Available online at http://scik.org
Commun. Math. Biol. Neurosci. 2014, 2014:6
ISSN: 2052-2541

DYNAMICS OF ONE-STRAIN PULMONARY TUBERCULOSIS MODEL WITH VACCINATION AND TREATMENT

GOODLUCK M. MLAY[1,4,*], LIVINGSTONE S. LUBOOBI[1,2], DMITRY KUZNETSOV[1], AND FRANCIS SHAHADA[3]

[1]School of CoCSE, Nelson Mandela African Institution of Science and Technology, P.O. Box 447, Arusha, Tanzania

[2]Department of Mathematics, Makerere University, P.O. Box 7062, Kampala, Uganda

[3]School of LiSBE, Nelson Mandela African Institution of Science and Technology, P.O. Box 447, Arusha, Tanzania

[4]Department of Mathematics, University of Dar es Salaam, P.O. Box 35062, Dar es Salaam, Tanzania

Abstract: Tuberculosis (TB) is bacterial infectious disease caused by pathogen *Mycobacterium tuberculosis*. TB inflicts many human deaths and suffering globally and Tanzania in particular due to absence, failure and delayed interventions. A continuous time deterministic model to assess the impact of vaccination and treatment on transmission dynamics of one-strain tuberculosis for the purpose of eliminating TB from community is considered. The model analysis is carried out by computing effective reproduction number R_e used to investigate the impact of vaccination and treatment interventions. Numerical sensitivity analysis of R_e is performed. We find that the parameters for proportion of babies vaccinated at birth and treatment of active TB cases have high impact on R_e. Numerical simulation results show that TB clears from community when $R_e < 1$ and the combination of both vaccination and treatment has desirable effect of curbing TB infections than when one strategy is taken at a time. We recommend that vaccination coverage of newly born babies should be accompanied by treatment of active TB individuals for significant reduction of disease transmission.

Keywords: Tuberculosis; Vaccination; Treatment; Sensitivity Analysis.

2010 AMS Subject Classification: 49Q12.

*Corresponding author

Received September 17, 2014

1. Introduction

Tuberculosis (TB) is bacterial infectious disease caused by pathogen *Mycobacterium tuberculosis* with more than one-third of the world human population as its reservoir [4, 11, 13]. A global annual estimate of 8.6 million people develop Tuberculosis, of which 1.3 million die from disease. It is reported in [23] that, the burden of disease caused by TB is high in developing world where poor nutrition, congested accommodation and emergency of HIV are manifested. The global estimates of incidence, prevalence and mortality rates per 100,000 population in 2012 were respectively 255, 303 and 26 and Tanzania incidence, prevalence and mortality rates per 100,000 population were 165, 176 and 13 respectively as per [23]. It therefore raises a quest to find desirable means to curtail TB morbidity and mortality rates.

Tuberculosis disease is mainly of two types: pulmonary and extra-pulmonary TB. Pulmonary TB is a common form of TB that affects lung while extra-pulmonary TB affects other parts of body and organs including central nervous system and bone [22]. This particular study focuses on pulmonary TB. Tuberculosis is an epidemic disease spreading in the air when the infectious person with pulmonary TB expel bacteria by coughing, singing, sneezing, speaking and so on [7]. An individual with active TB has usual symptoms which are general weakness or tiredness, fever, weight loss, loss of appetite and night sweats. Further symptoms are coughing, coughing up of sputum and/ or blood, shortness of breath and chest pains if the infection in the lung get worse [9]. TB draws back economics of the world and Tanzania in particular as it affects men than women and especially the productive working group [22]. A small proportion of about 10% of infected individuals with *Mycobacterium tuberculosis* develop TB and become infectious within two years upon infected [18]. Most become latent for the rest of their lives as long as their immune system is not compromised [7]. The recovered individuals from TB do not acquire the permanent immunity. Some of them they become latent again. Even with treatment interventions, the rates of reinfection TB are higher than those of new TB [18]. Mathematical modeling of epidemiology of Tuberculosis has recently become the powerful tool to study the dynamics of the disease and impact of various intervention strategies in order to advise public health policy makers to construct suitable intervention programs to combat TB infections. [14] formulated a mathematical model of tuberculosis with vaccination. They found that immunizing patients towards infection serves as guideline to a typical active TB control. [1] used an age structured mathematical model of TB to explore the benefit of vaccine, drug regimen and diagnostics. They find that, the combination of vaccine, drug regimen and diagnosis reduce TB incidence by 71%

and neonatal vaccination decreases TB incidence by 39% to 52% by the year 2050. [3] formulated and analyzed one-strain deterministic tuberculosis model that captures the effects of case findings and treatment intervention strategy. They find that case finding accompanied by treatment has high impact on TB dynamics than when each measure is taken separately at a time. [6] formulated one-strain and two strain tuberculosis models which involve treatment of drug sensitive and drug-resistant TB. They find that, the lack of compliance with antibiotic treatment cause relapse that leads to resistant TB to drug regimens. This article concentrates on formulating a one strain TB model with vaccination and treatment strategies in order to investigate their impact on TB transmission dynamics of population that is purely homogeneous. To add more complex interactions to the dynamics of TB, we subdivide the infectious class into mild and severe groups.

2. Model Formulation

Our population model is subdivided into six compartments and is developed from the basic SEIT (Susceptible-Exposed-Infectious-Treated) compartmental model. A compartment of Vaccinated population (V) is added to form SVEIT model. In addition compartment of infectious population (I) is subdivided into two compartments which are severely infected population (I_1) and mildly infected population (I_2). Severely infected population (I_1) progresses faster to treatment group compared to mild infected population (I_2). In this model susceptible population will be recruited at a rate λ. Some susceptible individuals will come into contact with infectious individuals and being infected at a rate of β. A proportion, ρ of babies will be vaccinated at birth while the remaining proportion $(1-\rho)$ will be left out of vaccination to join the susceptible population. Once vaccinated babies loose immunity they become susceptible at per-capita rate θ , whereby $1/\theta$ is the period after which a vaccinated baby looses immunity. The Latently infected individuals progress to active TB through endogenous reactivation. The proportion $(1-\eta)$ of Latently infected individuals progresses fast to severely infected class, I_1 while the remaining proportion, η progresses slowly to mildly infected class, I_2 at the same per-capita rate ε. Under usual circumstances mildly infected individuals take a long time to progress to treatment group, T than severely infected individuals. That is a proportion, ϕ of mildly infected individuals progresses to treatment group, T while the remaining proportion, $(1-\phi)$ progresses to severely infected class, I_1 at the same per-capita rate ω. The severely infected individuals progress to treatment group at a rate of υ. The treatment

group, T is assumed to undergo exogenous re-infection and relapse back to Latent group with infection level, γ. The infectious individuals I_1 and I_2 are assumed to die at disease induced mortality rates of δ_1 and δ_2 respectively while the rest die naturally at a rate of μ. All variables and parameters are assumed to be non-negative.

