << 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi << 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.*

ii. *$a < 0$, $b < 0$. When $\phi < 0$ with $|\phi| << 1$, 0 unstable; when $0 < \phi << 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium.*

iii. *$a > 0$, $b < 0$. When $\phi < 0$ with $|\phi| << 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi << 1$, 0 is stable, and a positive unstable equilibrium appears.*

iv. *$a < 0$, $b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Computations of a and b. The sign of a is associated with the following none vanishing partial derivatives of F

$$\begin{aligned}
&\frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -\frac{\beta_* c\mu(1+\delta_1)}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_2 \partial x_6} = \frac{\partial^2 f_2}{\partial x_6 \partial x_2} = -\frac{\beta_2 c\mu}{\Lambda},\\
&\frac{\partial^2 f_2}{\partial x_3^2} = -\frac{2\beta_* c\mu}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_5} = \frac{\partial^2 f_2}{\partial x_5 \partial x_3} = -\frac{\beta_* c\mu}{\Lambda},\\
&\frac{\partial^2 f_2}{\partial x_3 \partial x_6} = \frac{\partial^2 f_2}{\partial x_6 \partial x_3} = -\frac{\beta_* c\mu}{\Lambda}, \quad \frac{\partial^2 f_3}{\partial x_2 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -\frac{\delta_1 \beta_* c\mu}{\Lambda},\\
&\frac{\partial^2 f_3}{\partial x_3 \partial x_6} = \frac{\partial^2 f_3}{\partial x_6 \partial x_3} = -\frac{\beta_2 c\mu}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_2 \partial x_6} = \frac{\partial^2 f_5}{\partial x_6 \partial x_2} = -\frac{\beta_2 c\mu}{\Lambda},\\
&\frac{\partial^2 f_5}{\partial x_3 \partial x_5} = \frac{\partial^2 f_5}{\partial x_5 \partial x_3} = -\frac{\beta_* c\mu}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_3 \partial x_6} = \frac{\partial^2 f_5}{\partial x_6 \partial x_3} = -\frac{\beta_2 c\mu}{\Lambda},\\
&\frac{\partial^2 f_5}{\partial x_5 \partial x_6} = \frac{\partial^2 f_5}{\partial x_6 \partial x_6} = -\frac{\beta_2 c\mu(1+\delta_2)}{\Lambda}, \quad \frac{\partial^2 f_5}{\partial x_6^2} = -\frac{2\beta_2 c\mu}{\Lambda}
\end{aligned} \tag{2.11}$$

It follows from (2.7), (2.8), (2.10) and (2.11) that $a = \varphi_1 + \varphi_2 + \varphi_3 + \varphi_4$ where,

$$\begin{aligned}
\varphi_1 &= -\frac{2\beta_* c\mu v_3 u_3^2}{\Lambda h_2}\left(\frac{(1+\delta_1)h_1 + k_1}{k_1} + \frac{(1-p-q)r_2(\mu + d_2 + k_2)}{(\mu + k_2)(\mu + d_2)(1-\mathcal{R}_2)}\right)\\
&\quad - \frac{2\beta_2 c\mu v_3 u_3^2}{\Lambda h_2}\left(\frac{(1-p-q)r_2 k_2 h_1}{(\mu + d_2)(\mu + k_2)(1-\mathcal{R}_2)k_1}\right),\\
\varphi_2 &= \frac{2c\mu v_3 u_3^2}{\Lambda}\left(\frac{\delta_1 \beta_* h_1}{k_1} - \frac{\beta_2(1-p-q)r_2 k_2}{(\mu + k_2)(\mu + d_2)(1-\mathcal{R}_2)}\right),
\end{aligned}$$

$$\varphi_3 = -\frac{2(h_1h_2-(qr_2+\beta_*c)k_1)c\mu v_3\mu_3^2}{\Lambda h_2}\Big(\frac{\beta_*k_1(\mu+d_2)+\beta_2k_2h_1}{k_1(\mu+d_2)(\mu+k_2)(1-\mathcal{R}_2)}\Big)$$
$$-\frac{2(h_1h_2-(qr_2+\beta_*c)k_1)(\mu+d_2+k_2)\beta_2c\mu v_3\mu_3^2}{\Lambda h_2(\mu+d_2)(\mu+k_2)(1-\mathcal{R}_2)}$$
$$-\frac{2(h_1h_2-(qr_2+\beta_*c)k_1)(1-p-q)\Big((\mu+\delta_2)(\mu+d_2)+k_2\Big)k_2r_2\beta_2c\mu v_3\mu_3^2}{\Lambda h_2\Big((\mu+d_2)(\mu+k_2)(1-\mathcal{R}_2)\Big)^2},$$

$$\varphi_4 = \frac{2\beta_2c(h_1h_2-(qr_2+\beta_*c)k_1)(\beta_*(\mu+d_2)+k_2\beta_2)c\mu v_3u_3^2}{\Lambda h_2(\mu+d_2)^2(\mu+k_2)(1-\mathcal{R}_2)},$$

with $h_1=\mu+d_1+r_2$, $h_2=k_1+r_1+\mu$. For some $\varphi_i>0,\ i=1,2,3$ we have $a>0$ otherwise $a<0$.

