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Deterministic and Stochastic Models of the Dynamics of Drug Resistant Tuberculosis

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Abstract

This work attempts to develop a mathematical model for the dynamics of drug resistant tuberculosis with the assumption that exposed individuals develop active tuberculosis due to endogenous reactivation and exogenous re-infection. Numerical and qualitative analyses of the model discuss the impact of diagnosis, treatment and health education rates on the different epidemiological compartments. Results show that the disease-free equilibrium is locally asymptotically stable whenever the effective reproduction number is less than unity and the endemic equilibrium is locally asymptotically stable provided that the effective reproduction number is greater than unity. These results compare favourably with literature and further suggest that at the current level of control strategies in Nigeria, the drug sensitive tuberculosis can be completely eliminated from the population which in the process reduces drug resistant tuberculosis.

Keywords: *Deterministic model, Drug resistant, Stochastic model, Tuberculosis.*

1. Introduction

Tuberculosis (TB) is arguably one of the most devastating diseases that have afflicted mankind from time immemorial. Known by many different names throughout history, such as Phthisis, Scrofula, Consumption, King's Evil, Lupus Vulgaris, the White Plague, and 'Captain of all these men of death', the scourge remains a significant public health concern (Shamputa *et al*., 2015).

TB is a bacterial infection that is caused by a bacterium called mycobacterium tuberculosis, also known as tubercle bacillus which has been present in the human population since 2400 BC (Adetunde, 2008). TB is an airborne infection that primarily affects the lungs. It can also affect the central nervous system, the lymphatic system,

the brain, spine and the kidneys. Children aged five and below are at a very high risk of developing active TB because their immune system is less developed (Infectious Diseases Society of America (IDSA), 2007).

The emergence of HIV and other multi-drug resistant strains of mycobacterium tuberculosis have significantly changed the dynamics of infections all over the world (Murphy *et al*., 2002; Reichman & Tanne, 2002). The continual increased burden of tuberculosis infection in regions of Africa, Southeast Asia and some European countries has renewed global interest in the control of TB (Murphy *et al*., 2003; Reichman & Tanne, 2002). Nigeria has been ranked fifth among the world's high burden countries, with a number of TB cases of 450,000 annually (WHO, 2009).

Okuonghae & Korobeinikov (2002) in their model titled, "Dynamic of Tuberculosis: The effect of Direct Observation Therapy Strategy (DOTS)" suggested that the expansion of DOTS should not just concentrate on the improvement of the treatment alone, but emphasis should also be placed on detection as well; which is in line with what Chaulet (1983) suggested. The results of the simulation of the model suggested that, despite the improvement in TB treatment success rate achieved under DOTS, the high number of undetected cases remain a major obstacle, preventing the long term success of DOTS in TB control. The results further showed that despite all efforts, DOTS has not succeeded in reducing the incidence level. This was blamed on failure to detect a huge number of active TB cases which are primarily responsible for the spread of the infection.

Mugisha *et al*. (2005) focused on the density of individuals with an aim of calculating the size of the area an individual is supposed to occupy in order to eliminate the TB epidemic. The qualitative analysis was done to determine the existence and stability of disease-free equilibrium of the model. They calculated the reproduction number, R_0 and performed numerical analysis. The results showed the existence of a stable disease-free equilibrium point provided that the characteristic area is greater than the product of the probability of survival from the latent stage to the infectious stage and the number of latent infectious produced by a typical infectious individual during his or her mean infectious period. They recommended that the characteristic area per individual should be at least 0.25 square kilometers in order to minimize the TB incidence in a population.

Blower *et al*. (1995) formulated two mathematical models that considered infected individuals that can develop TB either by fast progression or endogenous reactivation. Both qualitative and numerical analyses of the models were done. The results showed

that for the TB epidemic to rise, fall and reach epidemic equilibrium, it may take several years. They suggested that any decline of TB may be due to natural behaviour of the epidemic.

Ziv *et al.* (2001) extended the model of Blower *et al*. (1995). Their mathematical model focused on the effectiveness of early therapy for latently infected individuals. Numerical analysis of the model showed that latently infected individuals who are in the early stages of the disease must be provided with therapy so as to control the tuberculosis epidemic.

Daly *et al*. (2004) developed a model which was intended to predict the potential public health effect of new TB vaccines on epidemic control in high TB incidence countries, for instance, the Republic of South Africa. In the model, an infected individual can develop active TB by either fast progression or endogenous reactivation. Monte-Carlo methods were employed to help in the analysis of the model. The results showed that, pre-exposure or post-exposure vaccines would be able to reduce the number of TB cases by just one third.

Bekele (2008) modelled the role of latent reservoirs and Isoniazid Preventive Therapy (IPT) on TB dynamics. The emphasis of the study was to assess the impact of IPT on reduction of TB incidence in a density-dependent population size. The model considered three scenarios namely: (i) no immigrants (ii) contacts leading to no disease transmission and (iii) both immigrants and contact causing disease. Both numerical and qualitative analyses of the model were done. Results showed that whenever there are immigrants of latent infection, the disease cannot diminish completely. He further determined the threshold values for IPT and the area covered by the population for the disease to be eliminated. It was found out that, in order to decrease the incidences of TB, the therapy should at least target more than 80% of the latent population or the characteristic area should exceed $571\,m^2$ per individual. Sanga (2008) looked at the role of diagnosis and treatment on TB management and eradication. The model exhibited two equilibria; the disease-free equilibrium which was locally and globally asymptotically stable for $R_0 < 1$, and the endemic equilibrium that was locally asymptotically stable for $R_0 > 1$. Numerical results showed that as the proportion of TB patients being presented to clinics for diagnosis is increased, the rate of treatment should be correlated to the number of diagnosed infected individuals.

Nishiura *et al.* (2004) predicted the future trend of drug-resistant TB in Thailand and also assessed the impact of the control strategies. They assumed that the present

status of TB and the emergence of drug-resistant TB in Thailand are the consequence of past epidemics.

Bhunu & Garira (2009) looked at a two strain tuberculosis transmission model with therapy and quarantine. In their model, treatment was offered to patients with drug sensitive TB only. The model was then extended to incorporate quarantine for active TB cases with Drug Resistant TB strains. Qualitative analysis of the model was conducted which included determining the threshold and equilibrium quantities. From the study, it was concluded that quarantine of the Drug Resistant TB cases reduces the Drug Resistant TB induced reproduction number to values below unit, thus this intervention strategy can control the development of Drug Resistant TB epidemic.