In addition the following assumptions are taken into consideration during the formulation of the model:

a. All individuals are born susceptible.
b. The members of population mix homogeneously.
c. Age, sex, social status, do not affect the probability of being infected.
d. Natural recovery is negligible and hence ignored.
e. Vaccinated population looses immunity and become Susceptible.
f. No more Vaccination can be administered to an individual infected with TB or to someone who previously was vaccinated.
g. Once recovered from Treatment an individual reverts to be Latent and may experience another episode of disease.
h. Once an individual is infected he/she will not recover if no treatment is given.

The description of model formulation in section 2, together with their assumptions lead to compartmental diagram in Figure 1.

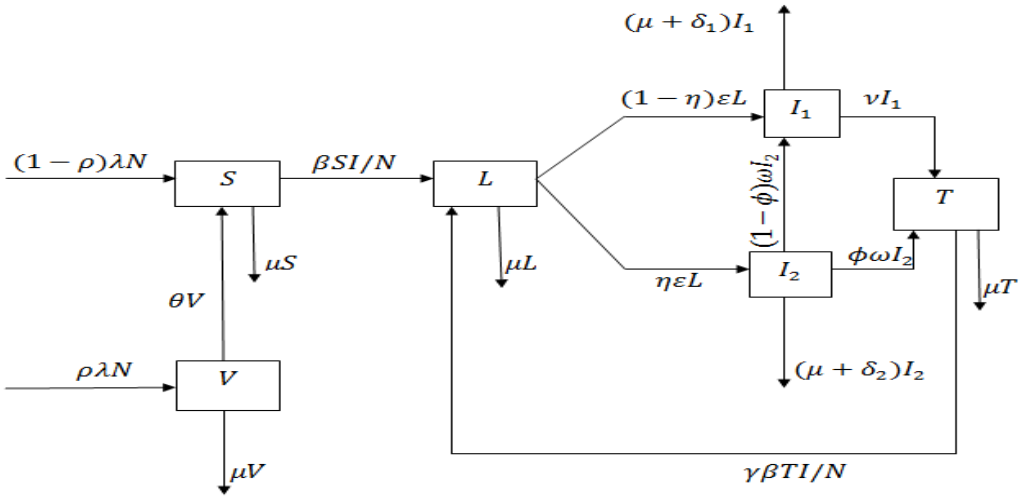

Figure 1: Schematic flow diagram showing dynamics of tuberculosis, where $I = I_1 + I_2$.

The full description of variables and parameters used to formulate the model are in Table 1 and Table 2 respectively:

Table 1: Description of variables of the model.

Variable	Description
$S(t)$	The Susceptible who are at risk of being infected at time t.
$L(t)$	The latently infected individuals at time t.
$V(t)$	Vaccinated individuals at time t.
$I_1(t)$	Individuals who are severely infected with TB at time t.
$I_2(t)$	Individuals who are mildly infected with TB at time t.
$T(t)$	Individuals Treated against TB at time t.

Table 2: Description of Parameters of the model.

Parameter	Description
λ	Per capita birth rate.
β	Per capita infection rate.
ρ	Proportional of babies who are being vaccinated at birth.
θ	The rate at which a vaccinated individual looses immunity.
ε	The rate of progression from Latent class to both severely and mildly Infected classes.
η	Proportional of Latently infected population progressing to mild infected class.
μ	Per capita natural death rate.
δ_1	Per capita additional death rate of severely infected class.
δ_2	Per capita additional death rate of mildly infected class.
ϕ	Proportional of mildly infected class who are treated.
ω	The rate at which a mildly infected individual is transferred to both severely infected and treatment classes.
υ	The rate at which a severely infected candidate is transferred to treatment class.
γ	The factor that reduces the level of reinfection.

2.1 Equations of the Model.

Basing on assumptions made and relationship that exists between variables shown in Figure 1, the system of six ordinary differential equations that describes the dynamics of tuberculosis in presence of vaccination and treatment is given by:

$$\begin{aligned}
\frac{dS}{dt} &= (1-\rho)N - \beta S\frac{(I_1+I_2)}{N} - \mu S + \theta V \\
\frac{dV}{dt} &= \rho N - (\mu+\theta)V \\
\frac{dL}{dt} &= \beta S\frac{(I_1+I_2)}{N} + \gamma\beta T\frac{(I_1+I_2)}{N} - (\mu+\varepsilon)L \\
\frac{dI_1}{dt} &= (1-\eta)\varepsilon L + (1-\phi)\omega I_2 - (\mu+\delta_1+\upsilon)I_1 \\
\frac{dI_2}{dt} &= \eta\varepsilon L - (\mu+\omega+\delta_2)I_2 \\
\frac{dT}{dt} &= \upsilon I_1 + \phi\omega I_2 - \left(\mu+\gamma\beta\frac{(I_1+I_2)}{N}\right)T \\
N &= S+V+L+I_1+I_2+T.
\end{aligned} \tag{1}$$

By adding the state equations in (1) we end up with rate of change of population,

$$\frac{dN}{dt} = (\lambda-\mu)N - \delta_1 I_1 - \delta_2 I_2 \tag{2}$$

2.2 Normalization of the model.

The model (1) can easily be analyzed after being normalized such that the total population is one. The normalization is done by scaling the population of each compartment by total population. We transform the actual proportions by setting:

$$s=\frac{S}{N}, v=\frac{V}{N}, l=\frac{L}{N}, i_1=\frac{I_1}{N}, i_2=\frac{I_2}{N}, h=\frac{T}{N} \tag{3}$$

where by $s+v+l+i_1+i_2+h=1.$

Substituting (3) into (2) we end up with:

$$\frac{dN}{dt} = \left(\lambda - \mu - \delta_1 i_1 - \delta_2 i_2\right) N \tag{4}$$

Upon differentiating the proportions in (3) with respect to time t and make simplification, leads to the following dimensionless system:

$$\begin{aligned}
\frac{ds}{dt} &= (1-\rho)\lambda + \theta v - \left(\lambda + \beta\left(i_1 + i_2\right) - \delta_1 i_1 - \delta_2 i_2\right) s, \\
\frac{dv}{dt} &= \rho\lambda - \left(\lambda + \theta - \delta_1 i_1 - \delta_2 i_2\right) v, \\
\frac{dl}{dt} &= \beta s\left(i_1 + i_2\right) + \gamma\beta h\left(i_1 + i_2\right) - \left(\lambda + \varepsilon - \delta_1 i_1 - \delta_2 i_2\right) l, \\
\frac{di_1}{dt} &= (1-\eta)\varepsilon l + (1-\phi)\omega i_2 - \left(\lambda + \delta_1 + \upsilon - \delta_1 i_1 - \delta_2 i_2\right) i_1, \\
\frac{di_2}{dt} &= \eta\varepsilon l - \left(\lambda + \omega + \delta_2 - \delta_1 i_1 - \delta_2 i_2\right) i_2, \\
\frac{dh}{dt} &= \upsilon i_1 + \phi\omega i_2 - \left(\lambda + \gamma\beta\left(i_1 + i_2\right) - \delta_1 i_1 - \delta_2 i_2\right) h.
\end{aligned} \tag{5}$$

subject to condition $s + v + l + i_1 + i_2 + h = 1$. All the feasible solutions of system (5) enter the region of biological interest defined by

$$\Omega = \left\{\left(s, v, l, i_1, i_2, h\right) \in \mathbb{R}_+^6 : s + v + l + i_1 + i_2 + h = 1\right\}$$

that is positive-invariant. We consider the dynamics of the flow generated by system (5) in Ω. In this region, the model (5) is considered to be both biologically and mathematically well posed [12].