The sign of b is associated with the following none vanishing partial derivatives of F at the disease-free equilibrium:

$$\frac{\partial^2 f_2}{\partial x_3\partial\beta_*}=c,\qquad \frac{\partial^2 f_1}{\partial x_3\partial\beta_*}=-c. \tag{2.12}$$

It follows from (2.7), (2.8), (2.10) and (2.12) that

$$b=\frac{k_1cv_3u_3}{k_1+r_1+\mu}>0. \tag{2.13}$$

Using Theorem 3, items (i) and (iv) we establish the following result.

Theorem 4. *If $\mathcal{R}_2<1$ and there is $\varphi_i<0,\ i=1,2,3,4$ such that $a<0$ then model system (2.1) has a unique endemic equilibrium $\mathcal{U}_1$ which is locally asymptotically stable for $\mathcal{R}_1>1$ but close to 1. If there is $\varphi_i>0$ such that $a>0$ then the direction of the bifurcation at $\mathcal{R}_1=1$ is backward.*

2.3.2 The drug resistant TB-strain only equilibrium

This equilibrium solution is obtained by setting $E_{T_1}=I_{T_1}=R_T=0$ in equation (2.1). The drug resistant TB expressed only in terms of the equilibrium value of the force of infection λ_2^* is given by $\mathcal{U}_2=(S^{**},E_{T_2}^{**},I_{T_2}^{**})$, where

$$S^{**}=\frac{\Lambda}{\mu+\lambda_2^*},\quad E_{T_2}^{**}=\frac{\lambda_2^*\Lambda}{(\mu+\lambda_2^*)(\mu+k_2+\delta_2\lambda_2^*)},$$
$$I_{T_2}^{**}=\frac{\lambda_2^*\Lambda(\delta_2\lambda_2^*+k_2)}{(\mu+\lambda_2^*)(\mu+k_2+\delta_2\lambda_2^*)(\mu+d_2)}. \tag{2.14}$$

Substituting $\mathcal{U}_2$ into the equation for the force of infection λ_2^* we have

$$\lambda_2^*h(\lambda_2^*)=\lambda_2^*(A\lambda_2^{*2}+B\lambda_2^*+C)=0,$$

where $\lambda_2^*=0$ corresponds to the disease-free equilibrium and $h(\lambda_2^*)=0$ corresponds to the existence of an endemic equilibria where

$$A=\frac{\delta_2}{(\mu+k_2)(\mu+d_2)},\quad B=\frac{k_2-\beta_2c\delta_2+(\delta_2+1)(\mu+d_2)}{(\mu+d_2)(\mu+k_2)},\quad C=1-\mathcal{R}_2.$$

Examining the quadratic equation $h(\lambda_2^*) = 0$ we see that there is a unique equilibria if $B < 0$ and $C = 0$ or $B^2 - 4AC = 0$, and if $C > 0,\ B < 0$ and $B^2 - 4AC > 0$, and there is no equilibria otherwise. The coefficient A at λ_2^{*2} is always positive and C is positive or negative if $\mathcal{R}_2$ is less than or greater than one respectively. We therefore rewrite these conditions in the following lemma.

Lemma 2. *Model system* (2.1) *has* (i) *precisely one unique endemic equilibrium if* $C < 0 \Leftrightarrow \mathcal{R}_2 > 1$, (ii) *precisely one unique endemic equilibrium if* $B < 0$ *and* $C = 0$ *or* $B^2 - 4AC = 0$, (iii) *precisely two endemic equilibria if* $C > 0,\ B < 0$ *and* $B^2 - 4AC > 0$, (iv) *otherwise there is none.*

To find the backward bifurcation point, we set the discriminant $B^2 - 4AC = 0$ and make $\mathcal{R}_2$ the subject of the formula to obtain

$$\mathcal{R}_2^c = 1 - B^2/(4A),$$

from which it can be shown that the backward bifurcation occurs for values of $\mathcal{R}_2$ in the range $\mathcal{R}_2^c < \mathcal{R}_2 < 1$.

We now state Theorem 5 on the existence of the endemic equilibrium $\mathcal{U}_2$.

Theorem 5. *The endemic equilibrium* $\mathcal{U}_2$ *exists for* $\mathcal{R}_2 > 1$.

Proof. Analyzing the equation $h(\lambda_2^*) = 0$, we get $\lambda_2^* = \frac{-B+(B^2-4AC)^{(1/2)}}{2A}$, from which it is clear that the disease is endemic when $\lambda_2^* > 0$ which implies $B^2 - 4AC > B^2 \Rightarrow 4(1 - \mathcal{R}_2) < 0 \Rightarrow \mathcal{R}_2 > 1$. Thus the endemic equilibrium $\mathcal{U}_2$ exists whenever $\mathcal{R}_2 > 1$. □

To determine the local asymptotic stability of $\mathcal{U}_2$ we can use the Centre Manifold theory similar to the analysis of $\mathcal{U}_1$.