The nonlinear Lyapunov functions used in studying the global behaviour of the endemic equilibria of the model in this work are the Goh-Volterra type functions and have been used in different forms in epidemic modelling. Safi & Garba (2012), and Vargas De-Leon (2011) made use of nonlinear Lyapunov functions in determining the global dynamics of SEIR, SEIS and SIR models. Okuonghae (2015) recently used Lyapunov functions to investigate the global properties of some tuberculosis models.

In this work, we consider both the deterministic and stochastic models of drug resistant tuberculosis, which incorporate a drug resistant class.

2. MODEL FORMULATION

The population of susceptible individuals (S) is increased by the recruitment of new borns into the population at a rate Λ. It is further increased by the loss of infection-acquired immunity of recovered or treated individuals at a per capita rate ε. It is decreased by infection, following effective contacts with infected individuals, at a rate λ, given by $\lambda = \beta(I + I_d)$. Here, β is the effective contact rate. The susceptible population is further decreased by natural death at a rate μ (this is assumed to be the same for all of the epidemiological compartments). Thus,

$$\frac{dS}{dt} = \Lambda - (\lambda + \mu)S + \varepsilon R \qquad (2.1)$$

The population of the latent individuals (E) is increased by the infection of susceptible individuals at a rate λ. It is decreased by progression of latent individuals into the infectious individuals at a rate α or natural death. Thus,

$$\frac{dE}{dt} = \lambda S - (\alpha + \mu)E \qquad (2.2)$$

The population of infectious individuals (I) is generated by progression of latent individuals into the infectious individuals. It is decreased by the recovery of infectious individuals or progression into drug-resistant infectious class. It is further decreased by natural death. Thus,

$$\frac{dI}{dt} = \alpha E - (\mu + \tau)I \tag{2.3}$$

The population of drug-resistant infectious individuals (I_d) is generated by progression of infectious individuals to the drug-resistant infectious class at a rate $(1-p)\tau$, where p is a fraction of infectious individuals who recover from TB. It is further decreased by disease-induced death at a rate δ or natural death. Thus,

$$\frac{dI_d}{dt} = (1-p)\tau I - (\mu + \delta)I_d \tag{2.4}$$

The recovered or treated population (R) is generated by the recovery of infectious individuals. It is further decreased by natural death or loss of infection-acquired immunity. Thus,

$$\frac{dR}{dt} = p\tau I - (\mu + \varepsilon)R \tag{2.5}$$

Based on the above assumptions and derivations, the model is given by the following deterministic system of non-linear differential equations:

$$\left.\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda S - \mu S + \varepsilon R \\
\frac{dE}{dt} &= \lambda S - (\alpha + \mu)E \\
\frac{dI}{dt} &= \alpha E - (\mu + \tau)I \\
\frac{dI_d}{dt} &= (1-p)\tau I - (\mu + \delta)I_d \\
\frac{dR}{dt} &= p\tau I - (\mu + \varepsilon)R
\end{aligned}\right\} \tag{2.6}$$

A flow diagram of the model is given in Fig. 2.1, and the associated variables and parameters are tabulated in Table 2.1(a) and Table 2.1(b) respectively.

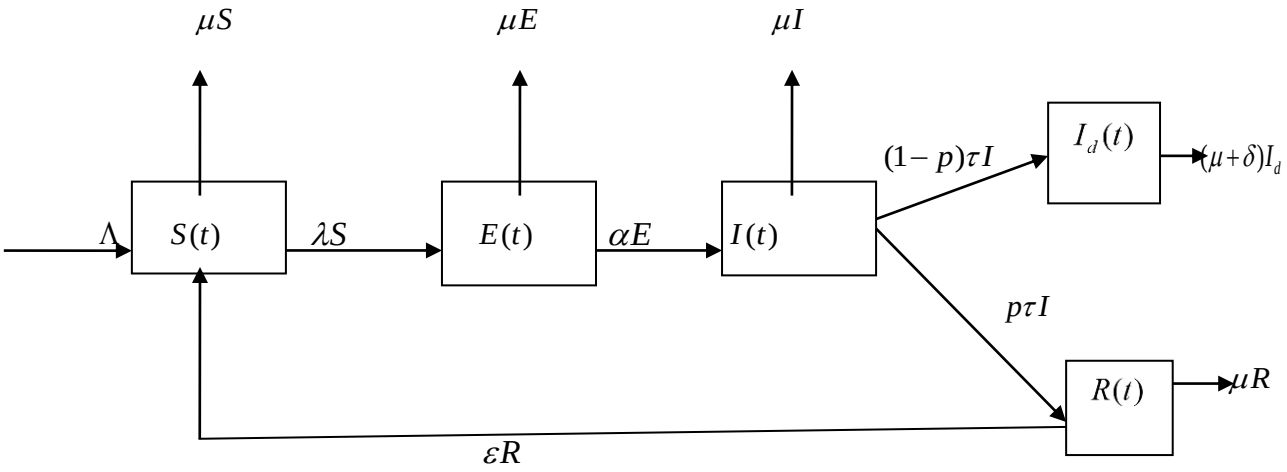

Fig. 2.1: Model Flow Diagram.

Table 2.1(a) Description of Model Variables

Variable	Description
$S(t)$	Number of susceptible individuals at time t
$E(t)$	Number of latent individuals at time t
$I(t)$	Number of infectious individuals at time t
$I_d(t)$	Number of drug resistant infectious individuals at time t
$R(t)$	Number of treated or recovered individuals at time t

Table 2.1(b) Description of Model Parameters

Parameter	Description
Λ	Recruitment rate
μ	Per-capita natural mortality rate
β	Contact rate
α	Rate at which exposed individual becomes infected
δ	Tuberculosis induced mortality rate of the drug resistant TB individuals
$(1-p)$	Proportion of infected individuals who progress to the drug-resistant Tuberculosis due to improper treatment
p	Proportion of infected individuals who progress to the recovered class due to proper treatment
τ	Treatment or recovery rate for the infected individuals
ε	Rate at which recovered/treated individuals become susceptible

2.1 Basic Properties of the model

Proposition 2.1: Let the initial data for the system (2.6) be $S(0)>0, E(0)>0, I(0)>0, I_d(0)>0, R(0)>0$. Then, the solutions $\left(S(t), E(t), I(t), I_d(t), R(t)\right)$ of the system (2.6) with positive initial data, will remain positive for all time $t>0$.

Proof: Let $t_1 = \sup\{t > 0 : S(t) > 0, E(t) > 0, I(t) > 0, I_d(t) > 0, R(t) > 0\} > 0$. Then it follows from the first equation of the system (2.6) that

$$\frac{dS}{dt} = \Lambda - \lambda S - \mu S + \varepsilon R \geq \Lambda - \lambda S - \mu S$$

which can be re-written as

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

Thus,

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

This implies

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

Similarly, it can be shown that $E > 0, I > 0, I_d > 0, R > 0$ for all time $t > 0$.