3. Analysis of the model.

The normalized model (5) will be analyzed qualitatively so as to get some insights on dynamics of tuberculosis and to get the better understanding of the effects of treatment and vaccination on transmission of TB infections in human population. The threshold that indicates whether the disease can be eliminated from or persist to the community will be determined.

3.1 Existence of Disease Free Equilibrium (DFE)

Equilibrium points are found by setting zeros to the right hand sides of equations of model (5). That is:

$$\frac{ds}{dt} = \frac{dv}{dt} = \frac{dl}{dt} = \frac{di_1}{dt} = \frac{di_2}{dt} = \frac{dh}{dt} = 0 \tag{6}$$

Let the disease free equilibrium point of tuberculosis model (5) be, $E_0 = \left(s^0, v^0, l^0, i_1^0, i_2^0, h^0\right)$. Supplying information (6) into (5) and setting $l = i_1 = i_2 = h = 0$ in absence of disease attack we find that

$$s^0 = \frac{\theta + \lambda(1-\rho)}{\lambda + \theta}; v^0 = \frac{\rho\lambda}{\lambda + \theta} \tag{7}$$

Therefore the disease free equilibrium of the model (5) exists and is given by:

$$E_0 = \left(s^0, v^0, l^0, i_1^0, i_2^0, h^0\right) = \left(\frac{\theta + \lambda(1-\rho)}{\lambda + \theta}, \frac{\rho\lambda}{\lambda + \theta}, 0, 0, 0, 0\right). \tag{8}$$

3.2 Effective Reproduction number, R_e

The effective reproduction number, R_e is defined as the measure of average number of infections caused by a single infectious individual introduced in a community in which intervention strategies (in our case is treatment and vaccination) is administered [16, 17]. We derive R_e by using the next generation operator method [21].

If we define F to be a non-negative $m \times m$ matrix and V to be a non-singular M-matrix such that

$$F = \left[\frac{\partial \mathcal{F}_i(E_0)}{\partial x_j}\right] \text{ and } V = \left[\frac{\partial \mathcal{V}_i(E_0)}{\partial x_j}\right] \text{ with } 1 \le i, j \le m,$$

where $\mathcal{F}_i$ is the rate of appearance of new infections in compartment i and $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ in which $\mathcal{V}_i^+$ is the rate of transfer of individual into compartment i by all other means, and $\mathcal{V}_i^-$ is the rate of transfer of individual out of compartment i. The point E_0 is of disease free equilibrium as appeared in (8). It follows that the effective reproduction number, R_e of model (5) is the spectral radius (dominant eigenvalue) of FV^{-1} denoted by $R_e = \rho\left(FV^{-1}\right)$.

By arranging equations of system (5) in such a way that the infectious classes come first we end up with a system of equations represented by

$$\dot{x}_i = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), i = 1, 2, \cdots, n$$

where $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$. Each function f_i is continuous and at least twice differentiable in the region defined by Ω.

We derive $\mathcal{F}_i$ and $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ respectively to be:

$$\mathcal{F}_i = \begin{bmatrix} \mathcal{F}_1 \\ \mathcal{F}_2 \\ \mathcal{F}_3 \\ \mathcal{F}_4 \\ \mathcal{F}_5 \\ \mathcal{F}_6 \end{bmatrix} = \begin{bmatrix} \beta s(i_1 + i_2) + \gamma\beta h(i_1 + i_2) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},$$

and

$$\mathcal{V}_i = \begin{bmatrix} \mathcal{V}_1 \\ \mathcal{V}_2 \\ \mathcal{V}_3 \\ \mathcal{V}_4 \\ \mathcal{V}_5 \\ \mathcal{V}_6 \end{bmatrix} = \begin{bmatrix} (\lambda + \varepsilon - \delta_1 i_1 - \delta_2 i_2) l \\ -(1-\eta)\varepsilon l - (1-\phi)\omega i_2 + (\lambda + \delta_1 + \upsilon - \delta_1 i_1 - \delta_2 i_2) i_1 \\ -\eta\varepsilon l + (\lambda + \omega + \delta_2 - \delta_1 i_1 - \delta_2 i_2) i_2 \\ -\upsilon i_1 - \phi\omega i_2 + (\lambda + \gamma\beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2) h \\ -(1-\rho)\lambda - \theta v + (\lambda + \beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2) s \\ -\rho\lambda + (\lambda + \theta - \delta_1 i_1 - \delta_2 i_2) v \end{bmatrix}.$$

By considering infected classes only and making use of linearization technique, the Jacobian matrices F and V at disease free equilibrium point E_0 are respectively given by:

$$F = \begin{bmatrix} 0 & \dfrac{\beta(\theta + \lambda(1-\rho))}{\lambda + \theta} & \dfrac{\beta(\theta + \lambda(1-\rho))}{\lambda + \theta} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} \lambda + \varepsilon & 0 & 0 \\ -(1-\eta)\varepsilon & \lambda + \delta_1 + \upsilon & -(1-\phi)\omega \\ -\eta\varepsilon & 0 & \lambda + \omega + \delta_2 \end{bmatrix}.$$

Representing the original parameters by a, b, c, d, e, f and g such that:

$$a = \lambda + \varepsilon, b = (1-\eta)\varepsilon, c = \lambda + \delta_1 + \upsilon, d = (1-\phi)\omega, e = \eta\varepsilon, \ f = \lambda + \omega + \delta_2 \text{ and } g = \frac{\beta(\theta + \lambda(1-\rho))}{\lambda + \theta},$$

then the inverse of V and matrix product FV^{-1} are computed and respectively found to be:

$$V^{-1}=\begin{bmatrix} \frac{1}{a} & 0 & 0 \\ \frac{bf+ed}{acf} & \frac{1}{c} & \frac{d}{cf} \\ \frac{e}{af} & 0 & \frac{1}{f} \end{bmatrix} \text{ and } FV^{-1}=\begin{bmatrix} g\left(\frac{(bf+ed)}{afc}+\frac{e}{af}\right) & \frac{g}{c} & \frac{g(d+c)}{fc} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

The matrix product FV^{-1} is upper triangular matrix whose eigenvalues are located at its main diagonal as $0,\ 0,$ and $g\left(\frac{(bf+ed)}{afc}+\frac{e}{af}\right)$. Thus the effective reproduction number, $\boldsymbol{R}_e$ is:

$$R_e = g\left(\frac{(bf+ed)}{afc}+\frac{e}{af}\right).$$

Expressing a,b,c,d,e,f and g in terms of original parameters it leads to effective reproduction number:

$$R_e=\frac{\beta(\theta+\lambda(1-\rho))}{(\lambda+\theta)}\left[\frac{(1-\eta)(\lambda+\omega+\delta_2)\varepsilon+(1-\phi)\omega\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\upsilon)}+\frac{\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)}\right] \tag{9}$$

3.3 Local stability of Disease free equilibrium (DFE)

Using Theorem 2 from [21], the following result is established.

