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THE ROLE OF RE-INFECTION IN MODELING THE DYNAMICS OF ONE-STRAIN TUBERCULOSIS INVOLVING VACCINATION AND TREATMENT

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Abstract. In this article a continuous time deterministic model with vaccination and treatment strategies is formulated to assess the effect of reinfection on the transmission dynamics of Tuberculosis (TB). The involvement of reinfection in our model causes relapse and leads to the possibility of backward bifurcation at critical value of effective reproduction number $R_e = 1$ and hence the existence of multiple equilibria when effective reproduction number $R_e < 1$. This indicates that even by reducing effective reproduction number R_e below one is no longer a sufficient condition to eradicate the disease from community. An additional reduction of effective reproduction number R_e below the saddle-node bifurcation value is required to eradicate disease from community provided that the disease free equilibrium is globally asymptotically stable. Numerical simulation results are presented to validate analytical results. We suggest that reinfection is an important feature of TB and has to be considered when modeling the complex dynamics of TB.

1. INTRODUCTION

Tuberculosis (TB) is a chronic bacterial infectious disease caused by pathogen *Mycobacterium tuberculosis* with more than one-third of the world human population as its reservoir [1, 9, 16]. A global annual estimate of 8.6 million people develop Tuberculosis, of which 1.3 million die from disease. It is reported in [24] 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 [24]. 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 [23]. 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 [6]. An individual with active TB has usual symptoms which are general weakness or tiredness, fever, weight loss, loss of appetite and night

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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 [7]. TB draws back economics of the world and Tanzania in particular as it affects men than women and especially the productive working group [23]. In absence of HIV a small proportion of about 10% of infected individuals with *Mycobacterium tuberculosis* develop TB and becomes infectious within two years upon infected [20]. Most become latent for the rest of their lives as long as their immune system is not compromised [6]. 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 [20]. Mathematical modeling of epidemiology of Tuberculosis has recently become the powerful tool to study the complex dynamics of the disease and explore the role of various TB features such as reinfection and reactivation. [9] formulated mathematical model of TB with exogenous re-infection. The results of their work suggest that exogenous reinfection has drastic effect on qualitative dynamics of TB and it allows the possibility of subcritical bifurcation at critical value of basic reproduction number $R_0 = 1$. Buonomo and Lacitignola [3] applied bifurcation method introduced in Castillo-Chavez and Song [6] based on the use of center manifold theory [4] to derive conditions for existence of either forward or backward bifurcation for vaccination model introduced in [10]. They clearly explain the role of vaccination, treatment and transmission parameters for the occurrence of forward or backward bifurcation. Okuonghae and Aihie [19] examined the effect of Direct Observation Therapy Strategy (DOTS) on dynamics of TB against the fraction of active cases detected. They formulated mathematical model that involves the fraction of detected cases undergoing treatment under DOTS and other fraction not detected. The qualitative analysis of this model shows that in presence of exogenous re-infection, reproduction number must be outside the bifurcation range for disease free equilibrium to be asymptotically stable. The parameter for case detection has shown to be important in reducing backward bifurcation range as well as reducing the reproduction number. They further argued that if the critical level for case detection parameter is not reached then TB persist in population and become endemic. [12] propose mathematical model of TB that includes exogenous reinfection in order to understand the recent increase of TB incidences in Korea. In their study, parameter for case finding effort was found to be significant impacting component on curbing active TB cases. They recommended that for dramatic reduction of TB incidences, the treatment of active TB cases should be accompanied by case finding (taking medication before the actual active TB has clinically diagnosed) effort than to take each measure alone. This paper concentrates on investigating the role of re-infection on the one strain TB model with vaccination and treatment and its impact on TB transmission dynamics. Bifurcation and stability analysis of equilibrium points are properly investigated.

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:

i. All individuals are born susceptible.
ii. The members of population mix homogeneously.
iii. Age, sex, social status, do not affect the probability of being infected.
iv. Natural recovery is negligible and hence ignored.
v. Vaccinated population looses immunity and become Susceptible.
vi. No more Vaccination can be administered to an individual infected with TB or to someone who previously was vaccinated.

vii. Once recovered from Treatment an individual reverts to be Latent and may experience another episode of disease.

viii. Once an individual is infected he/she will not recover if no treatment is given.

The above description of model formulation together with the assumptions leads to compartmental diagram in Figure 1.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.

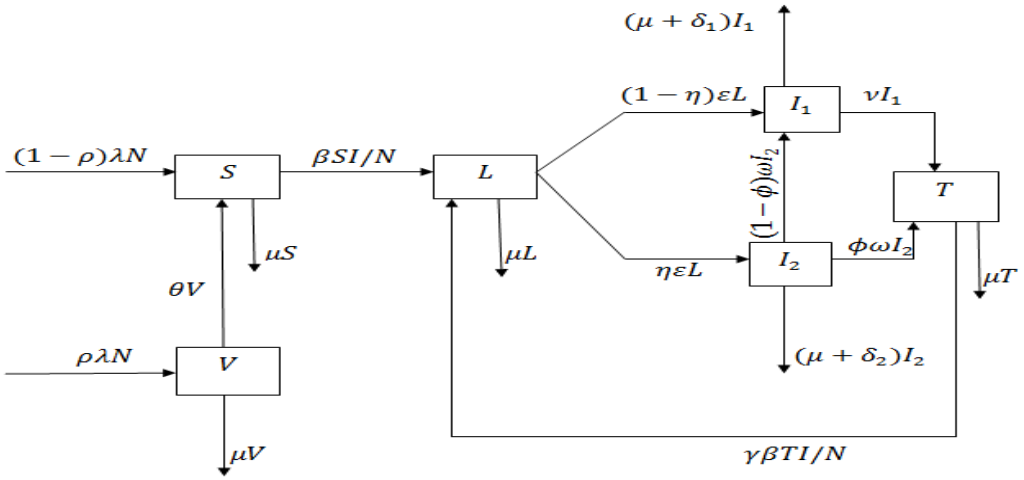

Figure 1: Schematic flow diagram showing dynamics of tuberculosis, where $I = I_1 + I_2$.

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 and parameters 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:

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

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

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

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

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

that is positive-invariant. It is enough to 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 [11].

3. ANALYSIS OF A MODEL

We analyze model (5) in order to get some insights on dynamics of TB disease and transmission.

3.1 Existence and Local Stability of DFE

Let $E_0 = \left(s^*, v^*, l^*, i_1^*, i_2^*, h^*\right)$ be a DFE point of model (5). We set zero to the right hand side of each equation in (5) and assume that in absence of disease attack, $l = i_1 = i_2 = h = 0$ to solve the steady state solution. The disease free equilibrium point is therefore given by :

$E_0 = \left(s^*, v^*, l^*, i_1^*, i_2^*, h^*\right) = \left(\frac{\theta + \lambda(1-\rho)}{\lambda + \theta}, \frac{\rho\lambda}{\lambda + \theta}, 0, 0, 0, 0\right)$. Before we prove for local stability of DFE we define and determine the effective reproduction number, R_e of model (5).