Proposition 2.2: The closed set $\Omega = \left\{(S, E, I, I_d, R) \in R_+^5 : N \leq \frac{\Lambda}{\mu}\right\}$ is positively invariant

Proof: Adding all the equations of the model gives

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dI_d}{dt} + \frac{dR}{dt}$$

$$= \Lambda - \mu N - \delta I_d$$

In the absence of infection

$I = I_d = 0$, so that

$$\frac{dN}{dt} \leq \Lambda - \mu N$$

We now apply Birkhoff and Rota's Theorem on differential inequality (Birkhoff & Rota, 1989). By separation of variables of the differential inequality, we obtain

$$\frac{dN}{\Lambda - \mu N} \leq dt$$

Integrating both sides gives

$$\int \frac{dN}{\Lambda - \mu N} \leq \int dt$$

$$\Rightarrow -\frac{1}{\mu}\ln(\Lambda - \mu N) \leq t + c$$

$$\Rightarrow \ln(\Lambda - \mu N) \geq -\mu(t + c)$$

Therefore,

$\Lambda - \mu N \geq Ae^{-\mu t}$, where A is a constant.

Now applying $N(0) = N_0$ we have

$A = \Lambda - \mu N_0$

Substituting gives

$\Lambda - \mu N \geq (\Lambda - \mu N_0)e^{-\mu t}$

Making μ the subject of the formula we have

$$N \leq \frac{\Lambda}{\mu} - \left[\frac{\Lambda - \mu N_0}{\mu}\right] e^{-\mu t}$$

As $t \to \infty$ in the population size, N approaches

$$0 \leq N \leq \frac{\Lambda}{\mu} \Rightarrow N \to \frac{\Lambda}{\mu}$$

Therefore, the feasibility solution set of the system of equations enters the region

$$\Omega = \left[(S, E, I, I_d, R) \in R_+^5 : N \leq \frac{\Lambda}{\mu}\right]$$

In this case, whenever $N > \frac{\Lambda}{\mu}$, then $\frac{dN}{dt} < 0$ which means that the population reduces asymptotically to the carrying capacity. On the other hand, whenever $N \leq \frac{\Lambda}{\mu}$, every solution with initial condition in R_+^5 remains in that region for $t > 0$.

Thus, the region Ω is positively-invariant and the model is well posed and biologically meaningful.

2.2 Stochastic Model Equations

We shall first compute the transition probabilities before deriving the stochastic model.

Table 2.2 Transition Probabilities

Change	Probability	Event
$[1 \quad 0 \quad 0 \quad 0 \quad 0]^T$	$p_1 = \Lambda\Delta t$	Birth or immigration
$[-1 \quad 0 \quad 0 \quad 0 \quad 0]^T$	$p_2 = \mu S\Delta t$	Death of a susceptible
$[-1 \quad 1 \quad 0 \quad 0 \quad 0]^T$	$p_3 = \beta SI\Delta t$	Susceptible becomes exposed
$[0 \quad -1 \quad 0 \quad 0 \quad 0]^T$	$p_4 = \mu E\Delta t$	Exposed dies a natural death
$[0 \quad -1 \quad 1 \quad 0 \quad 0]^T$	$p_5 = \alpha E\Delta t$	Exposed becomes infectious
$[0 \quad 0 \quad -1 \quad 0 \quad 0]^T$	$p_6 = \mu I\Delta t$	Infective dies naturally
$[0 \quad 0 \quad -1 \quad 1 \quad 0]^T$	$p_7 = (1-p)\tau I\Delta t$	Infective becomes resistant
$[0 \quad 0 \quad -1 \quad 0 \quad 1]^T$	$p_8 = p\tau I\Delta t$	Infective recovers
$[0 \quad 0 \quad 0 \quad -1 \quad 0]^T$	$p_9 = (\mu+\delta)I_d\Delta t$	Drug resistant infective dies
$[0 \quad 0 \quad 0 \quad 0 \quad -1]^T$	$p_{10} = \mu R\Delta t$	Recovered dies naturally
$[1 \quad 0 \quad 0 \quad 0 \quad -1]^T$	$p_{11} = \varepsilon R\Delta t$	Recovered becomes susceptible

Using the first modelling procedure developed by Allen *et al*. (2008), the stochastic model equations are given by

$$\left.\begin{aligned} d\vec{X} &= \vec{f}(t,\vec{X}(t))dt + B(t,\vec{X}(t))d\vec{W}(t) \\ \vec{X}(0) &= \left[X_1(0), X_2(0), X_3(0), X_4(0), X_5(0)\right]^T \end{aligned}\right\} \tag{2.7}$$

The drift vector is defined as

$$\vec{f} = \sum_{j=1}^{11} p_j \vec{\lambda}_j \tag{2.8}$$

where $\vec{\lambda}_j$ and p_j are the random changes and transition probabilities respectively (See Table 2.2).

The drift vector $\vec{f}$ is given by

$$\vec{f} = \begin{pmatrix} \Lambda - \mu S - \lambda S + \varepsilon R \\ \lambda S - (\alpha+\mu)E \\ \alpha E - (\mu+\tau)I \\ (1-p)\tau I - (\mu+\delta)I_d \\ p\tau I - (\mu+\varepsilon)R \end{pmatrix} \tag{2.9}$$

$$\vec{f} = P_1\vec{\lambda}_1 + P_2\vec{\lambda}_2 + P_3\vec{\lambda}_3 + P_4\vec{\lambda}_4 + P_5\vec{\lambda}_5 + P_6\vec{\lambda}_6 + P_7\vec{\lambda}_7 + P_8\vec{\lambda}_8 + P_9\vec{\lambda}_9 + P_{10}\vec{\lambda}_{10} + P_{11}\vec{\lambda}_{11} \tag{2.10}$$

$$= \Lambda \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \mu S \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \lambda S \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \mu E \begin{pmatrix} 0 \\ -1 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \alpha E \begin{pmatrix} 0 \\ -1 \\ 1 \\ 0 \\ 0 \end{pmatrix} + \mu I \begin{pmatrix} 0 \\ 0 \\ -1 \\ 0 \\ 0 \end{pmatrix} + (1-p)\tau I \begin{pmatrix} 0 \\ 0 \\ -1 \\ 1 \\ 0 \end{pmatrix}$$

$$+ p\tau I \begin{pmatrix} 0 \\ 0 \\ -1 \\ 0 \\ -1 \end{pmatrix} + (\mu+\delta) I_d \begin{pmatrix} 0 \\ 0 \\ 0 \\ -1 \\ 0 \end{pmatrix} + \mu R \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -1 \end{pmatrix} + \varepsilon R \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ -1 \end{pmatrix}$$

$$= \begin{pmatrix} \Lambda - \mu S - \lambda S + \varepsilon R \\ \lambda S - (\mu+\alpha) E \\ \alpha E - \mu I - ((1-p)+p)\tau I \\ (1-p)\tau I - (\mu+\delta) I_d \\ p\tau I - (\mu+\varepsilon) R \end{pmatrix} = \begin{pmatrix} \Lambda - \mu S - \lambda S + \varepsilon R \\ \lambda S - (\mu+\alpha) E \\ \alpha E - \mu I - \tau I \\ (1-p)\tau I - (\mu+\delta) I_d \\ p\tau I - (\mu+\varepsilon) R \end{pmatrix}$$