Theorem 3.1. *The disease free equilibrium of model (5), given the effective reproduction number, R_e is locally assymptotically stable if $R_e < 1$, and unstable if $R_e > 1$.*

Proof. It is enough to show that Disease Free equilibrium point of our system (5) is stable if and only if trace and determinant of Jacobian matrix at E_0, denoted by $J(E_0)$ are negative and positive respectively. Our Jacobian matrix evaluated at disease free equilibrium point is given by:

$$J(E_0)=\begin{bmatrix} -\lambda & \theta & 0 & -(\beta+\delta_1)\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) & -(\beta+\delta_2)\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) & 0 \\ 0 & -(\lambda+\theta) & 0 & \frac{\rho\lambda}{\lambda+\theta}\delta_1 & \frac{\rho\lambda}{\lambda+\theta}\delta_2 & 0 \\ 0 & 0 & -(\lambda+\varepsilon) & \beta\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) & \beta\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) & 0 \\ 0 & 0 & (1-\eta)\varepsilon & -(\lambda+\delta_1+\upsilon) & (1-\phi)\omega & 0 \\ 0 & 0 & \eta\varepsilon & 0 & -(\lambda+\omega+\delta_2) & 0 \\ 0 & 0 & 0 & \upsilon & \phi\omega & -\lambda \end{bmatrix}$$

Trace and determinant of matrix $J(E_0)$ denoted by $\mathrm{Tr}(J(E_0))$ and $\det(J(E_0))$ are respectively given by:

$$\mathrm{Tr}(J(E_0))=-(6\lambda+\theta+\varepsilon+\upsilon+\omega+\delta_1+\delta_2)<0$$

and

$$\begin{aligned}\det(J(E_0)) &= -\lambda^2(\lambda+\theta)\begin{vmatrix} -(\lambda+\varepsilon) & \beta\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) & \beta\left(\frac{\theta+\lambda(1-\rho)}{\lambda+\theta}\right) \\ (1-\eta)\varepsilon & -(\lambda+\delta_1+\upsilon) & (1-\phi)\omega \\ \eta\varepsilon & 0 & -(\lambda+\omega+\delta_2) \end{vmatrix} \\ &= -\lambda^2(\lambda+\theta)\begin{bmatrix} \frac{\beta(\theta+\lambda(1-\rho))}{(\lambda+\theta)}\{(1-\eta)(\lambda+\omega+\delta_2)\varepsilon+((1-\phi)\omega+\lambda+\delta_1+\upsilon)\eta\varepsilon\} \\ -(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\upsilon) \end{bmatrix} \\ &= -A\left[\frac{\beta(\theta+\lambda(1-\rho))}{(\lambda+\theta)}\left\{\frac{(1-\eta)(\lambda+\omega+\delta_2)\varepsilon+(1-\phi)\omega\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\upsilon)}+\frac{\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)}\right\}-1\right] \\ &= -A(R_e-1).\end{aligned}$$

where $A=\lambda^2(\lambda+\theta)(\lambda+\varepsilon)(\lambda+\delta_1+\upsilon)(\lambda+\omega+\delta_2)>0$.

Thus $\det(J(E_0))>0$ if and only if $R_e<1$. Since the trace of matrix $J(E_0)$ is negative and its determinant is strictly greater than zero when $R_e<1$, then disease free equilibrium point E_0 is locally asymptotically stable and completes our proof. □

The results of Theorem 3.1 indicate that TB clears from community if $R_e < 1$. That is when the initial population of model (5) is in basin of attraction of disease free equilibrium, E_0.

3.4 Analysis of Effective Reproduction number .

If we denote the effective reproduction number R_e of model (5) by R_{VT} (reproduction number when vaccination and treatment are administered) and combine denominators of equation (9) we end up with:

$$R_e = R_{VT} = \frac{\beta\left(\theta + \lambda(1-\rho)\right)\left[(1-\eta)(\lambda+\omega+\delta_2)\varepsilon + \left((1-\phi)\omega + \lambda + \delta_1 + \upsilon\right)\eta\varepsilon\right]}{(\lambda+\theta)(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\upsilon)} \tag{10}$$

We define the threshold R_{VT} as a number of secondary infections when one infectious individual is introduced in a population which is totally susceptible where V is the number of vaccinated newly born babies and T is treatment administered to active TB individuals.
In absence of vaccination and treatment we have

$$\lim_{(\rho,\theta,\phi,\upsilon)\to(0,0,0,0)} R_{VT} = R_0 = \beta\left[\frac{(1-\eta)(\lambda+\omega+\delta_2)\varepsilon + \omega\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1)} + \frac{\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)}\right] \tag{11}$$

We define

$$R_{0(severe)} = \beta\left[\frac{(1-\eta)(\lambda+\omega+\delta_2)\varepsilon + \omega\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1)}\right],$$
$$R_{0(\text{mild})} = \frac{\beta\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)} \tag{12}$$

where $R_{0(\text{severe})}$ and $R_{0(\text{mild})}$ are basic reproduction numbers for severely and mildly infected classes respectively.

The relation (11) simplifies to

$$\lim_{(\rho,\theta,\phi,\upsilon)\to(0,0,0,0)} R_{VT} = R_0 = \frac{\beta\left[(1-\eta)(\lambda+\omega+\delta_2)\varepsilon + (\omega+\lambda+\delta_1)\eta\varepsilon\right]}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1)} \tag{13}$$

which is the basic reproduction number (threshold quantity in absence of intervention strategies).
If vaccination alone is administered then, equation (10) is written as

$$\lim_{(\phi,\upsilon)\to(0,0)} R_{VT} = R_V = \frac{\beta\left(\theta+\lambda\left(1-\rho\right)\right)\left[\left(1-\eta\right)\left(\lambda+\omega+\delta_2\right)\varepsilon+\left(\omega+\lambda+\delta_1\right)\eta\varepsilon\right]}{\left(\lambda+\theta\right)\left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)\left(\lambda+\delta_1\right)} = \frac{\theta+\lambda\left(1-\rho\right)}{\left(\lambda+\theta\right)}R_0 = K_1R_0 \quad (14)$$

Since $K_1 = \frac{\theta+\lambda\left(1-\rho\right)}{\left(\lambda+\theta\right)} < 1$ then vaccinating babies at birth with TB vaccine helps reducing initial disease transmission. Differentiating R_V with respect to vaccination rate ρ, we have

$$\frac{\partial R_V}{\partial\rho} = -\frac{\lambda\beta\left[\left(1-\eta\right)\left(\lambda+\omega+\delta_2\right)\varepsilon+\left(\omega+\lambda+\delta_1\right)\eta\varepsilon\right]}{\left(\lambda+\theta\right)\left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)\left(\lambda+\delta_1\right)} = -\frac{\lambda}{\lambda+\theta}R_0 < 0 \quad (15)$$

The expression in (15) reveals that R_V is a decreasing function of ρ and inequality (15) confirms that increasing the proportion of vaccinated babies at birth has positive impacts on TB control and increases the efforts to cut out epidemic.