2.3.3 Interior equilibrium

The endemic equilibrium where both TB strains exist is denoted by

$$\mathcal{U}_3 = (S^{***}, E_{T_1}^{***}, I_{T_1}^{***}, R_T^{***}, E_{T_2}^{***}, I_{T_2}^{***}),$$

where the expressions for $S^{***},\ E_{T_1}^{***},\ I_{T_1}^{***},\ R_T^{***},\ E_{T_2}^{***}, I_{T_2}^{***}$ are too cumbersome to be written down explicitly. Stability analysis of $\mathcal{U}_3$ can be done using the Centre Manifold theory similar to the analysis of $\mathcal{U}_1$, but is not shown here to avoid repetition.

2.3.4 Invasion reproduction numbers

When the drug sensitive strain (strain 1) is at equilibrium a single drug resistant strain (strain 2) will be able to invade if the number of secondary infectives produced by strain 2 is greater than 1 that is when $\mathcal{R}^{2:1} > 1$, where

$$\mathcal{R}^{2:1} = \frac{\mathcal{R}^2}{\mathcal{R}^1} = \frac{\beta_2 c k_2 (\mu + k_1)(\mu + d_1)}{(\mu + k_2)(\mu + d_2)\beta_1 c k_1 H_1}. \tag{2.15}$$

If we assume $\beta_1 = \beta_2 = \beta$, $k_1 = k_2 = k$, $d_1 = d_2 = d$ which do not correspond to a reality in general, since individuals infected with resistant strain suffer increased disease induced death rate compared with their other counterparts. Then (2.15) becomes,

$$\mathcal{R}^{2:1} = \frac{1}{H_1} > 1, \text{ since } H_1 < 1.$$

Thus strain 2 is able to invade the equilibrium of strain 1. Considering the other way round, from $\mathcal{R}^{1:2} = H_1 < 1$ we get that strain 1 is not able to invade the equilibrium of strain 2.

Next we state Theorem 6 whose proof follows from Castillo-Chavez and Feng [7, 8].

Theorem 6. *The following three statements are valid:*

(a) *The endemic equilibrium $\mathcal{U}_1$ of system* (2.1) *is locally asymptotically stable if $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$, and unstable whenever $R_1 < 1$.*

(b) *The endemic equilibrium $\mathcal{U}_2$ of system* (2.1) *is locally asymptotically stable if $\mathcal{R}_2 > 1$ and $\mathcal{R}_1 < 1$.*

(c) *The endemic equilibrium $\mathcal{U}_3$ of system* (2.1) *is locally asymptotically stable if $\mathcal{R}_{rs} > 1$ and unstable otherwise.*

2.4 Analysis of the reproduction number, $\mathcal{R}_{rs}$

In the absence of any intervention strategy that is when $r_1 = r_2 = 0$ we have the reproduction number for model system (2.1) as,

$$\lim_{(r_1,r_2)\to(0,0)} \mathcal{R}_{rs} = \lim_{(r_1,r_2)\to(0,0)} \max\{\mathcal{R}_1, \mathcal{R}_2\} = \max\{\mathcal{R}_{1_N}, \mathcal{R}_2\},$$

where,

$$\mathcal{R}_{1_N} = \frac{\beta_1 c k_1}{(\mu + k_1)(d_1 + \mu)}.$$

Rewriting $\mathcal{R}_1$ in terms of $\mathcal{R}_{1_N}$ we have,

$$\mathcal{R}_1 = H_1 \mathcal{R}_{1_N}, \quad H_1 = \frac{(\mu + k_1)(\mu + d_1)}{(\mu + k_1 + r_1)(\mu + d_1 + r_2) - k_1 q r_2} < 1.$$

The fact that $H_1 < 1$ suggests that treating of infectives and chemoprophylaxis reduces the endemic. Analyzing the two reproduction numbers $\mathcal{R}_1$ and $\mathcal{R}_{1_N}$ we note that chemoprophylaxis and treatment of infectives greatly reduces epidemic:

$$\Delta_N = \mathcal{R}_{1_N} - \mathcal{R}_1 = \mathcal{R}_{1_N}(1 - H_1) > 0.$$

If chemoprophylaxis is the only intervention strategy we have the chemoprophylaxis induced reproduction number as,

$$\mathcal{R}_{1_c} = \frac{\beta_1 c k_1}{(\mu + k_1 + r_1)(\mu + d_1)} = H_2 \mathcal{R}_{1_N}, \quad H_2 = \frac{\mu + k_1}{\mu + k_1 + r_1}.$$

Clearly we obtain $H_2 < 1$, suggesting that chemoprophylaxis reduces the epidemic. Also supporting that argument we have the estimate

$$\Delta_c = \mathcal{R}_{1_N} - \mathcal{R}_{1_c} = \frac{r_1}{\mu + k_1 + r_1}\mathcal{R}_{1_N} > 0.$$

The critical chemoprophylaxis value is equal to

$$r_1^c = (\mu + k_1)(\mathcal{R}_{1_N} - 1).$$

If $r_1 < r_1^c$ chemoprophylaxis will not eradicate the epidemic, but if $r_1 > r_1^c$ then chemoprophylaxis will be able to eradicate the epidemic. A similar analysis for the case where we have introduced the treatment of infectives as the only intervention strategy can be easily done and the critical treatment value can be shown to be

$$r_2^c = (\mu + d_2)(\mathcal{R}_{1_N} - 1).$$

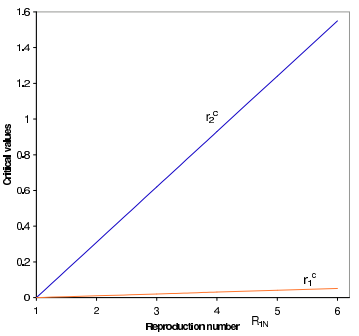

Figure 2. Graphs of the critical chemoprophylaxis (r_1^c) and treatment (r_2^c) values against $\mathcal{R}_{1_N}$ for $\mu = 0.01,\ d_1 = 0.3,\ k_1 = 0.0002$.