We shall derive the covariance matrix which is defined as

$$\vec{B} = \sum_{j=1}^{11} P_j \lambda_j \lambda_j^T \qquad (2.11)$$

$$= \Lambda \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \end{pmatrix} + \mu S \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} -1 & 0 & 0 & 0 & 0 \end{pmatrix} + \lambda S \begin{pmatrix} -1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} -1 & 1 & 0 & 0 & 0 \end{pmatrix}$$

$$+ \mu E \begin{pmatrix} 0 \\ -1 \\ 0 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} 0 & -1 & 0 & 0 & 0 \end{pmatrix} + \alpha E \begin{pmatrix} 0 \\ -1 \\ 1 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} 0 & -1 & 1 & 0 & 0 \end{pmatrix} + \mu I \begin{pmatrix} 0 \\ 0 \\ -1 \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & -1 & 0 & 0 \end{pmatrix}$$

$$+ (1-p)\tau I \begin{pmatrix} 0 \\ 0 \\ -1 \\ 1 \\ 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & -1 & 1 & 0 \end{pmatrix} + p\tau I \begin{pmatrix} 0 \\ 0 \\ -1 \\ 0 \\ 1 \end{pmatrix} \begin{pmatrix} 0 & 0 & -1 & 0 & 1 \end{pmatrix} + (\mu+\delta) I_d \begin{pmatrix} 0 \\ 0 \\ 0 \\ -1 \\ 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & 0 & -1 & 0 \end{pmatrix}$$

$$+\mu R\begin{pmatrix}0\\0\\0\\0\\-1\end{pmatrix}\begin{pmatrix}0&0&0&0&-1\end{pmatrix}+\varepsilon R\begin{pmatrix}1\\0\\0\\0\\-1\end{pmatrix}\begin{pmatrix}1&0&0&0&-1\end{pmatrix}$$

$$\vec{B}=\Lambda\begin{pmatrix}1&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{pmatrix}+\mu S\begin{pmatrix}1&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{pmatrix}+\lambda S\begin{pmatrix}1&-1&0&0&0\\-1&1&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{pmatrix}+\mu E\begin{pmatrix}0&0&0&0&0\\0&1&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{pmatrix}$$

$$+\alpha E\begin{pmatrix}0&0&0&0&0\\0&1&-1&0&0\\0&-1&1&0&0\\0&0&0&0&0\\0&0&0&0&0\end{pmatrix}+\mu I\begin{pmatrix}0&0&0&0&0\\0&0&0&0&0\\0&0&1&0&0\\0&0&0&0&0\\0&0&0&0&0\end{pmatrix}+(1-p)\tau I\begin{pmatrix}0&0&0&0&0\\0&0&0&0&0\\0&0&1&-1&0\\0&0&-1&1&0\\0&0&0&0&0\end{pmatrix}$$

$$+p\tau I\begin{pmatrix}1&0&0&0&0\\0&0&0&0&0\\0&0&1&0&-1\\0&0&0&0&0\\0&0&-1&0&1\end{pmatrix}+(\mu+\delta)I_d\begin{pmatrix}0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&1&0\\0&0&0&0&0\end{pmatrix}+\mu R\begin{pmatrix}0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&1\end{pmatrix}+\varepsilon R\begin{pmatrix}1&0&0&0&-1\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\-1&0&0&0&1\end{pmatrix}$$

$$\vec{B}=\begin{pmatrix}\Lambda+\mu S+\lambda S+\varepsilon R & -\lambda S & 0 & 0 & -\varepsilon R\\ -\lambda S & \lambda S+(\mu+\alpha)E & -\alpha E & 0 & 0\\ 0 & -\alpha E & \alpha E+((1-p)+p)\tau I & -(1-p)\tau I & -p\tau I\\ 0 & 0 & -(1-p)\tau I & (1-p)\tau I+(\mu+\delta)I_d & 0\\ -\varepsilon R & 0 & -p\tau I & 0 & p\tau I+(\mu+\varepsilon)R\end{pmatrix}$$

We shall be required to compute the square root of this covariance matrix. However, for an $n\times n$ positive semi-definite matrix with order greater than two, there is no explicit formula for calculating its square root. Hence, to proceed, we shall apply the second modelling procedure which results in a diffusion matrix, which square root may not be necessary.

Using the second modelling procedure developed by Allen *et al*. (2008), the stochastic model is given by

$$\left.\begin{aligned} d\vec{X} &= \vec{f}(t,\vec{X}(t))dt + G(t,\vec{X}(t))d\vec{W}(t) \\ \vec{X}(0) &= \left[X_1(0), X_2(0), X_3(0), X_4(0), X_5(0)\right]^T \end{aligned}\right\} \quad (2.12)$$

The drift vector $\vec{f}$ is the same as that obtained in the first modelling procedure.

The diffusion matrix G is defined by

$$G = \lambda_{i,j} p_j^{1/2}, \quad j = 1,2,.....,11, \quad i = 1,2,.....,5 \quad (2.13)$$

$$G = \begin{pmatrix} \sqrt{\Lambda} & -\sqrt{\mu S} & -\sqrt{\beta SI} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \varepsilon R \\ 0 & 0 & \sqrt{\lambda S} & -\sqrt{\mu E} & -\sqrt{\alpha E} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sqrt{\alpha E} & -\sqrt{\mu I} & -\sqrt{(1-P)\tau I} & -\sqrt{P\tau I} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{(1-P)\tau I} & 0 & -\sqrt{(\mu+\delta)I_d} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{P\tau I} & 0 & -\sqrt{\mu R} & -\sqrt{\varepsilon R} \end{pmatrix}$$

3.0 Model Analysis

3.1 Local Stability of the Disease Free Equilibrium (DFE)

In the absence of infection, i.e. ($I^0 = E^0 = I_d^0 = R^0 = 0$) the model has a steady state, E_0, called the disease free equilibrium. This statement will reduce the system (2.6) to

$$0 = \Lambda - \mu S^0$$

which implies that,

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

$S^0 = \frac{\Lambda}{\mu}$ is defined as the asymptotic carrying capacity of the population. Therefore, the disease free equilibrium point, $E_0 = (S^0, 0, 0, 0, 0)$. Thus $E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right)$.