In case only treatment is administered, it follows from equation (10) that,

$$\lim_{(\rho,\theta)\to(0,0)} R_{VT} = R_T = \frac{\beta\left[\left(1-\eta\right)\left(\lambda+\omega+\delta_2\right)\varepsilon+\left(\left(1-\phi\right)\omega+\lambda+\delta_1+\upsilon\right)\eta\varepsilon\right]}{\left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)\left(\lambda+\delta_1+\upsilon\right)} \quad (16)$$

Differentiating R_T with respect to proportional of treated mildly infected individuals ϕ we find that

$$\frac{\partial R_T}{\partial\phi} = -\frac{\beta\omega\eta\varepsilon}{\left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)\left(\lambda+\delta_1+\upsilon\right)} < 0 \quad (17)$$

Thus R_T is a decreasing function of ϕ and it shows that increasing the proportion of treated mildly infected individuals has a positive effect on TB control and increases the efforts to curtail TB spread.

Following an approach employed by [2, 3], the effective reproduction number R_{VT} can also be established by using the following relation:

$R_{VT} = K_2R_0$, where by expression for K_2 is given by:

$$K_2 = \frac{\left(\theta+\lambda\left(1-\rho\right)\right)\left[\left(1-\eta\right)\left(\lambda+\omega+\delta_2\right)\varepsilon+\left(\left(1-\phi\right)\omega+\lambda+\delta_1+\upsilon\right)\eta\varepsilon\right]\left(\lambda+\delta_1\right)}{\left(\lambda+\theta\right)\left(\left[\left(1-\eta\right)\left(\lambda+\omega+\delta_2\right)\varepsilon+\left(\omega+\lambda+\delta_1\right)\eta\varepsilon\right]\right)\left(\lambda+\delta_1+\upsilon\right)} < 1.$$

It follows that,

$$K_2 - K_1 = \frac{\left(\theta+\lambda(1-\rho)\right)\left[(1-\eta)(\lambda+\omega+\delta_2)\varepsilon+\left((1-\phi)\omega+\lambda+\delta_1+\upsilon\right)\eta\varepsilon\right](\lambda+\delta_1)}{(\lambda+\theta)\left(\left[(1-\eta)(\lambda+\omega+\delta_2)\varepsilon+(\omega+\lambda+\delta_1)\eta\varepsilon\right]\right)(\lambda+\delta_1+\upsilon)} - \frac{\theta+\lambda(1-\rho)}{\lambda+\theta}$$

$$= -\frac{\left(\theta+\lambda(1-\rho)\right)\left[\phi\omega\eta\varepsilon(\lambda+\delta_1)+\left((1-\eta)(\lambda+\omega+\delta_2)+\omega\eta\right)\varepsilon\upsilon\right]}{(\lambda+\theta)\left(\left[(1-\eta)(\lambda+\omega+\delta_2)\varepsilon+(\omega+\lambda+\delta_1)\eta\varepsilon\right]\right)(\lambda+\delta_1+\upsilon)} < 0$$

Thus $K_2 - K_1 < 0$. It follows that $R_{VT} - R_V = K_2 R_0 - K_1 R_0 = (K_2 - K_1)R_0 < 0$ so that $R_{VT} < R_V$. This implies that the combination of both treatment and vaccination has great impact in reducing disease transmission than to take the two measures one at a time.

Investigating the effect of vaccination in presence of treatment is considered by differentiating R_{VT} with respect to proportional of vaccinated babies at birth ρ as follows:

$$\frac{\partial R_{VT}}{\partial \rho} = -\frac{\beta\lambda\left[(1-\eta)(\lambda+\omega+\delta_2)\varepsilon+\left((1-\phi)\omega+\lambda+\delta_1+\upsilon\right)\eta\varepsilon\right]}{(\lambda+\theta)(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\upsilon)} < 0 \tag{18}$$

This implies that increasing vaccination coverage of babies at birth has significant impact to the control of TB if accompanied by treatment of active TB.

We have already showed algebraically that $R_{VT} < R_V$. The general relationship that associates the reproduction numbers R_{VT}, R_T, R_V, $R_{0(\text{severe})}$, $R_{0(\text{mild})}$ and R_0 algebraically is involving. Graphical Illustrations involving these relationships are presented in [15] , by using linear relationship that exists between the growth rate of reproduction number with respect to transmission rate β when other parameters remain fixed.

3.5 Numerical Sensitivity Analysis of Effective Reproduction number, R_e.

In this section numerical sensitivity analysis of effective Reproduction number is performed by using parameters in Table 3 whose numerical values are from existing literature as well as estimated to suit this particular intended study to determine the relative importance of each parameter involved in R_e to the transmission of tuberculosis.

Table 3: Parameter values for model (5).

Symbol	Value/range (yr^{-1})	Source
λ	0.05	Estimated
β	2.58	Estimated
ρ	0.4	Estimated
θ	0.1	Estimated
ε	0.03	[10]
η	0.7 (0.7-0.95)	[17]
μ	0.01923 (0.01-0.04)	[5]
δ_1	0.3 (0.07-0.365)	[20]
δ_2	0.2 (0.07-0.365)	[20]
ϕ	0.6	Estimated
ω	0.2	Estimated
υ	0.3	Estimated
γ	0.2	Estimated

Sensitivity analysis is used to determine which parameters have high impact on R_e so as to be targeted by intervention strategies [8, 19]. The approach of [8] is used to calculate the sensitivity indices of R_e to the parameters involved in it so as to determine how best to reduce human mortality and morbidity due to Tuberculosis. The normalized forward sensitivity index is the ratio of relative change of variable to the relative change in parameter. If the variable is a differentiable function of the parameter then the sensitivity index may be defined by using partial derivatives as follows.