Figure 2 is a graphical representation of critical values (chemoprophylaxis and treatment) against the no intervention reproduction number for the case where we have one infectious individual introduced into fully susceptible population. This shows that $r_1^c < r_2^c$ for all values of $\mathcal{R}_{1_N} > 1$ suggesting that chemoprophylaxis is superior as an intervention strategy than treatment of infectives if introduced at the beginning of the TB epidemic in a fully susceptible population.

3 Effects of Quarantine for Multi-drug Resistant TB

We explore the possible benefits of quarantining TB patients with multi-drug resistant TB. Individuals who are sick with multi-drug resistant TB are detected at a constant rate θ and moved to the quarantined state Q. Individuals

in Q die at the same rate as those infectious with multi-drug resistant TB but not quarantined, I_{T_2}. Incorporating quarantine Q for multi-drug resistant TB, the system (2.1) becomes

$$\begin{cases} S'(t)=\Lambda-(\lambda_1+\lambda_2)S-\mu S, \\ E'_{T_1}(t)=\lambda_1(S+R_T)-(\delta_1\lambda_1+\lambda_2)E_{T_1}-(k_1+\mu+r_1)E_{T_1}+qr_2I_{T_1}, \\ I'_{T_1}(t) = \delta_1\lambda_1E_{T_1} + k_1E_{T_1} - \lambda_2I_{T_1} - (r_2 + \mu + d_1)I_{T_1}, \\ R'_T(t)=pr_2I_{T_1}+r_1E_{T_1}-(\lambda_1+\lambda_2)R_T-\mu R_T, \\ E'_{T_2}(t)=\lambda_2S+(1-(p+q))r_2I_{T_1}+\lambda_2R_T-(\lambda_1+\delta_2\lambda_2)E_{T_2}-(\mu+k_2)E_{T_2}, \\ I'_{T_2}(t)=(\lambda_1+\delta_2\lambda_2)E_{T_2}+k_2E_{T_2}+\lambda_2E_{T_1}+\lambda_2I_{T_1}-(\mu+\theta+d_2)I_{T_2}, \\ Q'(t)=\theta I_{T_2}-(\mu+d_2)Q \end{cases} \tag{3.1}$$

with,

$$\lambda_{q_i} = \frac{\beta_i c I_{T_i}}{N_q},\ i = 1, 2, \quad N_q(t) = S + E_{T_1} + I_{T_1} + R_T + E_{T_2} + I_{T_2} + Q.$$

Model system (3.1) is studied in the following region,

$$\mathcal{K}_\triangledown = \Big\{(S, E_{T_1}, I_{T_1}, R_T, E_{T_2}, I_{T_2}, Q) \in \mathbb{R}^7_+ : N_q(t) \leq \Lambda/\mu\Big\},$$

which is positively invariant with respect to model system (3.1) as any solution of (3.1) starting in $\mathcal{K}_\triangledown$ remain in $\mathcal{K}_\triangledown$.

3.1 Disease free equilibrium and stability analysis

The disease free equilibrium of model system (3.1) is given by,

$$\mathcal{M}_0 = (S^0, E^0_{T_1}, I^0_{T_1}, R^0_T, E^0_{T_2}, I^0_{T_2}, Q^0) = \Big(\Lambda/\mu, 0, 0, 0, 0, 0, 0\Big).$$

Following van den Driessche and Watmough [13], the reproduction number for model system (3.1) is $\mathcal{R}_{0_q} = \max\big\{\mathcal{R}_1, \mathcal{R}_{2_q}\big\}$, where $\mathcal{R}_1$ is as defined in a previous section and $\mathcal{R}_{2_q} = \dfrac{\beta_2 c k_2}{(\mu + k_2)(\mu + d_2 + \theta)}$ is the quarantine induced reproduction number for the multi-drug resistant strain. Theorem 7 follows from van den Driessche and Watmough [13] (Theorem 2).

Theorem 7. *The disease-free equilibrium $\mathcal{M}_0$ is locally asymptotically stable whenever $\mathcal{R}_{0_q} < 1$ and unstable otherwise.*

We write system (3.1) as,

$$\begin{aligned} \frac{dX}{dt} &= F(X, Y), \\ \frac{dY}{dt} &= G(X, Y), \quad G(X, 0) = 0, \end{aligned} \tag{3.2}$$

where $X = (S, R_T)$ and $Y = (E_{T_1}, I_{T_1}, E_{T_2}, I_{T_2}, Q)$ with $X \in \mathbb{R}^2$ denoting the number of uninfected individuals and $Y \in \mathbb{R}^5$ denoting the number of the infected individuals including the latent and the infectious.