In order to assess the local stability of the disease free equilibrium E_0 established by the Next Generation Method on the system, the basic reproduction number is necessary. The basic reproduction number R_0 is defined as the average number of secondary infections that can occur when one infected individual is introduced into a completely susceptible population (van den Driessche & Watmough, 2002). It is obtained by taking the largest (dominant) eigenvalue (spectral radius) of FV^{-1}

where

$$F=\left[\frac{\partial F_i(E_0)}{\partial X_j}\right], V=\left[\frac{\partial V_i(E_0)}{\partial X_j}\right]$$

i is the component of the disease compartment

F_i is the rate of appearance of new infection in the compartment i

$V_i = V_i^- - V_i^+$

V_i^- is the rate of transfer of individuals out of compartment i

V^+_i is the rate of transfer of individuals into compartment i by all other means

E_0 is the disease free equilibrium

The disease compartments are E, I and I_d.

Re-writing the model equations for the disease compartments only, we have

$$\left.\begin{aligned}\frac{dE}{dt}&=\lambda S-(\alpha+\mu)E\\ \frac{dI}{dt}&=\alpha E-(\mu+\tau)I\\ \frac{dI_d}{dt}&=(1-p)\tau I-(\mu+\delta)I_d\end{aligned}\right\} \qquad (3.1)$$

$$F_i=\begin{bmatrix}\beta(I+I_d)S\\0\\0\end{bmatrix}$$

$$V_i^-=\begin{bmatrix}(\mu+\alpha)E\\(\mu+\tau)I\\(\mu+\delta)I_d\end{bmatrix},\ V_i^+=\begin{bmatrix}0\\\alpha E\\(1-p)\tau I\end{bmatrix}$$

$$V_i=V_i^- - V_i^+=\begin{bmatrix}(\mu+\alpha)E\\(\mu+\tau)I\\(\mu+\delta)I_d\end{bmatrix}-\begin{bmatrix}0\\\alpha E\\(1-p)\tau I\end{bmatrix}=\begin{bmatrix}(\mu+\alpha)E\\(\mu+\tau)I-\alpha E\\(\mu+\delta)I_d-(1-p)\tau I\end{bmatrix}$$

$$F=\begin{pmatrix}0&\beta S_0&\beta S_0\\0&0&0\\0&0&0\end{pmatrix}$$

Since $S_0=\frac{\Lambda}{\mu}$, we have

$$F=\begin{pmatrix} 0 & \frac{\beta\Lambda}{\mu} & \frac{\beta\Lambda}{\mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$$V=\begin{pmatrix} \mu+\alpha & 0 & 0 \\ -\alpha & \mu+\tau & 0 \\ 0 & -(1-p)\tau & \mu+\delta \end{pmatrix}$$

$$V^{-1}=\begin{pmatrix} \frac{1}{\mu+\alpha} & 0 & 0 \\ \frac{\alpha}{(\mu+\alpha)(\mu+\tau)} & \frac{1}{\mu+\tau} & 0 \\ \frac{\alpha(1-p)\tau}{(\mu+\alpha)(\mu+\tau)(\mu+\delta)} & \frac{(1-p)\tau}{(\mu+\tau)(\mu+\delta)} & \frac{1}{\mu+\delta} \end{pmatrix}$$

$$FV^{-1}=\begin{pmatrix} 0 & \frac{\beta\Lambda}{\mu} & \frac{\beta\Lambda}{\mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}\begin{pmatrix} \frac{1}{\mu+\alpha} & 0 & 0 \\ \frac{\alpha}{(\mu+\alpha)(\mu+\tau)} & \frac{1}{\mu+\tau} & 0 \\ \frac{\alpha(1-p)\tau}{(\mu+\alpha)(\mu+\tau)(\mu+\delta)} & \frac{(1-p)\tau}{(\mu+\tau)(\mu+\delta)} & \frac{1}{\mu+\delta} \end{pmatrix}$$

$$FV^{-1}=\begin{pmatrix} \frac{\alpha\beta\Lambda(\mu+\delta+\tau-p\tau)}{\mu(\mu+\alpha)(\mu+\tau)(\mu+\delta)} & \frac{\beta\Lambda(\mu+\delta+\tau-p\tau)}{\mu(\mu+\tau)(\mu+\delta)} & \frac{\beta\Lambda}{\mu(\mu+\delta)} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

The eigenvalues are

$$\lambda_1=\frac{\alpha\beta\Lambda(\mu+\delta+\tau-p\tau)}{\mu(\mu+\alpha)(\mu+\tau)(\mu+\delta)},\ \lambda_2=0,\ \lambda_3=0;$$

Clearly, the dominant eigenvalue (spectral radius) is λ_1.

Hence, $R_0=\frac{\alpha\beta\Lambda(\mu+\delta+\tau-p\tau)}{\mu(\mu+\alpha)(\mu+\tau)(\mu+\delta)}$.

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

Theorem 3.1: The DFE of the system (2.6) is locally asymptotically stable if $R_0<1$ and unstable if $R_0>1$.

3.2 Global Stability of the Disease Free Equilibrium

Consider the Lyapunov function

$$V = c_1 E + c_2 I + c_3 I_d \tag{3.2}$$

where

$$c_1 = \frac{\alpha(\mu+\delta+\tau-p\tau)}{(\mu+\alpha)(\mu+\tau)}\ ,\ c_2 = \frac{(\mu+\delta+\tau-p\tau)}{(\mu+\tau)}\ ,\ c_3 = 1$$

$$\dot{V} = \frac{\alpha(\mu+\delta+\tau-p\tau)}{(\mu+\alpha)(\mu+\tau)}\left[\beta(I+I_d)S-(\alpha+\mu)E\right]+\frac{\alpha(\mu+\delta+\tau-p\tau)}{(\mu+\tau)}\left[\alpha E-(\mu+\tau)\right]+\left[(1-p)\tau I-(\mu+\delta)I_d\right]$$

$$= \frac{\alpha(\mu+\delta+\tau-p\tau)}{(\mu+\alpha)(\mu+\tau)}\left[\beta(I+I_d)S\right]-(\mu+\delta+\tau-p\tau)I+(\tau-p\tau)I-(\mu+\delta)I_d$$

$$= \frac{\alpha\beta\Lambda}{\mu(\mu+\alpha)(\mu+\tau)}\left(I+I_d\right)-\left(\mu+\delta\right)\left(I+I_d\right)$$

$$= \left(\mu+\delta\right)\left[\frac{\alpha\beta\Lambda(\mu+\delta+\tau-p\tau)}{\mu(\mu+\alpha)(\mu+\tau)(\mu+\delta)}-1\right]\left(I+I_d\right)$$

$$= \left(\mu+\delta\right)\left[R_0-1\right]\left(I+I_d\right).$$

Since all the parameters and variables of the model are non-negative, it follows that $\dot{V} \le 0$ for $R_0 \le 1$ with $\dot{V} = 0$ if and only if $E = I = I_d = 0$. Hence, V is a Lyapunov function on Ω.