Definition 1. *The normalized forward sensitivity index of a variable p that depends on a parameter q is defined as*

$$Y_q^p = \frac{\partial p}{\partial q} \times \frac{q}{p} \tag{19}$$

Since we have explicit formula for effective reproduction number R_e in (12), it follows that the normalized forward sensitivity indices of R_e with respect to parameters q_i involved in R_e is given by:

$$Y_{q_i}^{R_e} = \frac{\partial R_e}{\partial q_i} \times \frac{q_i}{R_e} \tag{20}$$

For instance the sensitivity indices of $\boldsymbol{R}_e$ with respect to β and ρ are given respectively by: $Y_{\beta}^{R_e} = \frac{\partial R_e}{\partial \beta} \times \frac{\beta}{R_e} = +1$ and $Y_{\rho}^{R_e} = \frac{\partial R_e}{\partial \rho} \times \frac{\rho}{R_e} = -0.1538$. By using the same approach the indices $Y_{\theta}^{R_e}, Y_{\lambda}^{R_e}, Y_{\eta}^{R_e}, Y_{\omega}^{R_e}, Y_{\delta_1}^{R_e}, Y_{\varepsilon}^{R_e}, Y_{\phi}^{R_e}, Y_{\delta_2}^{R_e}$ and $Y_{\upsilon}^{R_e}$ are obtained and tabulated accordingly and ordered from highest sensitive to least sensitive parameter as in Table 4.

Table 4: Sensitivity indices of evaluated at baseline parameter values given in Table 3.

Parameter	Sensitivity Index
β	+1.0000
λ	-0.8382
ε	+0.6250
δ_2	-0.3516
η	+0.3034
ω	-0.2649
ρ	-0.1538
υ	-0.1365
δ_1	-0.1365
ϕ	-0.1300
θ	+0.1026

3.6 Interpretations of Sensitivity Indices.

From Table 4 we find that the parameters β, ε, η and θ have positive indices. This means that, increasing (decreasing) one of these parameters while keeping others constant increases (decreases) the value of effective reproduction number, $\boldsymbol{R}_e$ implying the increase (decrease) of endemicity of tuberculosis disease respectively. For instance, $Y_{\eta}^{R_e} = +0.3034$, implies that increasing proportional of latently infected population, η that is progressing to mild infected class by 10%, increases the value of $\boldsymbol{R}_e$ by 3.034% and hence increases the endemicity of the disease. In contrast reducing the proportional η by 10% decreases the value of $\boldsymbol{R}_e$ by 3.034%

and hence lowering the endemicity of the disease. On the other hand the parameters $\lambda, \delta_1, \omega, \rho, \nu, \delta_2$ and ϕ have negative indices, implying that increasing (decreasing) one of these parameters while keeping the rest constant decreases (increases) the value of effective reproduction number, R_e and hence decreases (increases) the endemicity of TB. For example, $Y_{\rho}^{R_e} = -0.1538$, implies that, increasing the proportional of vaccinated babies ρ by 50% decreases the value of R_e approximately by 7.69% and hence reducing the endemicity of TB. However, decreasing the proportional of vaccinated babies, ρ, by 50% increases the value of R_e by 7.69% and hence increases the endemicity of the disease. In particular, following the magnitudes of sensitive indices, R_e is most positively sensitive to parameters β, ε and η. In addition, R_e is most negatively sensitive to parameters $\lambda, \delta_2, \omega$ and ρ. However R_e is moderately negatively sensitive to parameters ν, δ_1 and ϕ followed by the least positive sensitive parameter, θ. In our case the most sensitive and moderate parameters should be careful estimated in order to determine the robustness of model predictions to parameter values and to determine parameters which have high impact on R_e and which should be targeted by intervention strategies [8].

4. Numerical Simulations

In this section numerical simulation of normalized model (5) is carried out in order to illustrate the qualitative results by using available parameter values from existing literature as well as estimated ones. Unless otherwise stated parameter values appeared in Table 3 will be used during the simulation process.

4.1 Impact of vaccination and treatment rates on effective reproduction number R_e.

In this section we analyze the effective reproduction number R_e in terms of vaccination rate ρ of newly born babies and treatment rate υ of severely infected individuals. The aim here is to determine by using the threshold R_e whether or not the vaccination and treatment coverage control or eliminate TB from the community.

Figure 2 shows the effect of vaccination rate ρ and treatment rate υ of severely infected individuals on effective reproduction number R_e when $\beta = 1.6$. All other parameters are given in Table 3. As expected when the vaccination rate ρ is fixed then the effective reproduction

number R_e decreases as treatment rate of severely infected individuals υ increases and vice versa. The combination of vaccination coverage and treatment of infectious individuals can reduce the threshold R_e to less than unity. Therefore the best intervention strategy can be vaccination of newly born babies and treatment of severely infected individuals or combination of vaccination and treatment.

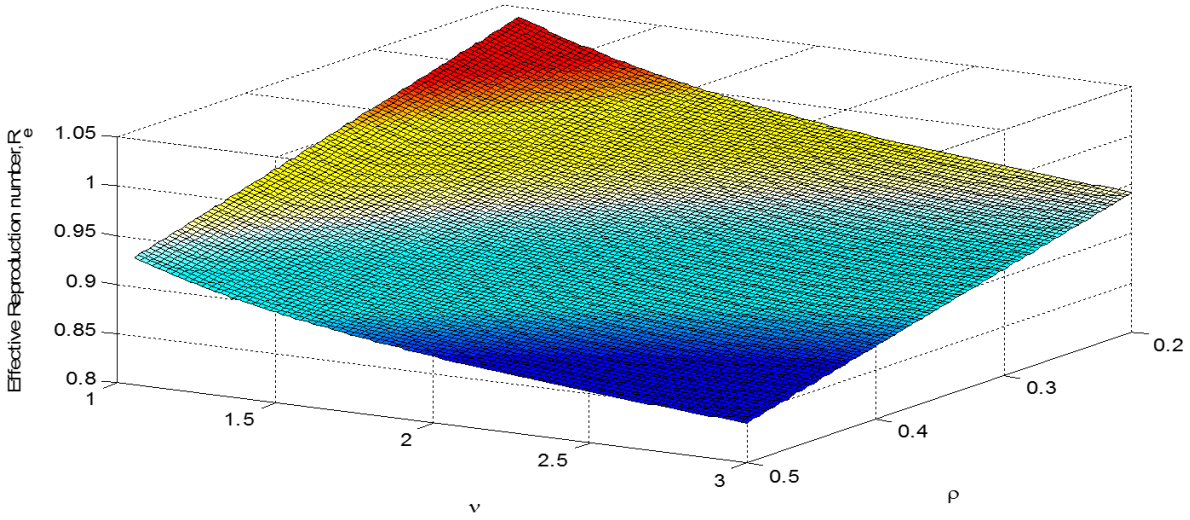

Figure 2: Graph of effective reproduction ratio R_e in terms of ρ and υ when $\beta = 1.6$. All other parameters are as in Table 3.