The disease-free equilibrium point is now denoted by

$$\mathcal{M}_0 = (X^*, 0), \quad X^* = \big(\Lambda/\mu, 0\big).$$

We now state conditions $(H1)$ and $(H2)$ in equation (3.3) which must be satisfied to guarantee local asymptotic stability.

$$\begin{array}{ll} H1 & \text{For } \dfrac{dX}{dt}=F(X,0),\ X^* \text{ is globally asymptotically stable (g.a.s)} \\ H2 & G(X,Y)=DY-\widehat{G}(X,Y), \quad \widehat{G}(X,Y)\geq 0 \text{ for } (X,Y)\in\mathcal{K}_5, \end{array} \tag{3.3}$$

where $D = D_Y G(X^*, 0)$ is an M-matrix (the off diagonal elements of D are nonnegative) and $\mathcal{K}_5$ is the region where the model makes biological sense. If system (3.2) satisfies the conditions in (3.3) then Theorem 8 holds.

Theorem 8. *The fixed point $\mathcal{M}_0 = (X^*, 0)$ is a globally asymptotically stable point of system* (2.1) *provided that $\mathcal{R}_{0_q} < 1$ and assumptions in* (3.3) *are satisfied.*

Proof. From Theorem 7, $\mathcal{M}_0$ is locally asymptotically stable for $\mathcal{R}_{0_q} < 1$. Consider

$$F(X,0) = \begin{bmatrix} \Lambda - \mu S \\ -\mu R_T \end{bmatrix},$$

$$D = \begin{bmatrix} -(k_1+r_1+\mu) & \beta_1 c + q r_2 & 0 & 0 & 0 \\ k_1 & -(r_2+\mu+d_1) & 0 & 0 & 0 \\ 0 & (1-(p+q))\, r_2 & -(\mu+k_2) & \beta_2 c & 0 \\ 0 & 0 & k_2 & -(\mu+\theta+d_2) & 0 \\ 0 & 0 & 0 & \theta & -(\mu+d_2) \end{bmatrix}$$

and

$$\widehat{G}(X,Y) = \begin{bmatrix} \widehat{G_1}(X,Y) \\ \widehat{G_2}(X,Y) \\ \widehat{G_3}(X,Y) \\ \widehat{G_4}(X,Y) \\ \widehat{G_5}(X,Y) \end{bmatrix} = \begin{bmatrix} \beta_1 c I_{T_1}\Big(1 - \dfrac{S + R_T - \delta_1 E_{T_1}}{N_q}\Big) + \lambda_{q_2} E_{T_1} \\ \lambda_{q_2} I_{T_1} - \delta_1 \lambda_{q_1} E_{T_1} \\ \dfrac{\beta_2 c I_{T_2}}{N_q}(N_q - S - R_T + \delta_2 E_{T_2}) + \lambda_{q_1} E_{T_2} \\ -(\lambda_{q_1} + \delta_2 \lambda_{q_2}) E_{T_2} - \lambda_{q_2}(E_{T_1} + I_{T_1}) \\ 0 \end{bmatrix}.$$

Thus $\widehat{G}(X,Y)$ is not greater than or equal to zero, for $(X,Y) \in \mathcal{K}_5$ since $\widehat{G_4}(X,Y) < 0$ implying $(H2)$ in (3.3) is not satisfied. Consequently M_0 may not be globally asymptotically stable. Thus in this case backward bifurcation as proved in Feng et al. [16] occurs at $\mathcal{R}_{0_q} = 1$ and that double endemic equilibria can be supported for $\mathcal{R}_q^c < \mathcal{R}_{0_q} < 1$, where $\mathcal{R}_q^c$ is a positive constant. However in the absence of exogenous reinfection $\mathcal{M}_0$ is globally asymptotically stable. □

3.2 Endemic equilibria

There are three possible endemic equilibria for model system (3.1): two boundary, $\mathcal{M}_1$ (when only the first strain is present) and $\mathcal{M}_2$ (when only the second strain is present) and the interior equilibrium $\mathcal{M}_3$.

3.2.1 The drug sensitive TB-strain only equilibrium

The drug sensitive TB-strain only equilibrium is given by

$$\mathcal{M}_1 = (S^*, E^*_{T_1}, I^*_{T_1}, R^*_T, 0, 0, 0), \tag{3.4}$$

where S^*, $E^*_{T_1}$, $I^*_{T_1}$, R^*_T are similar to the ones defined in equation (2.2) in terms of equilibrium value of the force of infection $\lambda^*_{1_q}$ and the analysis of $\mathcal{M}_1$ is thus similar to the analysis of $\mathcal{U}_1$ in subsubsection 2.3.1.