3.3 Global Stability of the endemic equilibrium (special case when $\varepsilon = 0$)

Theorem 3.2: The endemic equilibrium of the system (2.6) is globally asymptotically stable in Ω whenever $R_0\big|_{\varepsilon=0} > 1$.

Proof: Let the endemic equilibrium of the system (2.6) be denoted by $\xi_e = \left(S^*, E^*, I^*, I_d^*, R^*\right)$ and let $R_0\big|_{\varepsilon=0} > 1$ so that ξ_e exists. Consider the following nonlinear Goh-Volterra type Lyapunov function

$$V = S - S^* - S^* \ln\left(\frac{S}{S^*}\right) + E - E^* - E^* \ln\left(\frac{E}{E^*}\right) + \frac{\beta S^*}{\mu+\tau}\left(I - I^* - I^* \ln\left(\frac{I}{I^*}\right)\right) + \frac{\beta S^*}{\mu+\delta}\left(I_d - I_d^* - I_d^* \ln\left(\frac{I_d}{I_d^*}\right)\right)$$

with the Lyapunov derivative

$$\dot{V} = \left(1-\frac{S^*}{S}\right)\dot{S} + \left(1-\frac{E^*}{E}\right)\dot{E} + \frac{\beta S^*}{\mu+\tau}\left(1-\frac{I^*}{I}\right)\dot{I} + \frac{\beta S^*}{\mu+\delta}\left(1-\frac{I_d^*}{I_d}\right)\dot{I}_d$$

where the upper dot represents the differentiation with respect to time. Putting the appropriate equations of the system (2.6) into the above, we have

$$\dot{V} = \left(1-\frac{S^*}{S}\right)\left(\Lambda-\lambda S-\mu S\right)+\left(1-\frac{E^*}{E}\right)\left(\lambda S-(\alpha+\mu)E\right)+\frac{\beta S^*}{\mu+\tau}\left(1-\frac{I^*}{I}\right)\left(\alpha E-(\mu+\tau)I\right)$$

$$+\left(1-\frac{I_d^*}{I_d}\right)\left((1-p)\tau I-(\mu+\delta)I_d\right)$$

Now, at steady states,

$$\left.\begin{aligned}
&\Lambda = \beta(I^*+I_d^*)S^*+\mu S^* \\
&\beta(I^*+I_d^*)S^*+\mu S^* = (\alpha+\mu)E^* \\
&\alpha E^* = (\mu+\tau)I^* \\
&(1-p)\tau I^* = (\mu+\delta)I_d^*
\end{aligned}\right\} \qquad (3.3)$$

Substituting into the Lyapunov derivatives, we have

$$\dot{V} = \left(1-\frac{S^*}{S}\right)\left[\beta(I^*+I_d^*)S^*+\mu S^*-\beta(I+I_d)S-\mu S\right]$$

$$+\left(1-\frac{E^*}{E}\right)\left[\beta(I+I_d)S-(\mu+\alpha)E\right]$$

$$+\frac{\beta S^*}{\mu+\tau}\left(1-\frac{I^*}{I}\right)\left[\alpha E-(\mu+\tau)I\right]+\frac{\beta S^*}{\mu+\delta}\left(1-\frac{I_d^*}{I_d}\right)\left[(1-p)\tau I-(\mu+\delta)I_d\right]$$

which can be simplified into

$$\dot{V} = \mu S^*\left(2-\frac{S}{S^*}-\frac{S^*}{S}\right)+\beta I^*S^*\left(3-\frac{S^*}{S}-\frac{EI^*}{E^*I}-\frac{E^*IS}{EI^*S^*}\right)+\beta I_d^*S^*\left(3-\frac{S^*}{S}-\frac{E}{E^*}-\frac{II_d^*}{I^*I_d}-\frac{E^*I_dS}{EI_d^*S^*}\right)+\frac{\beta II_d^*S^*}{I^*}$$

$$\dot{V} \le \mu S^*\left(2-\frac{S}{S^*}-\frac{S^*}{S}\right)+\beta I^*S^*\left(3-\frac{S^*}{S}-\frac{EI^*}{E^*I}-\frac{E^*IS}{EI^*S^*}\right)+\beta I_d^*S^*\left(3-\frac{S^*}{S}-\frac{E}{E^*}-\frac{II_d^*}{I^*I_d}-\frac{E^*I_dS}{EI_d^*S^*}\right)$$

Finally, since the arithmetic mean exceeds the geometric mean, the following inequalities hold

$$\left(2-\frac{S}{S^*}-\frac{S^*}{S}\right)\le 0,\ \left(3-\frac{S^*}{S}-\frac{EI^*}{E^*I}-\frac{E^*IS}{EI^*S^*}\right)\le 0,\ \left(3-\frac{S^*}{S}-\frac{E}{E^*}-\frac{II_d^*}{I^*I_d}-\frac{E^*I_dS}{EI_d^*S^*}\right)\le 0$$

Thus, $\dot{V}\le 0$ for $R_0\big|_{\varepsilon=0}>1$. Hence, V is a Lyapunov function in Ω and it follows by the LaSalle invariance principle (Hale, 1969) that every solution to the equations of the

system (2.6) with an initial condition in $\Omega \setminus \Omega_0$ approaches the associated unique endemic equilibrium ξ_e, of the model as $t \to \infty$ for $R_0\big|_{\varepsilon=0} > 1$.