4.2 Numerical Simulation of model (5) when $R_e < 1$.

The system (5) is solved by using forward Runge-Kutta fourth order scheme and MATLAB software with in-built ordinary differential equation (ode 45) solver used to simulate it to produce time series plot as shown in Figure 3. In Figure 3 dynamic behaviors of susceptible, vaccinated, latently infected, severely infected, mildly infected and treated classes when effective reproduction number $R_e = 0.0169$ is shown. The plot is produced by using estimated parametric values $\beta = 0.88; \theta = 0.067; \varepsilon = 0.00396; \eta = 0.4; \lambda = 0.16; \delta_1 = 0.36; \omega = 0.6; \rho = 0.3; \nu = 0.6; \delta_2 = 0.3$ and $\phi = 0.5$. With initial values $s(0) = 0.55, v(0) = 0.15, l(0) = 0.1, i_1(0) = 0.1, i_2(0) = 0.05$ and $h(0) = 0.05$, the model (5) attains the asymptotic stability of disease free equilibrium point, $E_0 = (s^*, v^*, l^*, i_1^*, i_2^*, h^*) = (0.7885, 0.2115, 0, 0, 0, 0)$. In absence of attack, susceptible and vaccinated proportions increase with time to their carrying capacities. At disease free equilibrium

point both susceptible and vaccinated they add up to the maximum carrying capacity of population proportions in the community, i.e. $s^* + v^* = 0.7885 + 0.2115 = 1$. On the other hand, latently infected and treated proportions in Figure 3 respectively increase with time and decrease to zero with increasing time. In additional infectious groups (severely and mildly infected proportions) decrease and attain disease free equilibrium as time increases. That is in presence of intervention (control strategies) the disease seem to clear from community since the effective reproduction number is $R_e = 0.0169 < 1$. This result supports the theorem of local stability of disease free equilibrium.

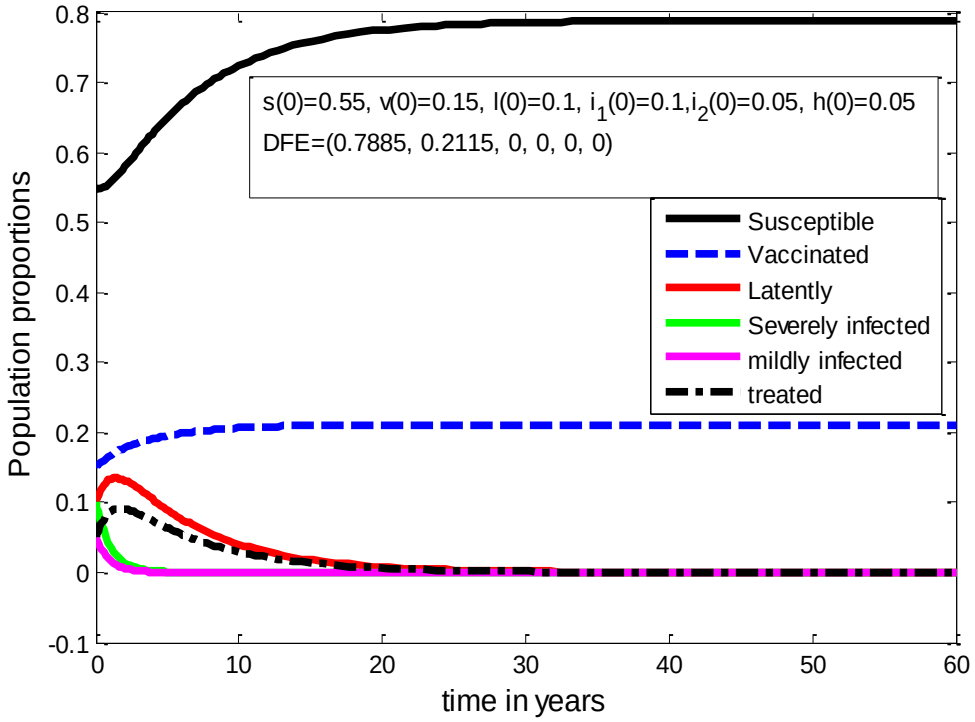

Figure 3: Shows the dynamics of susceptible, vaccinated, latently infected, severely infected, mildly infected and treated population proportions in presence of interventions with increasing time.

4.3 Phase portraits illustrating dynamical behavior of population proportions at DFE.

In this section phase portraits to illustrate the dynamics of the model (5) at disease free equilibrium point for susceptible class versus latently infected, severely infected, mildly infected, and treated classes are plotted by using estimated parametric values $\beta = 0.88; \theta = 0.067; \varepsilon = 0.00396; \eta = 0.4; \lambda = 0.16; \delta_1 = 0.36; \omega = 0.6; \rho = 0.3; \nu = 0.6; \delta_2 = 0.3$ and

$\phi = 0.5$. With different varying initial conditions, each curve of both latently infected and treated population proportions shown in Figure 4 (a) and Figure 4 (d) respectively increases for short period of time and finally sharply decrease and stabilize at disease free equilibrium point as time increases. Figure 4 (b) and Figure 4 (c) show that the proportions of severely infected and mildly infected decrease as susceptible proportion increases and stabilize at disease free equilibrium point.