3.2.2 The drug resistant TB-strain only equilibrium

The drug resistant TB only equilibrium is given by

$$\mathcal{M}_2 = (S^{**}, 0, 0, 0, E^{**}_{T_2}, I^{**}_{T_2}, Q^{**}), \tag{3.5}$$

and it is expressed in terms of the equilibrium value of the force of infection $\lambda^*_{q_2}$:

$$S^{**} = \frac{\Lambda}{\lambda^*_{q_2} + \mu}, \quad E^{**}_{T_2} = \frac{\Lambda\lambda^*_{2_q}}{(\lambda^*_{q_2} + \mu)(\delta_2\lambda^*_{q_2} + \mu + k_2)},$$
$$I^{**}_{T_2} = \frac{\Lambda\lambda^*_{2_q}(\delta_2\lambda^*_{q_2} + k_2)}{(\mu + d_2 + \theta)(\lambda^*_{q_2} + \mu)(\delta_2\lambda^*_{q_2} + \mu + k_2)},$$
$$Q^{**} = \frac{\theta\Lambda\lambda^*_{2_q}(\delta_2\lambda^*_{q_2} + k_2)}{(\mu + d_2)(\mu + d_2 + \theta)(\lambda^*_{q_2} + \mu)(\delta_2\lambda^*_{q_2} + \mu + k_2)}.$$

$\mathcal{M}_2$ can be analyzed similarly to $\mathcal{U}_2$ in subsubsection 2.3.2.

3.2.3 Interior equilibrium point

$$\mathcal{M}_3 = (S^{***}, E^{***}_{T_1}, I^{***}_{T_1}, R^{***}_T, E^{***}_{T_2}, I^{***}_{T_2}, Q^{***}), \tag{3.6}$$

where the expressions for S^{***}, $E^{***}_{T_1}$, $I^{***}_{T_1}$, R^{***}_T, $E^{***}_{T_2}, I^{***}_{T_2}, Q^{***}$ are too cumbersome to be written down explicitly. Using the approach by Castillo-Chavez and Feng [7, 8] it can be easily shown that the endemic equilibria (3.4), (3.5) and (3.6) are stable for $\mathcal{R}_{0_q} < 1$ and unstable otherwise.

3.3 Analysis of the quarantine induced reproduction number

If $\theta = 0$, then $\mathcal{R}_{2_q} = \mathcal{R}_2$. Rewriting the quarantine induced reproduction number $\mathcal{R}_{2_q}$ in terms of $\mathcal{R}_2$ we have

$$\mathcal{R}_{2_q} = H_q\mathcal{R}_2, \quad H_q = \frac{\mu + d_2}{\mu + d_2 + \theta}.$$

Clearly $H_q < 1$, thus the quarantining plays a significant role in reducing the spread of multi-drug resistant TB.

$$\Delta_q = \mathcal{R}_2 - H_q\mathcal{R}_2 = \frac{\theta}{\mu + d_2 + \theta} > 0,$$

for which $\Delta_q > 0$ implies that quarantine is effective in controlling the spread of multi-drug resistant TB. Differentiating $\mathcal{R}_{2_q}$ with respect to θ we obtain

$$\frac{\partial \mathcal{R}_{2_q}}{\partial \theta} = -\frac{\mathcal{R}_{2_q}}{\mu + d_2 + \theta}. \tag{3.7}$$

The fact that equation (3.7) is negative implies that quarantine is effective in controlling the spread of multi-drug resistant TB.

Now we have to find the critical values for the case when we have quarantine as an intervention strategy against multi-drug resistance. We set $\mathcal{R}_{2_q} = 1$ and obtain

$$\theta^c = (\mu + d_2)(\mathcal{R}_2 - 1).$$

If $\theta^c > \theta$, quarantine results in the reduction of multi-drug resistant TB but does not eradicate the epidemic. When $\theta > \theta^c$, the multi-drug resistant TB will be eradicated through quarantine.

4 Numerical Simulations

Systems (2.1) and (3.1) are simulated using the fourth order Runge-Kutta numerical scheme coded in C++. The parameter values in Table 1 and the initial conditions (in millions) are the following $S(0) = 11,\ E_{T_1}(0) = 3.15,\ I_{T_1}(0) = 0.42,\ R_T(0) = 0,\ E_{T_2}(0) = 0.35,\ I_{T_2}(0) = 0.08$. In Table 1, a* and b* denotes

Table 1. Model parameters.

Definition	Symbol	Estimate(Range)	Source
Recruitment rate	Λ	0.029year^{-1}	b*
Natural mortality rate	μ	0.02year^{-1}	b*
Contact rate	c	2year^{-1}	Estimate
TB induced death rate	d_1, d_2	$0.3,0.5\text{year}^{-1}$	a*
Probability of being infected	$\beta_i,\ i = 1, 2$	$0.35\ (0.1\text{-}0.6)\text{year}^{-1}$	a*
Natural rate of progression to active TB	k_1, k_2	$0.00013,0.001\text{year}^{-1}$	a*
Probability of recovery from active TB	p	0.8year^{-1}	Estimate
Probability of moving back to latency after treatment	q	0.0001year^{-1}	Estimate
Probability of recovery from latency	γ	0.9year^{-1}	Estimate
Relapsing rate	q	0.00001year^{-1}	Estimate
Treatment rate for the latently infected	r_1	0.2year^{-1}	Estimate
Treatment rate for the infectives	r_2	0.3year^{-1}	Estimate
Quarantine rate	θ	0.7year^{-1}	Estimate
Modification parameter	δ_1	0.5year^{-1}	Estimate
Modification parameter	δ_2	0.59year^{-1}	Estimate

values and ranges adapted from Dye et al. [14], and Central Statistics Office of Zimbabwe. We simulate both drug sensitive and multi-drug resistant dynamics of TB in the absence of any intervention, in the presence of chemoprophylaxis, and treatment.