Definition 1. *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) are administered* [18].

The effective reproduction number R_e is computed by using next generation operator method [22] and found to be:

$$\begin{aligned} R_e &= \frac{\beta\left(\theta + \lambda(1-\rho)\right)}{(\lambda+\theta)}\left[\frac{(1-\eta)(\lambda+\omega+\delta_2)\varepsilon + (1-\phi)\omega\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\upsilon)} + \frac{\eta\varepsilon}{(\lambda+\varepsilon)(\lambda+\omega+\delta_2)}\right] \\ &= \frac{\beta\left(\theta + \lambda(1-\rho)\right)\left[(1-\eta)(\lambda+\omega+\delta_2)\varepsilon + \left((1-\phi)\omega + \lambda + \delta_1 + \upsilon\right)\eta\varepsilon\right]}{(\lambda+\theta)(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\upsilon)} \end{aligned} \tag{6}$$

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

We prove Theorem 3.1 for local stability of DFE by asserting that the trace and determinant of Jacobian matrix at DFE denoted by $J(E_0)$ are strictly negative and positive respectively. 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

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

$$=-\lambda^2(\lambda+\theta)\begin{bmatrix} \frac{\beta(\theta+\lambda(1-\rho))}{(\lambda+\theta)}\left\{(1-\eta)(\lambda+\omega+\delta_2)\varepsilon+\left((1-\phi)\omega+\lambda+\delta_1+\upsilon\right)\eta\varepsilon\right\} \\ -(\lambda+\varepsilon)(\lambda+\omega+\delta_2)(\lambda+\delta_1+\upsilon) \end{bmatrix}$$

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

$$=-A(R_e-1).$$

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

We find that $\mathrm{Tr}(J(E_0))$ is strictly negative and $\det(J(E_0))$ is strictly positive if and only if $R_e<1$. We therefore conclude that DFE is locally asymptotically stable. □

3.2 Global Analysis of DFE of a model with interventions

We analyze the global stability of disease free equilibrium point of model (5) by using an approach presented in [5]. The model (5) can be written in the following format:

$$\begin{cases} \dfrac{dX_n}{dt} = A\left(X_n - X_{E_0,n}\right) + A_1 X_i. \\ \dfrac{dX_i}{dt} = A_2 X_i. \end{cases} \tag{7}$$

From (7), X_n and X_i are vectors of non-transmitting and transmitting compartments respectively. $X_{E_0,n}$ is a vector at disease free equilibrium point E_0 of the same length as X_n. From model (5) we define:

$X_n = (s, v, h)^T$, $X_i = (l, i_1, i_2)^T$, $X_{E_0,n} = \left(\dfrac{\theta + \lambda(1-\rho)}{\lambda + \theta}, \dfrac{\rho\lambda}{\lambda + \theta}, 0\right)^T$; and

$X_n - X_{E_0,n} = \begin{bmatrix} s - \dfrac{\theta + \lambda(1-\rho)}{\lambda + \theta} \\ v - \dfrac{\rho\lambda}{\lambda + \theta} \\ h \end{bmatrix}$. For global stability of DFE we need to show that matrix A has real negative eigenvalues and A_2 is a Metzler matrix (i.e. the off-diagonal elements of A_2 are non-negative, symbolically denoted by $A_2(x_{ij}) \geq 0, \forall i \neq j$). Using system (5), then the first and second equations in (7) can be written respectively in expanded form as:

$$\begin{bmatrix} (1-\rho)\lambda + \theta v - \left(\lambda + \beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2\right)s \\ \rho\lambda - \left(\lambda + \theta - \delta_1 i_1 - \delta_2 i_2\right)v \\ v i_1 + \phi\omega i_2 - \left(\lambda + \gamma\beta(i_1 + i_2) - \delta_1 i_1 - \delta_2 i_2\right)h \end{bmatrix} = A \begin{bmatrix} s - \dfrac{\theta + \lambda(1-\rho)}{\lambda + \theta} \\ v - \dfrac{\rho\lambda}{\lambda + \theta} \\ h \end{bmatrix} + A_1 \begin{bmatrix} l \\ i_1 \\ i_2 \end{bmatrix}$$

and

$\begin{bmatrix} \beta s(i_1 + i_2) + \gamma\beta h(i_1 + i_2) - \left(\lambda + \varepsilon - \delta_1 i_1 - \delta_2 i_2\right)l \\ (1-\eta)\varepsilon l + (1-\phi)\omega i_2 - \left(\lambda + \delta_1 + \upsilon - \delta_1 i_1 - \delta_2 i_2\right)i_1 \\ \eta\varepsilon l - \left(\lambda + \omega + \delta_2 - \delta_1 i_1 - \delta_2 i_2\right)i_2 \end{bmatrix} = A_2 \begin{bmatrix} l \\ i_1 \\ i_2 \end{bmatrix}$. For compatibility, matrices A, A_1 and A_2 should be of order 3×3. By using non-transmitting elements from Jacobian matrix of system (5) and representation in (7) we find that:

$A = \begin{bmatrix} -\lambda & \theta & 0 \\ 0 & -(\lambda + \theta) & 0 \\ 0 & 0 & -\lambda \end{bmatrix}$, $A_1 = \begin{bmatrix} 0 & (-\beta + \delta_1)s & (-\beta + \delta_2)s \\ 0 & \delta_1 v & \delta_2 v \\ 0 & \upsilon + h(\delta_1 - \gamma\beta) & \phi\omega + h(\delta_2 - \gamma\beta) \end{bmatrix}$ and,

$A_2 = \begin{bmatrix} -(\lambda+\varepsilon) & \beta(s+\gamma h)+\delta_1 l & \beta(s+\gamma h)+\delta_2 l \\ (1-\eta)\varepsilon & -(\lambda+\upsilon+\delta_1(1-i_1)) & (1-\phi)\omega+\delta_2 i_1 \\ \eta\varepsilon & \delta_1 i_2 & -(\lambda+\omega+\delta_2(1-i_2)) \end{bmatrix}$. We find that A is upper triangular matrix whose eigeinvalues are located on its main diagonal. Therefore eigenvalues of A (i.e. $-\lambda, -(\lambda+\theta)$ and $-\lambda$) are real and negative. In addition A_2 is a Metzler matrix since its off-diagonal elements are non-negative. That is $0 \le l, i_1, i_2, h < 1$ and both $(1-i_1)$ and $(1-i_2)$ are strictly positive. Therefore DFE for system (5) is globally asymptotically stable in region Ω. We have established important theorem:

Theorem 3.2. *The disease-free equilibrium point is globally asymptotically stable in Ω if $R_e < 1$ and unstable if $R_e > 1$.*

3.3 Existence of Endemic Equilibrium Point (EEP) of model with interventions

Let $E_2(s^*, v^*, l^*, i_1^*, i_2^*, h^*)$ be an endemic equilibrium point of model (5). The conditions of existence of endemic equilibrium point E_2 are obtained by setting the right hand side of each equation in (5) equal to zero and solve model (5) in terms of force of infection $f^* = \beta(i_1^* + i_2^*)$ at steady state. Let $k = \lambda - \delta_1 i_1^* - \delta_2 i_2^* > 0$, for any pairwise choice of i_1^* and i_2^* values at endemic equilibrium. An endemic equilibrium point in terms of force of infection is given by:

$$\left.\begin{aligned}
s^* &= \frac{\lambda(\theta + k(1-\rho))}{(f^*+k)(\theta+k)} \\
v^* &= \frac{\rho\lambda}{\theta+k} \\
l^* &= \frac{\lambda(\omega+\delta_2+k)\{(1-\eta)(\omega+\delta_2+k)+(1-\phi)\omega\eta\}(\theta+k(1-\rho))(\gamma f^*+k) f^*}{\eta(f^*+k)(\theta+k)\{(\varepsilon+k)(\omega+\delta_2+k)(\gamma f^*+k)(\delta_1+\upsilon+k)-\varepsilon\gamma f^*(\upsilon a_1+a_2)\}} \\
i_1^* &= \frac{\lambda\varepsilon\{(1-\eta)(\omega+\delta_2+k)+(1-\phi)\omega\eta\}(\theta+k(1-\rho))(\gamma f^*+k) f^*}{(f^*+k)(\theta+k)\{(\varepsilon+k)(\omega+\delta_2+k)(\gamma f^*+k)(\delta_1+\upsilon+k)-\varepsilon\gamma f^*(\upsilon a_1+a_2)\}} \\
i_2^* &= \frac{\lambda\eta\varepsilon(\theta+k(1-\rho))(\gamma f^*+k)(\delta_1+\upsilon+k) f^*}{(f^*+k)(\theta+k)\{(\varepsilon+k)(\omega+\delta_2+k)(\gamma f^*+k)(\delta_1+\upsilon+k)-\varepsilon\gamma f^*(\upsilon a_1+a_2)\}} \\
h^* &= \frac{\lambda\varepsilon(\theta+k(1-\rho))(\upsilon a_1+a_2) f^*}{(f^*+k)(\theta+k)\{(\varepsilon+k)(\omega+\delta_2+k)(\gamma f^*+k)(\delta_1+\upsilon+k)-\varepsilon\gamma f^*(\upsilon a_1+a_2)\}} \\
\text{we define, } a_1 &= (1-\eta)(\omega+\delta_2+k)+(1-\phi)\omega\eta;\ a_2 = \phi\omega\eta(\delta_1+\upsilon+k)
\end{aligned}\right\} \quad (8)$$

If we substitute representations of i_1^* and i_2^* from (8) into the force of infection, $f^* = \beta\left(i_1^* + i_2^*\right)$ or $f^* - \beta\left(i_1^* + i_2^*\right) = 0$ we find that:

$$f^* - \beta\left[\frac{\lambda\varepsilon\left(\theta + k\left(1-\rho\right)\right)\left(\gamma f^* + k\right)f^*\left[\left\{\left(1-\eta\right)\left(\omega+\delta_2+k\right)+\left(1-\phi\right)\omega\eta\right\}+\eta\left(\delta_1+\upsilon+k\right)\right]}{\left(f^*+k\right)\left(\theta+k\right)\left\{\left(\varepsilon+k\right)\left(\omega+\delta_2+k\right)\left(\gamma f^*+k\right)\left(\delta_1+\upsilon+k\right)-\varepsilon\gamma f^*\left(\upsilon a_1+a_2\right)\right\}}\right] = 0 \quad (9)$$

Manipulating and simplifying (9) we end up with the following cubic polynomial:

$$f^*\left(A_1 f^{*2} + B_1 f^* + C_1\right) = 0 \quad (10)$$

where by

$$\begin{aligned} A_1 &= \gamma\left[M - \left(\upsilon P + Q\right)\left(\theta + k\right)\right], \\ B_1 &= k\left(M + \gamma\left[M - \left(\upsilon P + Q\right)\left(\theta + k\right)\right]\right) - \beta a_1\gamma\left(P + \left(\delta_1 + \upsilon + k\right)\eta\varepsilon\right), \\ C_1 &= k\left(Mk - \beta a_1\left[P + \left(\delta_1 + \upsilon + k\right)\eta\varepsilon\right]\right). \end{aligned} \quad (11)$$

Furthermore in terms of parameters of model (5) we define:
$M = \left(\theta+k\right)\left(\varepsilon+k\right)\left(\omega+\delta_2+k\right)\left(\delta_1+\upsilon+k\right)$; $P = \left(1-\eta\right)\left(\omega+\delta_2+k\right)\varepsilon + \left(1-\phi\right)\omega\eta\varepsilon$;
$Q = \phi\omega\eta\varepsilon\left(\delta_1+\upsilon+k\right)$ and $a_1 = \lambda\left(\theta + k\left(1-\rho\right)\right)$. We write C_1 in the following format:

$$C_1 = \left(\theta+k\right)\left(\varepsilon+k\right)\left(\omega+\delta_2+k\right)\left(\delta_1+\upsilon+k\right)k^2\left(1-R_e\right) \quad (12)$$

From (12), $\left(\theta+k\right)\left(\varepsilon+k\right)\left(\omega+\delta_2+k\right)\left(\delta_1+\upsilon+k\right)k^2 > 0$ and R_e is effective reproduction number as indicated in (6).

From (10), $f^* = \beta\left(i_1^* + i_2^*\right) = 0$ corresponds to Disease Free Equilibrium (DFE) that we have already discussed while $A_1 f^{*2} + B_1 f^* + C_1 = 0$, that can be also be written in the form:

$$f^* = \frac{-B_1 \pm \sqrt{B_1^2 - 4A_1C_1}}{2A_1} \quad (13)$$

Satisfies Endemic Equilibrium. The value of A_1 is strictly positive. Depending on the signs of B_1 and C_1 we have three cases to consider in order to have positive root of force of infection as follows:

Case 1: In absence of re-infection we find that the parameter for level of reinfection, $\gamma = 0$. This implies from (11) that $A_1 = 0$. The polynomial $A_1 f^{*2} + B_1 f^* + C_1 = 0$ becomes linear, i.e. $B_1 f^* + C_1 = 0$ or $f^* = \frac{-C_1}{B_1}$. If $B_1 > 0$ then system (5) has stable endemic equilibrium when $C_1 < 0$. This equilibrium happens when $R_e > 1$as interpreted from (12). In this case backward bifurcation is not possible due to absence of multiple equilibria.