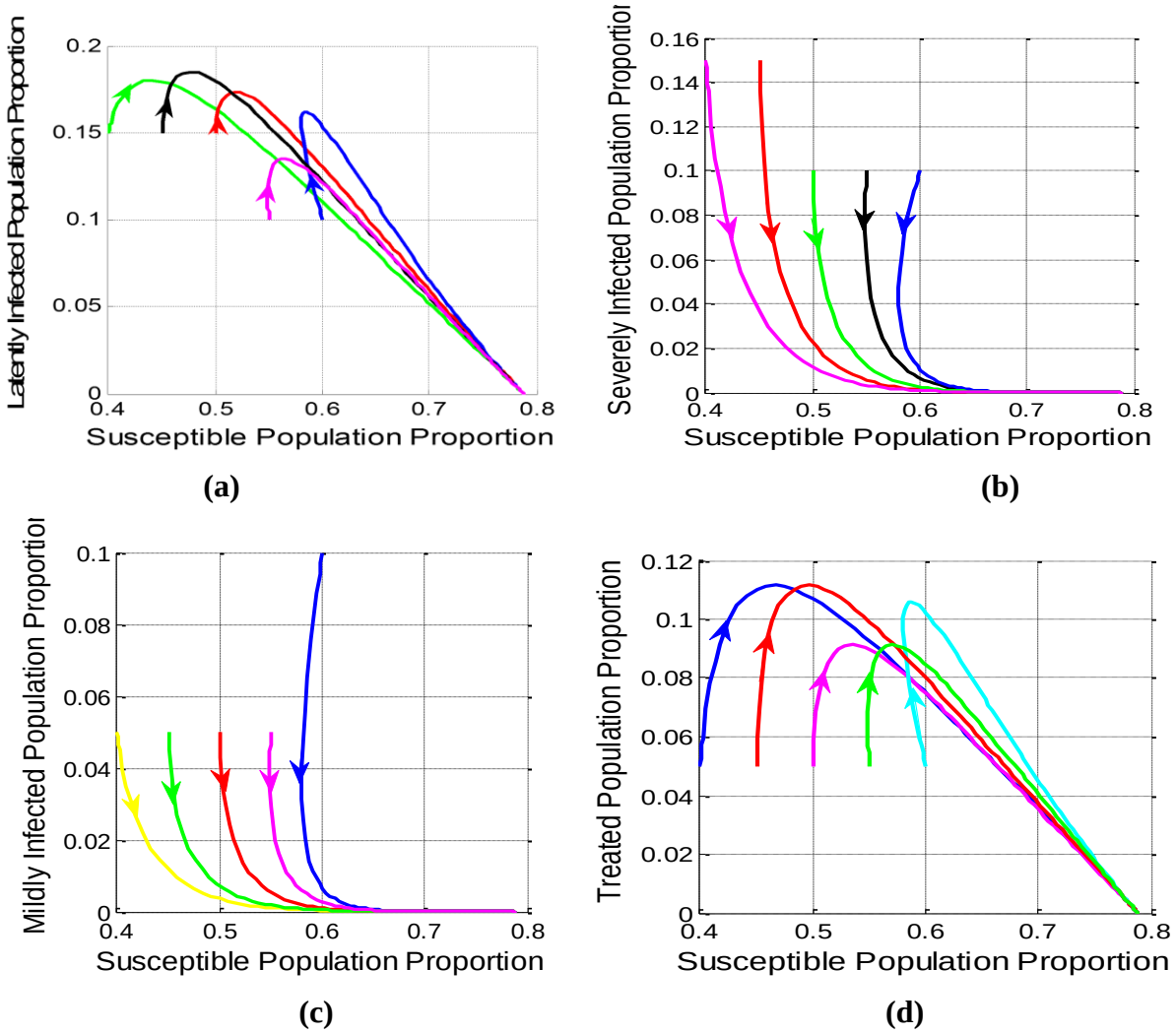

Figure 4: Shows Phase plane portraits for dynamics of susceptible population proportion and (a) latently infected (b) severely infected (c) mildly infected (d) treated population proportions showing disease free equilibrium point with varying initial values as time increases.

5. Conclusion

In this paper, a continuous time deterministic model with vaccination and treatment as intervention strategies has been formulated to assess their impacts on transmission dynamics of Tuberculosis Infections. The disease free equilibrium has been proved to be stable when effective reproduction number, $R_e < 1$ and unstable otherwise. The numerical simulation results show that in presence of interventions, both severely and mildly infected population proportions decrease to zero and stabilize at disease free equilibrium as time increases. In addition, the numerical results show that, the combination of both vaccination and treatment reduce threshold R_e to less than unity and have desirable effect of clearing TB from community than when each strategy is taken at a time.

Conflict of Interests

Authors declare that no conflicts of interests.

Acknowledgments

Mlay would like to thank University of Dar es Salaam for granting him a study leave and Nelson Mandela African Institution of Science and Technology for financial support.

REFERENCES

[1] L. J. Abu-Raddad, L. Sabatelli, J. T. Achterberg, J. D. Sugimoto,I. M. Longin, Jr.,C. Dye, M. E. Halloran. Epidemiology benefits of more-effective tuberculosis vaccines, drugs, and diagnostics, PNAS. 106(2009), 13980-13985.

[2] C. P. Bhunu, Z. Mukandavire, W. Garira, M. Zimba. Tuberculosis transmission model with chemoprophylaxis and treatment, Bull. Math. Biol. 70(2008), 1163-1191.

[3] C. P. Bhunu, S. Mushayabasa, G. Magombedze, L. I. Roeger. Tuberculosis transmission model with case detection and treatment, Journal of Applied Math. & Informatics 29(2011), 529-546.

[4] B. R. Bloom, Tuberculosis: Pathogenesis, Protection and Control, Washington, D.C.: ASM Press (1994).

[5] S. M. Blower, A. R. Mclean,T. C. Porco,P. M. Amall, M. A. Sanchez, R. Moss, The intrinsic transmission dynamics of tuberculosis epidemics, *Nature Medicine* 1(1995), 815-821.

[6] C. Castillo-Chavez, Z. Feng, To treat or not to treat: the case of tuberculosis, Journal of Mathematical Biology 35 (1997), 629-656.

[7] C. Castillo-Chavez, B. Song, Dynamical models of tuberculosis and their applications, Mathematical Biosciences and Engineering 1(2004), 361-404.

[8] N. Chitnis, N, J. M. Hyman, J. M. Cushing, Determining Important Parameters in the Spread of Malaria Through the Sensitivity Analysis of a Mathematical Model, Bulletin of Mathematical Biology 70(2008), 1272-1296.

[9] T. Cohen, M. Murray, On modeling epidemics of multidrug-resistant M. tuberculosis of heterogeneous fitness, Nature Medicine 10(2004), 1117-1121.

[10] T. Cohen, C. Colijn, B. Finklea, M. Megan, Exogenous Re-infection and the Dynamics of Tuberculosis Epidemics: Local Effects in a Network Model of Transmission, J. R. Soc. Interface 4(2007), 523-531.

[11] Z. Feng, C. Castillo-Chavez, A. F. Capurro, A model for tuberculosis with exogenous reinfection, Theor. Popul. Biol. 57(2000), 235–247.

[12] H. W. Hethcote, The mathematics of infectious diseases, SIAM Review 42(2000), 599-653.

[13] B. Miller, Preventive therapy for tuberculosis, Med. Clin. North Am. 77(1993), 1263-1275.

[14] B. K. Mishra, J. Srivastava, Mathematical model on pulmonary and multidrug-resistant tuberculosis patients with vaccination, Journal of the Egyptian Mathematical Society 22 (2014), 311-316.

[15] N. Nyerere, L. S. Luboobi, Y. Nkansah-Gyekye, Modeling the Effect of Screening and Treatment on Transmission of Tuberculosis Infections, Mathematical Theory and Modelling 4(2014), 51-62.

[16] D. Okuonghae, A. Korobeinikov, Dynamics of Tuberculosis: The Effect of Direct Observation Therapy Strategy (DOTS) in Nigeria, Mathematical Modeling of Natural Phenomena 2 (2007) , 101-113.

[17] D. Okuonghae, V. Aihie, Case detection and Direct Observation Therapy Strategy (DOTS) in Nigeria: its effect on TB dynamics, Journal of Biological Systems 16(2008), 1–31.

[18] P. Rodriques, Modeling tuberculosis: a compromise between biological realism and mathematical tractability, Unpublished PhD thesis. University of Lisbon (2009).

[19] H. S. Rodrigues, M. T. T. Monteiro,D. F. M. Torres, Sensitivity Analysis in Dengue Epidemiological Model, Conference Papers in Mathematics, 2013(2013), Article ID 721406, 7 pages.

[20] A. Ssematimba,J. Y. T. Mugisha, L. S. Luboobi, 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(2005), 217-224.

[21] P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci. 180(2002), 29–48.

[22] World Health Organization (WHO) Global Tuberculosis Report (2012), 2010/2011 Tuberculosis Global Facts.

[23] World Health Organization (WHO) Global Tuberculosis Report (2013), 2011/2012 Tuberculosis Global Facts.