In the absence of quarantine for MDRTB, even with chemoprophylaxis and treatment for the drug sensitive strain, the susceptible population increases slightly, then falls and remains constant as shown by Figure 3 trend 3. In the

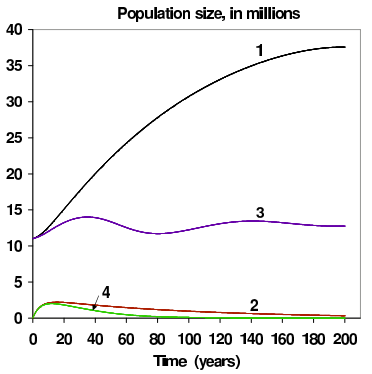

Figure 3. Simulated quarantine on the susceptible (S) and recovered (R_T). Trends 1, 2, 3 and 4 represent the susceptible population with quarantine for MDRTB, recovered population with quarantine for MDRTB, susceptible population without quarantine for MDRTB, and recovered population without quarantine for MDRTB. Parameter values are those of Table 1.

presence of quarantine for MDRTB, treatment and chemoprophylaxis for the drug sensitive strain, the susceptible population size increases to an asymptotic level as shown in Figure 3 trend 1. Even in the presence of quarantine for MDRTB, chemoprophylaxis, and treatment for the drug sensitive strain TB is not eradicated because not all cases are detected.

In the presence of quarantine for MDRTB, the population of the recovered increases then gradually declines to low levels a shown in Figure 3. In the absence of quarantine for MDRTB the recovered population increases and and falls off to very low levels when the recovered are infected by multi-drug resistant (MDR) Mycobacterium tuberculosis strains.

In the absence or presence of quarantine, for MDRTB as long as there is chemoprophylaxis and treatment for drug sensitive TB, the latently infected (E_{T_1}) and the infectious (I_{T_1}) individuals will decrease to low levels as shown in Figures 4 (a) and (b). Chemoprophylaxis and treatment of infectives is can eradicate drug sensitive TB. As most of MDRTB results from incomplete treatment and mis-use of the drugs, if chemoprophylaxis for the latently infected and treatment for the infectives is implemented well, MDRTB cases decrease. In the absence of treatment for MDRTB, individuals in this class die quickly.

In the presence of quarantine for MDRTB, the population size of infective (I_{T_2}) increases slightly at the beginning, then declines steadily to low levels as most of the cases are detected and quarantined as shown in Figure 4 (a). Once quarantined, infectious cases cannot infect and this decreases the latently infected (E_{T_2}). A decrease in E_{T_2} results in a decrease of the the infective population. In the absence of quarantine, the infective population (I_{T_2}) increases then declines until it reaches a stable state, in which the rate at which individuals become active with MDRTB is the same as the rate at which active MDRTB cases die (natural and disease induced).

In the presence of quarantine for MDRTB, population size of the latently

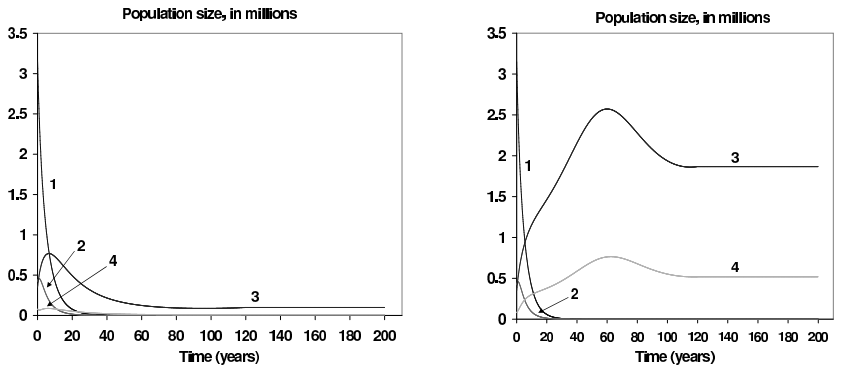

Figure 4. Simulated the effect of quarantine for MDRTB on the latently infected (E_{T_1} and E_{T_2}) and the infectious (I_{T_1} and I_{T_2}). Series 1, 2, 3 and 4 represent individuals latently infected with the drug sensitive strain, infectious individuals with drug sensitive strain, individuals latently infected with MDR strain and infectious individuals with MDR strains. Figures (a) and (b) represent quarantine for MDRTB, treatment and chemoprophylaxis for the drug sensitive TB, and treatment and chemoprophylaxis for the drug sensitive TB and no quarantine for MDRTB.

infected (E_{T_2}) increases slightly then declines to very low levels as a result of quarantine as shown in Figure 4 (a). The absence of quarantine increases the total number of individuals in the latency class E_{T_2} as shown in Figure 4 (b).