Case 2: Exactly one endemic equilibrium point. From (13), suppose $B_1 < 0$ and $C_1 = 0$ or $B_1^2 - 4A_1C_1 = 0$. This means the polynomial has just one positive root and hence the system (5) has unique endemic equilibrium.

Case 3: Two endemic equilibria

If $B_1 < 0$, $C_1 > 0$ and $B_1^2 - 4A_1C_1 > 0$, then the polynomial $A_1 f^{*2} + B_1 f^* + C_1 = 0$ has two positive roots. This means that the system (5) has two endemic equilibria and hence the possibility of backward bifurcation. These three cases are summarized under the following theorem:

Theorem 3.3: *The number of positive endemic equilibria of Tuberculosis model* (5) *is hereunder summarized as follows*:

i. *If* $C_1 < 0$, $R_e > 1$*, the system has a unique endemic equilibrium.*
ii. *If* $B_1 < 0$ *and* $C_1 = 0$ *or* $B_1^2 - 4A_1C_1 = 0$, *the system has exactly one endemic equilibrium.*
iii. *If* $B_1 < 0$, $C_1 > 0$ and $B_1^2 - 4A_1C_1 > 0$, *the system has exactly two endemic equilibria.*
iv. *Otherwise there are no endemic equilibria, i.e. when* $A_1C_1 > 0$ *and* $B_1 > 0$.

From (iii), the critical point of effective reproduction number R_e^c at which a backward bifurcation occurs is computed by setting the discriminant in (13) equals to zero. Thus, $B_1^2 - 4A_1C_1 = 0$ implies that

$B_1^2 - 4A_1(\theta + k)(\varepsilon + k)(\omega + \delta_2 + k)(\delta_1 + \upsilon + k)k^2(1 - R_e^c) = 0$ and,

$R_e^c = 1 - \dfrac{B_1^2}{4A_1(\theta + k)(\varepsilon + k)(\omega + \delta_2 + k)(\delta_1 + \upsilon + k)k^2}$. Thus backward bifurcation occurs in the range $R_e^c < R_e < 1$. Furthermore, we note from (13) that disease will be endemic if force of infection is strictly positive (i.e. $f^* > 0$) and both B_1 and A_1C_1 are strictly negative. Thus, $A_1 > 0$ and $A_1C_1 = A_1(\theta + k)(\varepsilon + k)(\omega + \delta_2 + k)(\delta_1 + \upsilon + k)k^2(1 - R_e) < 0$ if and only if $R_e > 1$. Therefore endemic equilibrium point $E_2(s^*, v^*, l^*, i_1^*, i_2^*, h^*)$ is stable if and only if $R_e > 1$.

3.4 Stability of Endemic Equilibrium Point (EEP) of model with intervention

The stability of an endemic equilibrium E_2 of model (5) is analyzed by using Centre Manifold theory [4] as described in Theorem 4.1 of Castillo-Chavez and Song [6]. We change the variables of model (5) by setting $s = x_1, v = x_2, l = x_3, i_1 = x_4, i_2 = x_5, h = x_6$ such

that $\sum_{i=1}^{6} x_i = 1$. We define vector $X = \left(x_1, x_2, x_3, x_4, x_5, x_6\right)^T$ and $F = \left(f_1, f_2, f_3, f_4, f_5, f_6\right)^T$ in such a way that the model (5) is re-written in the form $\frac{dX}{dt} = F$ as follows:

$$\begin{cases} \dot{x}_1 = f_1 = (1-\rho)\lambda + \theta x_2 - \left(\lambda + \beta\left(x_4 + x_5\right) - \delta_1 x_4 - \delta_2 x_5\right)x_1, \\ \dot{x}_2 = f_2 = \rho\lambda - \left(\lambda + \theta - \delta_1 x_4 - \delta_2 x_5\right)x_2 \\ \dot{x}_3 = f_3 = \beta x_1\left(x_4 + x_5\right) + \gamma\beta x_6\left(x_4 + x_5\right) - \left(\lambda + \varepsilon - \delta_1 x_4 - \delta_2 x_5\right)x_3, \\ \dot{x}_4 = f_4 = (1-\eta)\varepsilon x_3 + (1-\phi)\omega x_5 - \left(\lambda + \delta_1 + \upsilon - \delta_1 x_4 - \delta_2 x_5\right)x_4, \\ \dot{x}_5 = f_5 = \eta\varepsilon x_3 - \left(\lambda + \omega + \delta_2 - \delta_1 x_4 - \delta_2 x_5\right)x_5, \\ \dot{x}_6 = f_6 = \upsilon x_4 + \phi\omega x_5 - \left(\lambda + \gamma\beta\left(x_4 + x_5\right) - \delta_1 x_4 - \delta_2 x_5\right)x_6. \end{cases} \tag{14}$$

The Jacobian matrix $J\left(E_0\right)$ of system (14) at disease free equilibrium E_0 presented in Section 3.1 is given by

$$J\left(E_0\right) = \begin{bmatrix} -\lambda & \theta & 0 & \left(-\beta + \delta_1\right)r_1 & \left(-\beta + \delta_2\right)r_1 & 0 \\ 0 & -(\lambda + \theta) & 0 & \delta_1 r_2 & \delta_2 r_2 & 0 \\ 0 & 0 & -(\lambda + \varepsilon) & \beta r_1 & \beta r_1 & 0 \\ 0 & 0 & (1-\eta)\varepsilon & -\left(\lambda + \delta_1 + \upsilon\right) & (1-\phi)\omega & 0 \\ 0 & 0 & \eta\varepsilon & 0 & -\left(\lambda + \omega + \delta_2\right) & 0 \\ 0 & 0 & 0 & \upsilon & \phi\omega & -\lambda \end{bmatrix} \tag{15}$$

From (15) we define $r_1 = \frac{\theta + \lambda(1-\rho)}{\lambda + \theta}$ and $r_2 = \frac{\rho\lambda}{\lambda + \theta}$. In particular case when basic reproduction number $R_e = 1$, we choose our bifurcation parameter be β and consider our bifurcation to take place at $\beta = \beta^*$. Solving β from (6) when $R_e = 1$ we find that:

$$\beta = \beta^* = \frac{\left(\lambda + \theta\right)\left(\lambda + \varepsilon\right)\left(\lambda + \omega + \delta_2\right)\left(\lambda + \delta_1 + \upsilon\right)}{\left(\theta + \lambda(1-\rho)\right)\left[(1-\eta)\left(\lambda + \omega + \delta_2\right)\varepsilon + \left((1-\phi)\omega + \lambda + \delta_1 + \upsilon\right)\eta\varepsilon\right]} \tag{16}$$

