A Mathematical Model of a Tuberculosis Transmission Dynamics Incorporating First and Second Line Treatment

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ABSTRACT: This paper presents a new mathematical model of a tuberculosis transmission dynamics incorporating first and second line treatment. We calculated a control reproduction number which plays a vital role in biomathematics. The model consists of two equilibrium points namely disease free equilibrium and endemic equilibrium point, it has been shown that the disease free equilibrium point was locally asymptotically stable if the control reproduction number is less than one and also the endemic equilibrium point was locally asymptotically stable if the control reproduction number is greater than one. Numerical simulation was carried out which supported the analytical results.

Tuberculosis (TB) is a protracted bacterial infectious disease caused by *Mycobacterium tuberculosis* which position a major health, social and economic burden globally, especially in low and middle income countries (WHO, 2013). The surge in HIV-TB co-infection and growing emergence of multidrug-resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) strains has further fuelled TB epidemic (WHO,2013; WHO, 2016). It is the second fatal disease due to a single infectious agent only after HIV/AIDS (WHO, 2013; WHO, 2016). TB usually affects the lungs but it can also affect other sites as well (extra-pulmonary TB). Tuberculosis is conveyed by tiny airborne droplets which are ejected into the air when a person with active pulmonary TB coughs or talks (Issarowa *et al.,* 2015). According to the World Health Organization (WHO), in 2013, about 9million people were infected, worldwide, with TB and 1.5 million deaths from the disease were reported, 360,000 of whom were HIV-positive (Yang *et al.,* 2014). Tuberculosis is seen to be declining slowly each year and an estimated 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment (Yang *et al.,* 2014; Okuonghae and

Ikhimwin, 2016). Numerous mathematical models have been developed and used to study the transmission dynamics of TB in a population (Aparicio and Castillo-Chavez, 2009; Castillo-Chavez and Song, 2004; Feng, 2000). For instance, Okuonghae (2013) worked on a deterministic TB model with genetic heterogeneity in susceptibility and disease progression. Zhang and Feng (2000) constructed and analyzed a dynamical model to investigate the spread of TB in a community with isolation and incomplete treatment. The purpose of this article is to formulate a mathematical model of a tuberculosis transmission dynamics incorporating first and second line treatment which provides insights into the drug resistant cases in first and second line treatment. The model considers human population N. The population at time t is divided into six (6) subpopulations. Susceptible (S): this class include those individuals who are at risk for developing an infection from Tuberculosis (TB). Latent Class (E): this class refers to susceptible individuals who become infected. Infected (I): this class includes all

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individuals who are showing the symptom of the disease. First Line Treatment (R_1) : this class include all individual that failed to take drugs (treatment). Second Line Treatment (R_2) : this class include all individual that failed to take drugs (treatment) for the second treatment term. Recovered (R) : this class include all individual that have recovered from the disease and got temporary immunity. The susceptible class is increased by birth or emigration at the rate of Λ. The susceptible class will get TB when they mingled with infectious individuals at the λ ,where $\lambda = \beta IS/N$, β is the effective contact rate. The latent class is generated at a rate $\lambda = \beta IS/N$, it decrease at rate σ which is the progression rate. The Infectious class is generated at a rate σ, it also reduces at rate of treatment τ_1 and it further reduce at a rate γ_1 which is default of treatment. The first line treatment is generated at rate γ_1 , it reduces at a rate of treatment τ_2 and it further reduce at a rate γ_2 which is second default of treatment. The second line treatment class is generated at rate γ_2 , it reduces at a rate of treatment τ_3 and recovered class is generated at rate $\tau_1, \tau_2 \ and \ \tau_3$. The Infectious, First line treatment and Second line treatment class are reduced at the rates $\delta_1, \delta_2 \ and \ \delta_3$ while the whole classes reduces at the rate μ which is the natural mortality rate. Hence we have that

$$N(t) = S(t) + E(t) + I(t) + R_1(t) + R_2(t) + R(t) \qquad (1)$$

The above assumptions result in the following system of nonlinear ordinary differential equations:

$$
\left.
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{\beta SI}{N} - \mu S \\
\frac{dE}{dt} &= \frac{\beta SI}{N} - (\mu + \sigma)E \\
\frac{dI}{dt} &= \sigma E - (\gamma_1 + \tau_1 + \mu + \delta_1) I \\
\frac{dR_1}{dt} &== \gamma_1 I - (\gamma_2 + \tau_2 + \mu + \delta_2)R_1 \\
\frac{dR_2}{dt} &= \gamma_2 R_1 - (\tau_3 + \mu + \delta_3)R_2 \\
\frac{dR}{dt} &= \tau_1 I + \tau_2 R_1 + \tau_3 R_2 - \mu R
\end{aligned}
\right\} \qquad (2)
$$