5 Conclusions

We have presented and analyzed the two strain TB model with chemoprophylaxis and treatment for the drug sensitive strain, with and without quarantine for the MDRTB. We computed and compared the basic reproduction numbers of the models to assess the effectiveness of chemoprophylaxis and treatment in the control of drug sensitive TB and quarantine in the control of MDRTB. Ordinary TB can be eradicated with chemoprophylaxis for the latent and with treatment for the infective. We conclude that effective chemoprophylaxis and treatment of infective for the drug sensitive TB results in a reduction of MDRTB cases, as most MDRTB cases come from a failure to administer TB drugs. The quarantine induced reproduction number suggests that quarantine is the answer in the control of MDRTB in absence of alternative treatment plan. Quarantine for MDRTB alters TB epidemics because it reduces the spread of MDR strains. Reducing MDRTB cases means also reducing TB related deaths as MDRTB are more fatal than ordinary TB. Given the non-availability of second line drugs for MDRTB in most developing countries, quarantine remains the only option to effectively control the spread of MDRTB in developing countries.

Acknowledgements

This work was made possible through a fellowship received by C. P. Bhunu from the Forgarty International Centre through the International Clinical, Operational and Health Services and Training Award (ICOHRTA) Programme. The authors would like to thank the anonymous reviewers for the comments and suggestions which resulted in the improvement of our work.

References

[1] A.S. Ackleh and L.J.S. Allen. Competitive exclusion in SIS and SIR epidemic models with total cross immunity and density-dependent host mortality. *Discrete and Continuous Dynamical Systems Series B*, 2004. (in press)

[2] L.J.S. Allen, M. Langais and C.J. Phillips. The dynamics of two viral infections in a single host population with applications to hantavirus. *Mathematics Biosciences*, **186**:191–217, 2003.

[3] G. Birkoff and G.C. Rota. *Ordinary Differential Equations*. Ginn, 1982.

[4] S.M. Blower and J.L. Gerberding. Understanding, predicting and controlling the emergence of drug-resistant tuberculosis: a theoretical framework. *Journal of Molecular Medicine*, **76**:624–636, 1998.

[5] K. B. Blyuss and Y. N. Kyrychko. On a basic model of a two-disease epidemic. *Applied Mathematics and Computation*, **160**:177–187, 2005.

[6] J. Carr. *Applications Centre Manifold theory*. Springer-Verlag, New York, 1981.

[7] C. Castillo-Chavez and Z. Feng. To treat or not to treat: The case of tuberculosis. *Journal of Mathematical Biology*, **35**:629–656, 1997.

[8] C. Castillo-Chavez and Z. Feng. Mathematical models for the disease dynamics of tuberculosis. pp. 629–656. World Scientific Press, 1998.

[9] C. Castillo-Chavez and B. Song. Dynamical models of tuberculosis and their applications. *Mathematical Bioscience and Engineering*, **1**(2):361–404, 2004.

[10] D. C. Coleman and G. Slutkin. Chemoprophylaxis against tuberculosis [Topics in primary care medicine]. *West. J. Med.*, **40**(1):106–110, 1984.

[11] E.L. Corbet, C.J. Watt and N. Walker. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch. Intern. Med.*, **163**:1009–1021, 2003.

[12] P.D.O. Davies. *Multi-drug resistant tuberculosis*. Priory Lodge Education Ltd, 1999.

[13] P.van den Driesche and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for the compartmental models of disease transmission. *Mathematics Biosciences*, **180**:29–48, 2002.

[14] C. Dye, S. Schele, P. Dolin, V. Pathania and M. Raviglione. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *The Lancet*, **352**:1886–1891, 1998.

[15] C. Dye and B. G. William. Criteria for the control of drug resistant tuberculosis. *Proc. Natl. Acad. Sci. USA*, **97**:8180–8185, 2000.

[16] Z. Feng, C. Castillo-Chavez and A. F. Capurro. A model for tuberculosis with exogenous reinfection. *Theor. Pop. Bio.*, **57**:235–247, 2000.

[17] T. Frieden, T.R. Sterling, S.S. Munsiff, C. J. Watt and C. Dye. Tuberculosis. *Lancet*, **362**:887–899, 2003.

[18] M. Martcheva, M. Ianelli and Xue-Zhi-Li. Subthreshold coexistence of strains: The impact of vaccination and mutation. *Mathematical Bioscience and Engineering*, **4**(2):287–317, 2007.

[19] R. May and M. Nowak. Coinfection and the evolution of parasite virulence. *Proc. Royal Soc. London*, **261**:209–215, 1995.

[20] B. Miller. Preventive therapy for tuberculosis. *Medical Clinics of North America*, **77**:1263–1275, 1993.

[21] R. Naresh and A. Tripath. Modelling and analysis of HIV-TB co-infection in a variable size population. *Math. Model. Anal.*, **10**:275–286, 2005.

[22] M.A. Nowak and K. Sigmund. Super-and coinfection: The two extremes. In *Adaptive dynamics of infectious diseases: In pursuit of virulence management*. Cambridge University Press, 2002.

[23] World Health Organisation. Anti-tuberculosis drug resistance in the world in people living with HIV. *Prevalence and trends. Geneva: WHO*, 2000. Report 2.

[24] M.V. Shilov and C. Dye. The resurgence of tuberculosis in Russia. *Philos Trans R Soc Lond Bio Sci*, **356**:1069–1075, 2001.

[25] J. Singh. *Isolating TB patients: prevention better than cure*. SciDevNet, 2007.