The Jacobian of transformed system (14) at $\beta = \beta^*$ has simple zero eigenvalue that allows us to study the dynamics of the system (5) at $\beta = \beta^*$ using Centre Manifold theory [4]. The Jacobian of (14) denoted by $J\left(E_0\right)$ at $\beta = \beta^*$ has right eigenvector that corresponds with zero eigenvalue given by $\omega = \left(w_1, w_2, w_3, w_4, w_5, w_6\right)^T$, where by:

$$\begin{cases} w_1 = \left[\dfrac{\left(k_1-\beta^* r_1\eta\varepsilon\right)\left(\delta_1 r_2\theta+\left(-\beta^*+\delta_1\right)\left(\lambda+\theta\right)r_1\right)+\beta^* r_1\eta\varepsilon\left(\delta_2 r_2\theta+\left(-\beta^*+\delta_2\right)\left(\lambda+\theta\right)r_1\right)}{\lambda\left(\lambda+\theta\right)\beta^* r_1\eta\varepsilon}\right]w_5, \\ w_2 = \left[\dfrac{\delta_1 r_2\left(\left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)-\beta^* r_1\eta\varepsilon\right)+\delta_2 r_2\beta^* r_1\eta\varepsilon}{\left(\lambda+\theta\right)\beta^* r_1\eta\varepsilon}\right]w_5>0, \\ w_3 = \dfrac{\left(\lambda+\omega+\delta_2\right)}{\eta\varepsilon}w_5>0, \\ w_4 = \left[\dfrac{\left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)-\beta^* r_1\eta\varepsilon}{\beta^* r_1\eta\varepsilon}\right]w_5>0, \\ w_5 = w_5>0,\ \text{free}. \\ w_6 = \left[\dfrac{\upsilon\left[\left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)-\beta^* r_1\eta\varepsilon\right]+\phi\omega\beta^* r_1\eta\varepsilon}{\lambda\beta^* r_1\eta\varepsilon}\right]w_5>0. \end{cases} \tag{17}$$

From (17), $k_1=\left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)-\beta^* r_1\eta\varepsilon$ and $r_1=\dfrac{\theta+\lambda\left(1-\rho\right)}{\lambda+\theta}$. By using (16) we show that k_1 is strictly positive justifying that the components $w_2, w_4, w_6>0$ as follows:

$$\begin{aligned} k_1 &= \left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)-\beta^* r_1\eta\varepsilon \\ &= \left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)\left(1-\frac{\beta^* r_1\eta\varepsilon}{\left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)}\right) \\ &= \left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)\left(1-\frac{\left(\lambda+\theta\right)\left(\lambda+\delta_1+\upsilon\right)r_1\eta\varepsilon}{\left(\theta+\lambda\left(1-\rho\right)\right)\left[\left(1-\eta\right)\left(\lambda+\omega+\delta_2\right)\varepsilon+\left(\left(1-\phi\right)\omega+\lambda+\delta_1+\upsilon\right)\eta\varepsilon\right]}\right) \\ &= \left(\lambda+\varepsilon\right)\left(\lambda+\omega+\delta_2\right)\left(1-\frac{\left(\lambda+\delta_1+\upsilon\right)\eta\varepsilon}{\left(1-\eta\right)\left(\lambda+\omega+\delta_2\right)\varepsilon+\left(\left(1-\phi\right)\omega+\lambda+\delta_1+\upsilon\right)\eta\varepsilon}\right)>0. \end{aligned}$$

Moreover, the Jacobian matrix $J\left(E_0\right)$ at $\beta=\beta^*$ has left eigenvector $\Psi=\left[\Psi_1,\Psi_2,\Psi_3,\Psi_4,\Psi_5,\Psi_6\right]^T$ associated with zero eigenvalue satisfying the relation $\Psi\cdot\boldsymbol{\omega}=1$, where by:

$$\Psi_1=\Psi_2=\Psi_6=0, \Psi_3=\frac{\left(\lambda+\delta_1+\upsilon\right)}{\beta^* r_1}\Psi_4>0,\ \Psi_4=\Psi_4>0,\ \Psi_5=\frac{\left(\left(1-\phi\right)\omega+\lambda+\delta_1+\upsilon\right)}{\lambda+\omega+\delta_2}\Psi_4>0. \tag{18}$$

We compute the value of a and b that will govern totally the local dynamics of system (14) and determine whether it exhibits forward or backward bifurcation by employing Theorem 4.1 of Castillo-Chavez and Song [6] and as restated in Theorem 3.4.

Theorem 3.4. *Consider the general system of ordinary differential equations (14) with a parameter* β *such that* $\frac{dx}{dt} = f(x,\beta), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}$ *and* $f \in \mathbb{C}^2\left(\mathbb{R}^n \times \mathbb{R}\right)$, *where* 0 *is an equilibrium point of the system (i.e.* $f(0,\beta) \equiv 0$ *for all* β *) and*

1. $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial f_j}(0,0)\right)$ *is Jacobian (linearization) matrix of the system around the equilibrium* 0 *with* β *evaluated at* 0,
2. *Zero is a simple eigenvalue of* A *and other eigenvalues of* A *have negative real parts;*
3. *Matrix* A *has a right eigenvector* ω *and a left eigenvector* Ψ *corresponding to zero eigenvalue.*

Let f_k *be the* k^{th} *component of* f *and* $a = \sum_{k,i,j=1}^{n} \Psi_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0)$ *and*

$b = \sum_{k,i=1}^{n} \Psi_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(0,0)$ *then the local dynamics of the system around the equilibrium point* 0 *is totally determined by the signs of* a *and* b. *In particular, if* $a > 0$ *and* $b > 0$ *then a backward bifurcation occur at* $\beta = 0$. *Signs of* a *and* b *play the vital role in describing the local dynamics of model (14) around equilibrium point* 0 *as follows:*

a) $a > 0, b > 0$, *when* $\beta < 0$ *with* $|\beta| \ll 1$, 0 *is locally asymptotically stable and there exists a positive unstable equilibrium, when* $0 < |\beta| \ll 1$, 0 *is unstable and there exists a negative and locally asymptotically stable equilibrium.*

b) $a < 0, b < 0$, *when* $\beta < 0$ *with* $|\beta| \ll 1$, 0 *is unstable, when* $0 < |\beta| \ll 1$, 0 *is asymptotically stable and there exists a positive unstable equilibrium.*

c) $a > 0, b < 0$, *when* $\beta < 0$ *with* $|\beta| \ll 1$, 0 *is unstable and there exists a locally asymptotically stable negative equilibrium, when* $0 < |\beta| \ll 1$, 0 *is stable and a positive unstable equilibrium appears.*

d) $a < 0, b > 0$ *when* β *changes from negative to positive,* 0 *changes its stability from stable to unstable. Correspondingly, negative unstable equilibrium becomes positive and locally asymptotically stable.*

Computation of a **and** b

We compute the value of a and b that will govern totally the local dynamics of system (14) and determine the conditions for existence of backward bifurcation following the signs of

a and b by employing Theorem 4.1 of Castillo-Chavez and Song [6] and as implied in Theorem 3.4 of this article.