Simplifying (2), we have

$$
\left.
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda S - \mu S \\
\frac{dE}{dt} &= \lambda S - K_1 E \\
\frac{dI}{dt} &= \sigma E - K_2 I \\
\frac{dR_1}{dt} &== \gamma_1 I - K_3 R_1 \\
\frac{dR_2}{dt} &= \gamma_2 R_1 - K_4 R_2 \\
\frac{dR}{dt} &= \tau_1 I + \tau_2 R_1 + \tau_3 R_2 - \mu R
\end{aligned}
\right\} \qquad (3)
$$

where

$$K_1 = \mu + \sigma \qquad (4)$$
$$K_2 = \gamma_1 + \tau_1 + \mu + \delta_1 \qquad (5)$$
$$K_3 = \gamma_2 + \tau_2 + \mu + \delta_2 \qquad (6)$$
$$K_4 = \tau_3 + \mu + \delta_3 \qquad (7)$$
$$\lambda = \frac{\beta I}{N} \qquad (8)$$

Boundedness of Solutions: Consider the region

$$
D_0 = \left\{ \begin{pmatrix} S \\ E \\ I \\ R_1 \\ R_2 \\ R \end{pmatrix} \in R_+^6 \middle| \begin{array}{l} S \geq 0 \\ E \geq 0 \\ I \geq 0 \\ R_1 \geq 0 \\ R_2 \geq 0 \\ R \geq 0 \\ N \leq \dfrac{\Lambda}{\mu} \end{array} \right\} \qquad (9)
$$

It can be shown that the set D_0 is positively invariant and a global attractor of all positive solution of the system (1)

Lemma 1 *The region D_0 is positively invariant for the system (1).*

Proof: The rate of change of the total human population is give as

$$\frac{dN}{dt} = \Lambda - \mu N - \delta_1 I - \delta_2 R_1 - \delta_3 R_2 \qquad (10)$$

by standard comparison theorem,

$$\frac{dN}{dt} \leq \Lambda - \mu N \qquad (11)$$

using the integrating factor method

$$T_h e^{\mu_h t} \leq \frac{\Lambda_h}{\mu_h} e^{\mu_h t} + T_h(0) - \frac{\Lambda_h}{\mu_h} \qquad (12)$$

$$T_h = T_h\left(0\right)e^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}\left[1 - e^{-\mu_h t}\right] \tag{13}$$

If $N(0) \leq \dfrac{\Lambda}{\mu}$ then $N \leq \dfrac{\Lambda}{\mu}$ so, D_0 is a positively invariant set under the flow described in (1). Hence, no solution path leaves through and boundary of D_0. Also, since solution paths cannot leave D_0, solutions remain non-negative for non-negative initial conditions. Solutions exist for all time t. In this region, the model (1) is said to be well posed mathematically and epidemiologically.

Positivity of Solution
Lemma 2 *Let the initial data for the model (1)*
$S(0) > 0, E(0) > 0, I(0) > 0, R_1(0) > 0, R_2(0) > 0,$ *and $R(0) > 0$ be then the solution of*
$S(t), E(t), I(t), R_1(t), R_2(t),$ *and $R(t)$ with*
positive initial data will remain positive for all time t > 0
Proof: Let
$t_1 = \{t > 0 : S(0) > 0, E(0) > 0, I(0) > 0, R_1(0) > 0, R_2(0) > 0, R(0) > 0\} > 0$

$$\frac{dS}{dt} = \Lambda - \left(\lambda + \mu\right)S \tag{14}$$

to solve the ODE using the integrating factor method

$$\frac{d}{dt}\left[S(t)exp\left\{\mu t + \int_0^t (\lambda(\tau) + \mu(\tau))d(\tau)\right\}\right] = \Lambda\left[exp\left\{\mu t + \int_0^t (\lambda(\tau) + \mu(\tau))d(\tau)\right\}\right]$$

$$S\left(t_1\right) = S\left(0\right)exp\left\{-\mu t_1 - \int_0^{t_1}(\lambda\left(\tau\right) + \mu\left(\tau\right))d\left(\tau\right)\right\}$$

$$+\left[exp\left\{-\mu t_1 - \int_0^{t_1}(\lambda(\tau) + \mu(\tau))d(\tau)\right\}\right]\int_0^{t_1}\left[\Lambda exp\left\{\mu y + \int_0^y(\lambda(\tau) + \mu(\tau))d(\tau)\right\}\right]dy > 0$$