4.0 Numerical simulation

Description of the variables and parameters of the model

Variable/Parameter	Description	Values	Unit	Reference
Λ	Recruitment rate	$\mu \times 10^5$	year $^{-1}$	Song *et al*. (2002)
μ	Natural death rate	0.020	year $^{-1}$	Sharomi *et al.* (2008)
α	Rate of progression to active infection	0.05	year $^{-1}$	Blower *et al.* (2013)
δ	Disease-induced death rate	0.365	year $^{-1}$	Borgdorff (2004)
β	Effective contact rate	2.0	year $^{-1}$	Assumed
τ	Treatment rate	2.0	year $^{-1}$	Jung, *et al.*(2002)
γ	Recovery rate	2.5	year $^{-1}$	Garba *et al*. (2008)
ε	Waning immunity rate	0.2	year $^{-1}$	Okuonghae and Omosigho (2011)
p	The proportion of recovered individuals	0.1	year $^{-1}$	Jung, *et al* (2002)

The initial populations are assumed to be:

$S(0) = 50, E(0) = 20, I(0) = 10, I_d(0) = 15, R(0) = 20$

4.1 Graphs

4.1.1 Deterministic graphs

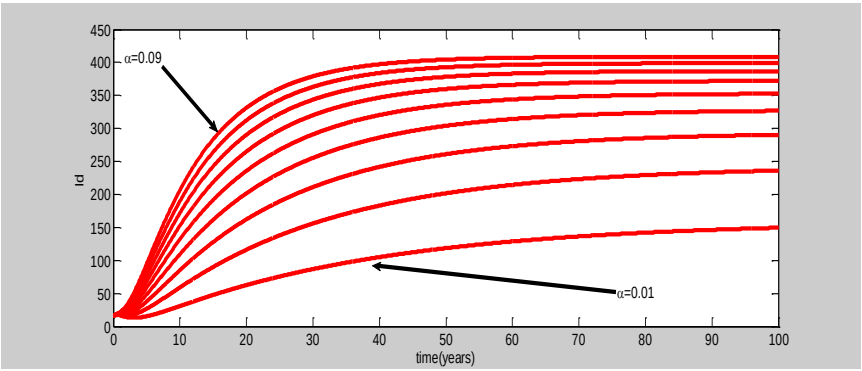

Fig. 4.1: Population of drug resistant infected individuals at different values of α

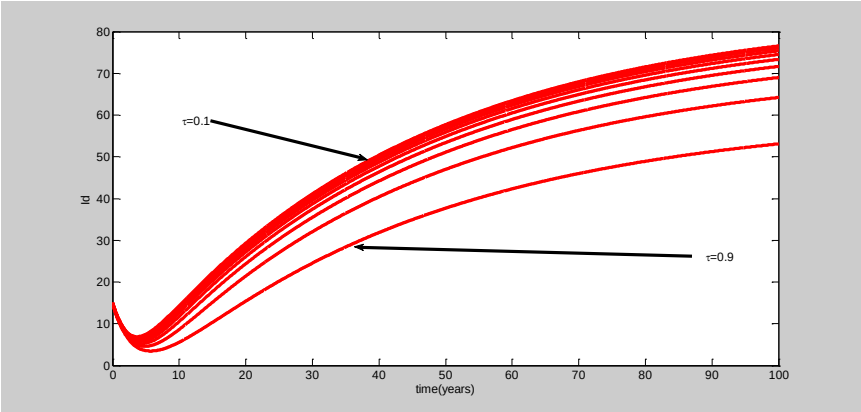

Fig. 4.2: Population of drug resistant infected individuals at different values of τ

From Fig. 4.1, the population of drug resistant infected individuals is shown at different values of α. As α is increased the population of drug resistant infected is also increased with time. That is to say, as more individuals progress from the exposed to the infected class, the population of drug resistant infceted is also increased. Fig. 4.2 shows the variations of drug resistant infected at varying levels of τ. Though, the population of drug resistant infected individuals seem to be on the increase with time, it is evident that increasing the treatment rate decreases the population of drug resistant infected individuals.

4.1.2 Stochastic graphs

The graphs from the stochastic simulations are shown below:

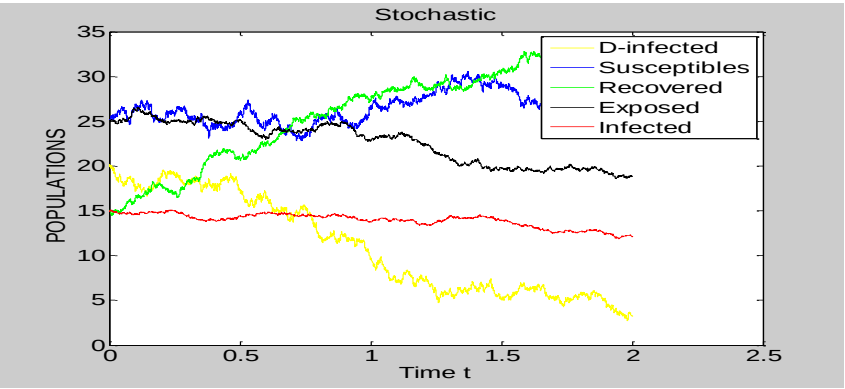

Fig. 4.3: Populations of the different compartments when treatment rate $\tau = 0.7$

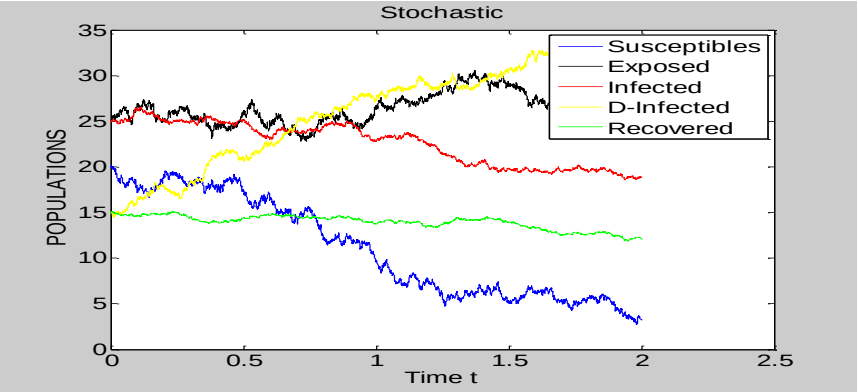

Fig. 4.4: Populations of the different compartments when treatment rate $\tau = 0.2$

The populations of the different compartments over a period of time are presented in Figs. 4.3 and 4.4. The remaining parameter values are as given in Table 2.1(b). From Fig. 4.3, we see that if the recovery rate of the infected individuals is very high, more people move into the recovered class. The drug resistant class rises and then falls drastically again. In Fig. 4.4, when the recovery rate of the infected individuals is very low, more people contact the disease and due to lack of proper treatment, they die as a result of the disease.

5. Conclusion

Based on the results of this work, we conclude that treatment of sensitive TB results in the reduction of Drug Resistant TB as most Drug Resistant TB cases come from failure to properly administer TB drugs. On the other hand, diagnosis and health education of infectives with sensitive TB are very important in the reduction of new Drug Resistant TB cases because they lead to appropriate treatment. However, there is need to diagnose, treat and educate more people if we are to ever dream of completely eliminating Drug Resistant tuberculosis.

Also, from the results of this work, it is recommended that;

(i). Tuberculosis control programs should increase the number of people receiving timely treatment when diagnosed with TB in order to reduce Drug Resistant TB.