Since the components of left eigenvector $\Psi_1 = \Psi_2 = \Psi_6 = 0$ (for $k = 1, 2$ and 6) we compute the values of a and b for only $k = 3, 4, 5$. The only non-zero second order partial derivatives of (14) at DFE when $\beta = \beta^*$ are:

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_4} = \frac{\partial^2 f_3}{\partial x_1 \partial x_5} = \beta^*, \quad \frac{\partial^2 f_3}{\partial x_4 \partial x_6} = \frac{\partial^2 f_3}{\partial x_5 \partial x_6} = \gamma\beta^*, \quad \frac{\partial^2 f_4}{\partial x_4^{\,2}} = 2\delta_1, \quad \frac{\partial^2 f_5}{\partial x_5^{\,2}} = 2\delta_2.$$

By using $a = \sum_{k,i,j=1}^{n} \Psi_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0)$ we compute a as follows:

$$\begin{aligned} a &= \Psi_3 \left(w_1 w_4 \beta^* + w_1 w_5 \beta^* + w_3 w_4 \delta_1 + w_3 w_5 \delta_2 + w_4 w_6 \gamma\beta^* + w_5 w_6 \gamma\beta^* \right) \\ &\quad + \Psi_4 \left(2 w_4^{\,2} \delta_1 + w_4 w_5 \delta_2 \right) + \Psi_5 \left(w_4 w_5 \delta_1 + 2 w_5^{\,2} \delta_2 \right) \\ &= \Psi_3 \beta^* w_1 \left(w_4 + w_5 \right) + w_6 \gamma \Psi_3 \beta^* \left(w_4 + w_5 \right) + w_4 \delta_1 \left(\Psi_3 w_3 + 2\Psi_4 w_4 + \Psi_5 w_5 \right) \\ &\quad + w_5 \delta_2 \left(\Psi_3 w_3 + \Psi_4 w_4 + 2\Psi_5 w_5 \right). \end{aligned} \tag{19}$$

On the other hand, the value of b is computed by using the formula, $b = \sum_{k,i=1}^{n} \Psi_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(0,0)$.

The associated non-zero second order partial derivatives of (14) at DFE when $\beta = \beta^*$ and $k = 3, 4, 5$ are:

$\frac{\partial^2 f_3}{\partial x_4 \partial \beta^*} = \frac{\partial^2 f_3}{\partial x_5 \partial \beta^*} = x_1^* = \frac{\theta + \lambda(1-\rho)}{\lambda + \theta}$ The value of b is therefore given by:

$$b = \Psi_3 \left(w_4 \frac{\theta + \lambda(1-\rho)}{\lambda + \theta} + w_5 \frac{\theta + \lambda(1-\rho)}{\lambda + \theta} \right) = \Psi_3 \left(\frac{\theta + \lambda(1-\rho)}{\lambda + \theta} \right) \left(w_4 + w_5 \right) > 0 \tag{20}$$

From (19), let $\zeta_1 = \Psi_3 \beta^* w_1 \left(w_4 + w_5 \right)$ and

$\zeta_2 = w_6 \gamma \Psi_3 \beta^* \left(w_4 + w_5 \right) + w_4 \delta_1 \left(\Psi_3 w_3 + 2\Psi_4 w_4 + \Psi_5 w_5 \right) + w_5 \delta_2 \left(\Psi_3 w_3 + \Psi_4 w_4 + 2\Psi_5 w_5 \right)$. It follows that the sign of a depends on the value of w_1. If $w_1 > 0$ or $w_1 < 0$ and $\zeta_2 > \zeta_1$ then $a > 0$. We formulate the following theorem.

Theorem 3.5: *If $w_1 > 0$ or $w_1 < 0$ and $\zeta_2 > \zeta_1$, $a > 0$ then model (5) exhibits backward bifurcation at $R_e = 1$. If $\beta < 0$ then there exists unstable positive endemic equilibrium point and correspondingly if $\beta > 0$ then there exists a stable negative endemic equilibrium point. Therefore endemic equilibrium point is locally asymptotically stable if $R_e > 1$ but close to 1.*

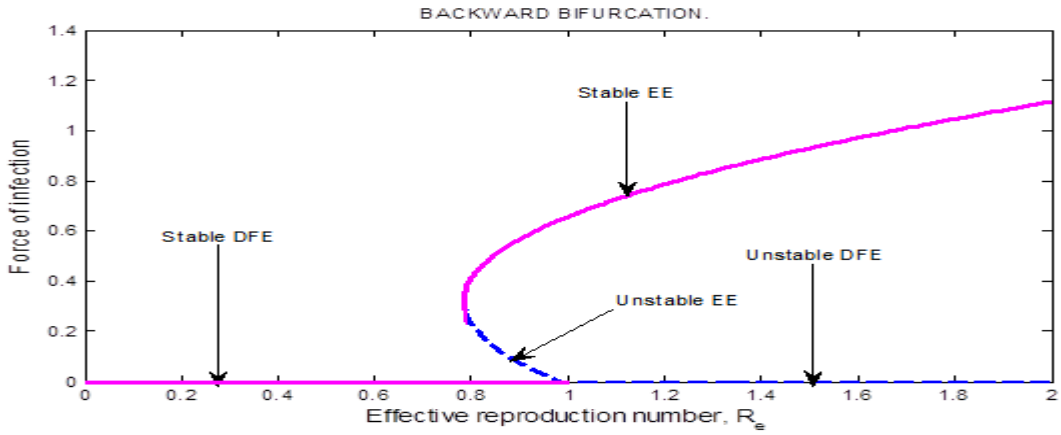

Figure 2: Bifurcation diagram showing backward bifurcation with estimated parameters $\beta = 14$; $\gamma = 1.8$; $\theta = 0.8$; $\varepsilon = 0.396$; $\eta = 0.1$; $\lambda = 0.9$; $\delta_1 = 0.3$; $\omega = 0.6$; $\rho = 0.1$; $\nu = 0.9$; $\delta_2 = 0.2$ ω=0.6; and $\phi = 0.1$ for numerical simulation.