Similarly, we can also show that,
$E(t) > 0, I(t) > 0, R_1(t), > 0\ R_2(t) > 0,$ and $R(t) > 0$
for all the time $t > 0$

Local stability of the disease-free equilibrium and Reproduction Number: The system (1) has a disease free equilibrium attained by setting the right hand side to zero and the disease classes to zero to obtain

$$\Omega = \left(S^0, E^0, I^0, R_1^0, R_2^0, R^0\right) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0\right) \tag{15}$$

Using the notation in van den Driessche and Watmough (2002) the matrices F and V for the new infection terms and the remaining transfer terms respectively, are respectively given as

$$F = \begin{pmatrix} 0 & \beta & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{16}$$

and

$$V = \begin{pmatrix} K_1 & 0 & 0 & 0 \\ -\sigma & K_2 & 0 & 0 \\ 0 & -\gamma_1 & K_3 & 0 \\ 0 & 0 & -\gamma_2 & K_4 \end{pmatrix} \tag{17}$$

Now, it follows that the control reproduction number is given as

$$R_C = \frac{\sigma\beta}{K_1 K_2} = \frac{\sigma\beta}{(\mu + \sigma)(\gamma_1 + \tau_1 + \mu + \delta_1)} \tag{18}$$

The following result is established using Theorem 2 in (van den Driessche & Watmough, 2002).

Lemma 3: *The DFE of the system (1) is locally asymptotically stable if $R_C < 1$ and unstable if $R_C > 1$.* The value R_C is the humans effective reproduction number since there is the presence of control strategies. The threshold quantity R_C is the control reproduction number for the model (1). By Theorem 1, biologically speaking, Tuberculosis is eliminated from the population when $R_C < 1$ if the initial sizes of the populations of the model are in the region of attraction of D_0. However, the disease free equilibrium may not be globally asymptotically stable even if $R_C < 1$ in the case when a backward bifurcation occurs. That is, there is the presence of a stable EEP co-existing with the DFE.

Existence of Endemic Equilibrium Point (EEP) of the Model: Let the endemic equilibrium point be $\xi^{**} = (S^{**}, E^{**}, I^{**}, R_1^{**}, R_2^{**}, R^{**})$. At steady state, solving (1) in terms of force of infection we have

$$S^{**} = \frac{\Lambda}{\lambda^{**} + \mu}, \quad E^{**} = \frac{\lambda^{**}\Lambda}{K_1(\lambda^{**} + \mu)},$$

$$I^{**} = \frac{\lambda^{**}\sigma\Lambda}{K_1 K_2(\lambda^{**} + \mu)},$$

$$R_1^{**} = \frac{\lambda^{**}\gamma_1\sigma\Lambda}{K_1 K_2 K_3(\lambda^{**} + \mu)},$$

$$R_2^{**} = \frac{\lambda^{**}\gamma_1\gamma_2\sigma\Lambda}{K_1 K_2 K_3 K_4(\lambda^{**} + \mu)},$$

$$R^{**} = \frac{\lambda^{**}K_3 K_4\tau_1\sigma\Lambda + \lambda^{**}K_4\tau_2\gamma_1\sigma\Lambda + \lambda^{**}\tau_3\gamma_1\gamma_2\sigma\Lambda}{\mu K_1 K_2 K_3 K_4(\lambda^{**} + \mu)} \tag{19}$$

Now,

$$\lambda^{**} = \frac{\beta I^{**}}{N^{**}} \tag{20}$$

Substituting the values of I^{**} and N^{**} into (20) gives

$$\lambda^{**}\left(A_1\lambda^{**}+A_2\right)=0 \qquad (21)$$

Where

$$A_1=K_1^2K_2^2K_3K_4+K_1K_2K_3K_4\delta_1\sigma+K_1K_2K_3K_4\delta_2\gamma_1\sigma-K_1K_2\delta_3\gamma_1\gamma_2\sigma \quad (22)$$

$$A_2 = \mu K_1 K_2 K_3 K_4 \left(1-R_C\right) \qquad (23)$$

From (21), either

$$\lambda^{**}=0 \qquad (24)$$

or

$$\lambda^{**} = \frac{\mu K_1 K_2 K_3 K_4 \left(R_C-1\right)}{A_2} \qquad (25)$$

So system (1) has a unique (stable) endemic equilibrium if $R_C>1$, since $\lambda^{**}>1$ if $R_C>1$.