(ii). More awareness campaigns should be conducted across the country to sensitize people on the importance of completing their TB dosage and also the advantages of rushing to the hospitals for TB diagnosis when they experience Symptoms.

(iii). More TB diagnosis centres should be opened across the country to ensure that many people have access to the facilities hence, reduce the tendency of harbouring TB bacteria which might develop resistance to TB drugs.

Also, based on the model of this study, it is proposed that future work should consider:

(i). Carrying out an effective analysis of the control strategies of Drug Resistant TB in the model.

(ii). Expanding the model to incorporate media coverage and vaccination of susceptible population.

(iii). An investigation on the efficacy of Drug Resistant TB drugs and up-take in educational programs.

References

Adetunde, I.A. (2008). The mathematical models of the dynamical behaviour of tuberculosis disease in the upper east region of the northern part of Ghana: A case study of Bawku. *Current Research in Tuberculosis*, *1*(1), 1 – 6.

Allen, E. J., Allen, L. J. S., Arciniega, A., & Greenwood, P. E. (2008). Construction of equivalent stochastic differential equation models. *Stoch. Anal. Appl., 26* (2), 274 – 297.

Bekele, B.T. (2008). Modelling the role of latent reservoirs and IPT on TB dynamics, African Institute for Mathematical Sciences, PGD Thesis.

Bhunu, C. P. & Garira, W. (2009). A two strain tuberculosis transmission model with therapy and quarantine. *Mathematical Modelling and Analysis, 14* (3), 291 – 312.

Birkhoff, G. & Rota, G. C. (1989). *Ordinary differential equations* (4th ed.). New York: John Wiley and Sons.

Blower, S. M., Mclean, A. R., Porco, T. C., Amall, P. M., Sanchez, M. A., Hopewell, P. C., & Moss, R. (1995). The intrinsic transmission dynamics of tuberculosis epidemics. *Nature Medicine, 1* (8), 815 – 821.

Borgdorff, M. W. (2004). New measurable indicator for tuberculosis case detection. *Emerg. Infec. Dis., 10* (9), 1523 – 1528.

Chaulet, P. (1983). Treatment of tuberculosis: Case holding until cure. Geneva: World Health Organization, 141.

Collins, T. F. B. (1981). Applied epidemiology and logic in tuberculosis control. *South African Medical Journal, 59* (16), 566 – 569.

Daly, C. L., Blower, S., & Ziv, E. (2004). Potential public health impact of new tuberculosis vaccines. *Emerging Infectious Diseases*, *10* (9), 1529 – 1535.

Hale, J. K. (1969). *Ordinary differential equations*. New York: John Wiley and Sons.

Hans, L. R. (1999). *Epidemiologic basis of tuberculosis*. Boulevard Saint-Michel, 75006 Paris: International Union Against Tuberculosis and Lung Disease 68.

Infectious Diseases Society of America. (2007). *HIV/TB coinfection: Basic facts*. The Forum for Collaborative HIV Research.

Jung, E., Lenhart, S., & Feng, Z. (2002). Optimal control of treatments in a two strain tuberculosis model. *Discrete continuous Dynamical System, B2*, 473 – 482.

Mugisha, J. Y. T., Luboobil, S., & Ssematimba, A. (2005). Mathematical models for the dynamics of tuberculosis in density-dependent populations: The case of internally displaced peoples camps (IDPCs) in Uganda. *Journal of Mathematics and Statistics*, *1* (3), 217 – 224.

Murphy, B. M., Singer, B. H., Anderson, S., & Kirschner, D. (2002). Comparing epidemic tuberculosis in demographically distinct heterogeneous populations. *Mathematical Biosciences, 180*, 161 – 185.

Murphy, B. M., Singer, B. H., & Kirschner, D. (2003). On treatment of tuberculosis in heterogeneous populations. *Journal of Theoritical Biology, 223*, 391 – 404.

Nishiura, H., Patanarapelert, K., & Tang, M. I. (2004). Predicting the future trend of drug-resistant tuberculosis in Thailand: Assessing the impact of control strategies. *South East Asian J. Trop. Med. Public Health*, *35* (3), 649 – 656.

Okuonghae, D. (2015). Lyapunov functions and global properties of some tuberculosis models. *Journal of Applied Mathematical Computations, 48*, 421 – 439.

Okuonghae, D., & Korobeinikov, A. (2007). Dynamics of tuberculosis: The effect of direct observation therapy strategy (DOTS). *Mathematical Modelling of Natural Phenomena*, *2* (1), 101 – 113.

Okuonghae, D., & Omosigho, S. E. (2011). Analysis of a mathematical model for tuberculosis: What could be done to increase case defection. *Journal of Theoritical Biology, 269*, 31 – 45.

Reichman, L., & Tanne, J. H. (2002). *Timebomb: The global epidemic of multidrug-resistant tuberculosis*. New York: McGraw Hill.

Safi, M. A., & Garba, S. M. (2012). Global stability analysis of an SEIR model with holling type II incidence function. *Comp. Math. Med*., 1 – 8. doi:10.1155/2012/826052.

Sanga, G. G. (2008). *Modelling the role of diagnosis and treatment on tuberculosis (TB) dynamics*. South Africa: African Institute for Mathematical Sciences (AIMS).

Shamputa, I. C., Cho, S. N., Lebron, J., & Via, L. E. (2015). Introduction and epidemiology of mycobacterium tuberculosis, in tuberculosis, leprosy and microbacterial diseases of man and animals. H. Mukundan, M. Chambers and R. Waters (eds) *The many hosts of mycobacteria.*

Sharomi, O., Podder, C., & Gumel, A. B. (2008). Mathematical analysis of the transmission dynamics of HIV/TB coinfection in the presence of treatment. *Math. Bios. Eng., 5*, 145 – 174.

Song, B., Castillo-Chavez, C., & Aparicio, J. P. (2002). Tuberculosis models with fast and slow dynamics: The role of close and casual contacts. *Mathematical Biosciences, 180*, 187 – 205.

Van Den Driessche, P., & Watmough, J. (2002). Reproduction numbers and sub threshold endemic equilibria for compartmental models of disease transmission, *Mathematical Biosciences, 180*, 29 – 48.

Vargas-De-Leon, C. (2011). On the global stability of SIS, SIR and SIRS epidemic models with standard incidence. *Chaos, Solitos and Fractals, 44*, (12) 1106 – 1110.

WHO. (2009). *Global tuberculosis control-Surveillance, planning, financing*. WHO Report, Geneva: Retrieved March 11, 2015.

Ziv, E., Daley, L., & Blower, S. M. (2001). Early therapy for latent tuberculosis infection. *American Journal of Epidemiology, 153* (4), 318 – 385.