Figure 2 shows the backward bifurcation of system (5) that occurs at threshold parameter $R_e = 1$, due to presence of multiple equilibria and re-infection. DFE stands for Disease Free equilibrium and EE stands for Endemic Equilibrium. In the neighborhood of 1 when $R_e < 1$ then stable DFE coexists with two endemic equilibria: the small unstable EE (with smaller number of TB infectives) and larger stable endemic equilibrium with large number of infectives. This implies that even with classically reducing the threshold parameter to less than unity does not clear TB from community. That is why we say backward bifurcation is an undesirable feature of TB. When $R_e > 1$ then we have two equilibria: unstable DFE and large stable EE. According to Buonomo and Lacitignola [3] if R_e is nearly below one then disease control depends on initial sub-populations of the model under consideration. That is reducing R_e below the critical value $R_e^c < 1$ eradicate disease from community given that the disease free equilibrium is globally asymptotically stable.

3.5 Global Stability of Endemic Equilibrium Point of a model with intervention.

In this section we prove the global stability of endemic equilibrium point E_2 of system (5) by using Lyapunov's direct method. Our Lyapunov function is constructed from suitable choice of logarithmic function. The global properties of endemic equilibrium point are studied by stating and proving the following theorem.

Theorem 3.6 *If $R_e > 1$ then the unique endemic equilibrium E_2 of system (5) is globally asymptotically stable in the interior of Ω.*

Proof: We use approach of Korobeinikov [13] as it is used to most complicated compartmental epidemiological models, to construct the Lyapunov function from suitable choice of the following logarithmic function:

$$W = \sum a_i \left(y_i - y_i^* \ln\left(y_i\right)\right),$$

where a_i are properly chosen positive constants, y_i is population of compartment i and y_i^* is the equilibrium level. We define the function $W : \left\{\left(s, v, l, i_1, i_2, h\right) \in \Omega : s, v, l, i_1, i_2, h > 0\right\} \to \mathbb{R}$ by:

$$\begin{aligned} W\left(s, v, l, i_1, i_2, h\right) = A_1\left(s - s^* \ln\left(s\right)\right) + A_2\left(v - v^* \ln\left(v\right)\right) + A_3\left(l - l^* \ln\left(l\right)\right) \\ + A_4\left(i_1 - i_1^* \ln\left(i_1\right)\right) + A_5\left(i_2 - i_2^* \ln\left(i_2\right)\right) + A_6\left(h - h^* \ln\left(h\right)\right). \end{aligned}$$

The constants $A_1, A_2, \cdots A_6$ are non-negative in Ω and W is Lyapunov function. The function W together with its constants $A_1, A_2, \cdots A_6 > 0$ are chosen in such way that W is continuous and differentiable in a space C^1 and on the interior of Ω, E_2 is global minimum of W on Ω, and $W\left(s^*, v^*, l^*, i_1^*, i_2^*, h^*\right) = 0$. The time derivative of Lyapunov function W computed along the solutions of system (5) is:

$$\begin{aligned} W' = A_1\left(1 - \frac{s^*}{s}\right)\frac{ds}{dt} + A_2\left(1 - \frac{v^*}{v}\right)\frac{dv}{dt} + A_3\left(1 - \frac{l^*}{l}\right)\frac{dl}{dt} + A_4\left(1 - \frac{i_1^*}{i_1}\right)\frac{di_1}{dt} \\ + A_5\left(1 - \frac{i_2^*}{i_2}\right)\frac{di_2}{dt} + A_6\left(1 - \frac{h^*}{h}\right)\frac{dh}{dt}. \end{aligned} \tag{21}$$

At Endemic equilibrium point (EEP) we have:

$$\begin{aligned} \left(1-\rho\right)\lambda &= \left(\lambda + \beta\left(i_1^* + i_2^*\right) - \delta_1 i_1^* - \delta_2 i_2^*\right)s^* - \theta v^*, \\ \rho\lambda &= \left(\lambda + \theta - \delta_1 i_1^* - \delta_2 i_2^*\right)v^*, \\ \lambda + \varepsilon &= \frac{1}{l^*}\left(\beta s^*\left(i_1^* + i_2^*\right) + \gamma\beta h^*\left(i_1^* + i_2^*\right) + \left(\delta_1 i_1^* + \delta_2 i_2^*\right)l^*\right), \\ \lambda + \delta_1 + \upsilon &= \frac{1}{i_1^*}\left(\left(1-\eta\right)\varepsilon l^* + \left(1-\phi\right)\omega i_2^*\right) + \delta_1 i_1^* + \delta_2 i_2^*, \\ \lambda + \omega + \delta_2 &= \frac{\eta\varepsilon l^*}{i_2^*} + \delta_1 i_1^* + \delta_2 i_2^*, \\ \lambda &= \frac{1}{h^*}\left(\upsilon i_1^* + \phi\omega i_2^* - \gamma\beta\left(i_1^* + i_2^*\right)\right) + \delta_1 i_1^* + \delta_2 i_2^*. \end{aligned} \tag{22}$$

We re-write W' by using (22) as follows:

$$
\begin{aligned}
W' = {} & A_1\left(\frac{s-s^*}{s}\right)\left[\left(\lambda+\beta\left(i_1^*+i_2^*\right)-\delta_1 i_1^*-\delta_2 i_2^*\right)s^*-\theta v^*+\theta v-\left(\lambda+\beta\left(i_1+i_2\right)-\delta_1 i_1-\delta_2 i_2\right)s\right] \\
& +A_2\left(\frac{v-v^*}{v}\right)\left[\left(\lambda+\theta-\delta_1 i_1^*-\delta_2 i_2^*\right)v^*-\left(\lambda+\theta-\delta_1 i_1-\delta_2 i_2\right)v\right] \\
& +A_3\left(\frac{l-l^*}{l}\right)\left[\beta s\left(i_1+i_2\right)+\gamma\beta h\left(i_1+i_2\right)-\frac{1}{l^*}\left\{\beta s^*\left(i_1^*+i_2^*\right)+\gamma\beta h^*\left(i_1^*+i_2^*\right)+\left(\delta_1 i_1^*+\delta_2 i_2^*\right)l^*-\left(\delta_1 i_1+\delta_2 i_2\right)l^*\right\}l\right] \\
& +A_4\left(\frac{i_1-i_1^*}{i_1}\right)\left[\left(1-\eta\right)\varepsilon l+\left(1-\phi\right)\omega i_2-\frac{1}{i_1^*}\left\{\left(1-\eta\right)\varepsilon l^*+\left(1-\phi\right)\omega i_2^*+\left(\delta_1 i_1^*+\delta_2 i_2^*\right)i_1^*-\left(\delta_1 i_1+\delta_2 i_2\right)i_1^*\right\}i_1\right] \\
& +A_5\left(\frac{i_2-i_2^*}{i_2}\right)\left[\eta\varepsilon l-\frac{1}{i_2^*}\left\{\eta\varepsilon l^*+\left(\delta_1 i_1^*+\delta_2 i_2^*\right)i_2^*-\left(\delta_1 i_1+\delta_2 i_2\right)i_2^*\right\}i_2\right] \\
& +A_6\left(\frac{h-h^*}{h}\right)\left[\upsilon i_1+\phi\omega i_2-\frac{1}{h^*}\left\{\upsilon i_1^*+\phi\omega i_2^*-\gamma\beta\left(i_1^*+i_2^*\right)+\left(\delta_1 i_1^*+\delta_2 i_2^*\right)h^*+\gamma\beta\left(i_1+i_2\right)h^*-\left(\delta_1 i_1+\delta_2 i_2\right)h^*\right\}h\right]
\end{aligned}
\tag{23}
$$