Local Stability of Endemic Equilibrium Point (EEP) of the Model: The Jacobian expressed in terms of force of infection gives

$$J\left(\xi^{**}\right)=\begin{pmatrix} -\left(\lambda^{**}+\mu\right) & 0 & 0 & 0 & 0 & 0 \\ \lambda^{**} & -K_1 & 0 & 0 & 0 & 0 \\ 0 & \sigma & -K_2 & 0 & 0 & 0 \\ 0 & 0 & \gamma_1 & -K_3 & 0 & 0 \\ 0 & 0 & 0 & \gamma_2 & -K_4 & 0 \\ 0 & 0 & \tau_1 & \tau_2 & \tau_3 & -\mu \end{pmatrix} \quad (26)$$

Using elementary row-transformation, we have

$$J\left(\xi^{**}\right)=\begin{pmatrix} -\lambda^{**}-\mu & 0 & 0 & 0 & 0 & 0 \\ 0 & -K_1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -K_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & -K_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & -K_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu \end{pmatrix} \quad (27)$$

The Eigenvalues are giving as

$$\lambda_1 = -\lambda^{**}-\mu \qquad (28)$$

from (25) if $R_C>1$ then $\lambda_1<0$

$$\lambda_2 = -K_1<0 \qquad (29)$$
$$\lambda_3 = -K_2<0 \qquad (30)$$
$$\lambda_4 = -K_3<0 \qquad (31)$$
$$\lambda_5 = -K_4<0 \qquad (32)$$
$$\lambda_6 = -\mu<0 \qquad (33)$$

We claimed the following results
Lemma 4: *The positive endemic equilibrium state of the model (1) is locally asymptotically stable (LAS) when the control reproduction number, $R_C>1$ but close to 1.*

RESULTS AND DISCUSSION
In this session we carried out the simulation of model (2), examining the effect of treating infectious individuals on different classes using Maple software. Table 1 contains all the values used in simulations.

Table 1: Variable and Parameter Values

| Variable	Description	Baseline Values	References
$S(0)$	Susceptible Individuals	24000 Ind/Year	Assumed
$E(0)$	Latent Individuals	200 Ind/Year	(Andrawus *et al.*,2017)
$I(0)$	Infectious Individuals	100 Ind/Year	Assumed
$R_1(0)$	First Line Treatment	40 Ind/Year	Assumed
$R_2(0)$	Second Line Treatment	50 Ind/Year	Assumed
$R(0)$	Recovered Individuals	98 Ind/Year	(Egonmwan and Okuonghae, 2009)
Parameters	**Description**	**Values**	**References**
Λ	Constant recruitment rate	200 Ind/Year	[8]
β	Effective contact rate	10 Ind/Year	(Adewale *et al.*,2009)
μ	Natural mortality rate	0.02041/year	(Egonmwan and Okuonghae, 2009)
σ	Progression rate	0.048/year	(WHO, 2013; WHO, 2016)
γ_1	Default treatment of Infectious Individuals	(0,1)	(Yang *et al.*,2014)
γ_2	Default treatment of First Line treatment	(0,1)	(Yang *et al.*,2014)
τ_1,τ_2,τ_3	Treatment rates	(0,1), (0,1), (0,1)	--
$\delta_1,\delta_2,\delta_3$	Disease Induced death rates	(0,1), (0,1), (0,1)	--
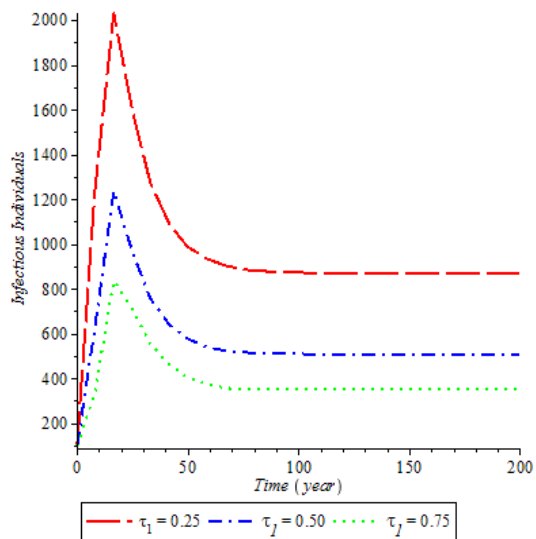
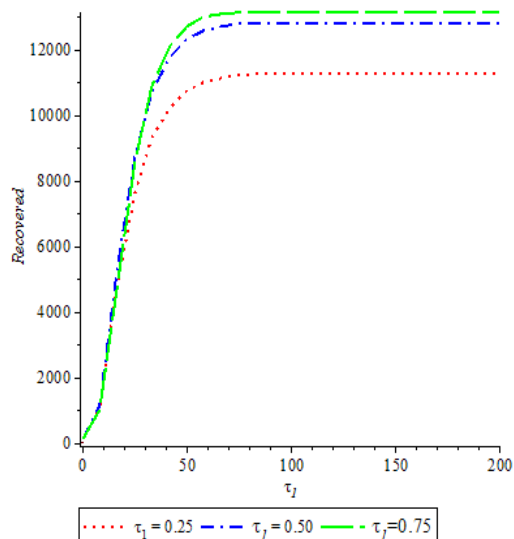**Fig 2:** The Effect of Varying Treatment Rates on Infectious Individuals
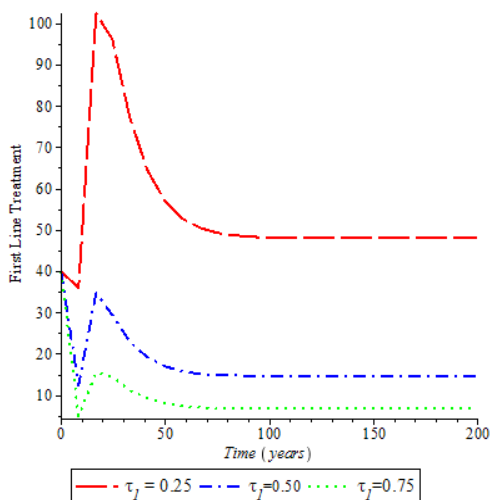

Fig 3: The Effect of Varying Treatment Rates on First Line Treatment

Fig 4: The Effect of Varying Treatment Rates on Second Line Treatment
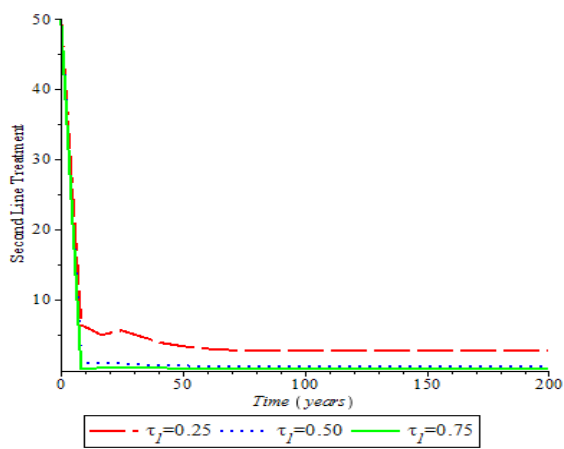

Fig 5: The Effect of Varying Treatment Rates on Recovered Individuals

Figure 2 is showing the effect of varying the treatment rate on Infectious individual, increasing treatment rate leads to reduction of Infectious individuals in a society. Epidemiologically, this will reduced the disease burden in a society. Figure 3 is showing the effect of varying a treatment rates on First line treatment (those that defaulted in treatment which will lead to antidrug resistant), increasing the treatments rates which will leads to fewer case of First line treatment.

Figure 4 shows the effect of varying the treatment rates on Second line treatment (those that defaulted in treatment for the second time which will lead to antidrug resistant), increasing the treatment rates leads to a small number of such cases in a society that is the cases of second line treatment. Figure 5 shows the effect of varying treatment rates on recovered individuals, increasing the treatment rates which will leads to the recovered individual as years goes by.

Conclusion: In this paper, a mathematical model of a tuberculosis transmission dynamics incorporating first and second line treatment was formulated and analyzed in order to gain better understanding of the disease dynamics. The DFE was shown to be locally asymptotically stable when the R_C is less than one and the EEP was also shown to be locally asymptotically stable when the R_C is greater than one. Numerical simulation shows that treating Infectious Individuals can leads to drastic reduction in second line treatment cases in a society which will also leads to reduction of Tuberculosis (TB) burden in a society.

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