Simplification of (23) results to:

$W' = -A_1\lambda\frac{\left(s-s^*\right)^2}{s}-A_2\left(\lambda+\theta\right)\frac{\left(v-v^*\right)^2}{v}+P\left(s,v,l,i_1,i_2,h\right)$. The function $P\left(s,v,l,i_1,i_2,h\right)$ balances the right hand side of (23). The function $P\left(s,v,l,i_1,i_2,h\right)$ is non-positive following the approaches of McCluskey [15] and Mukandavire [17].

That is $P\le 0$ for every $s,v,l,i_1,i_2,h>0$. Thus $W'\le 0$ for all $s,v,l,i_1,i_2,h>0$ and zero when $s=s^*, v=v^*, l=l^*=0, i_1=i_1^*=0, i_2=i_2^*=0, h=h^*=0$. Therefore the largest compact invariant set in Ω such that $W'=0$ is the singleton $\{E_2\}$ which is Endemic Equilibrium point of model (5). LaSalles's invariant principle [14] then implies that E_2 is globally asymptotically stable in the interior of the region Ω if $R_e>1$ and that completes our proof. □

4. NUMERICAL SIMULATIONS AND DISCUSSIONS

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.

Table 3: Parameter values for normalized 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	[8]
η	0.7 (0.7-0.95)	[19]
μ	0.01923 (0.01-0.04)	[2]
δ_1	0.3 (0.07-0.365)	[21]
δ_2	0.2 (0.07-0.365)	[21]
ϕ	0.6	Estimated.
ω	0.2	Estimated.
υ	0.3	Estimated.
γ	0.2	Estimated.

4.1 Numerical Simulation of a model (5) in presence of intervention and TB.

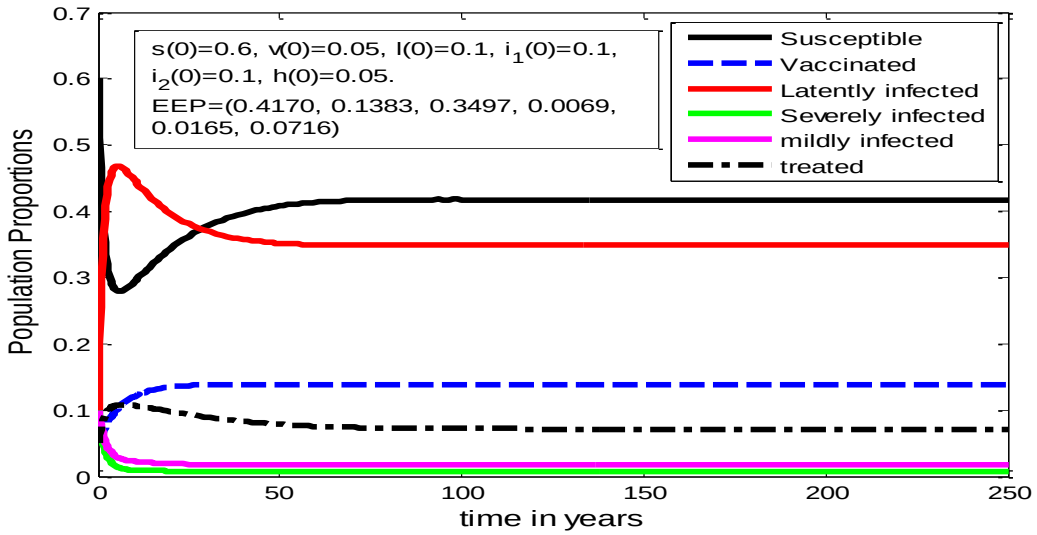

Figure 3: Shows the dynamics of susceptible, vaccinated, latently infected, severely infected, mildly infected and treated population proportions in presence of interventions and TB with increasing time.

Figure 3 shows dynamic behavior of susceptible, vaccinated, latently infected, severely infected, mildly infected and treated classes when $R_e = 1.8519$. The plot is produced by MATLAB by using $\beta = 2.58; \gamma = 0.2; \theta = 0.1; \varepsilon = 0.03; \eta = 0.7; \lambda = 0.05; \delta_1 = 0.3; \omega = 0.2; \rho = 0.4; \upsilon = 0.3; \delta_2 = 0.2\ \phi = 0.6$ as estimated parametric values and whose definitions are given in Table 2. Starting with initial values $s(0) = 0.60, v(0) = 0.05, I(0) = 0.1, i_1(0) = 0.1,$

$i_2(0)=0.1$ and $h(0)=0.05$, the system (5) attains the local asymptotic stability of endemic equilibrium point, $E_2=(s^*,v^*,l^*,i_1^*,i_2^*,h^*)=(0.4170,0.1383,0.3497,0.0069,0.0165,0.0716)$. In presence of interventions and TB, susceptible population proportion initially decreases to lower levels and later increases to its carrying capacity with time as shown in Figure 3. Vaccinated population proportion initially increases to higher levels and stabilizes as time increases. On the other hand both latently infected and treated population proportions increase to higher levels and gradually decreases to their carrying capacities. However both mildly and severely infected population proportions decreases to their lowest endemic levels. Again even with intervention, disease does not clear from community since effective reproduction number is $R_e=1.8519>1$. Classically this result supports the theorem of local stability of endemic equilibrium.

4.2 Phase portraits illustrating dynamical behavior of population proportions at EEP.

In this section phase portraits to illustrate the dynamics of the model (5) at endemic equilibrium point for susceptible class versus vaccinated, latently infected, severely infected, mildly infected, and treated classes are plotted by using parameter values indicated in Table 3. With different varying initial conditions, each solution curve in Figure 4 tends to endemic equilibrium point E_2 presented in Section 4.1. Therefore we conclude that the system (5) is globally stable about endemic equilibrium point E_2 for the parameters displayed in Table 3.

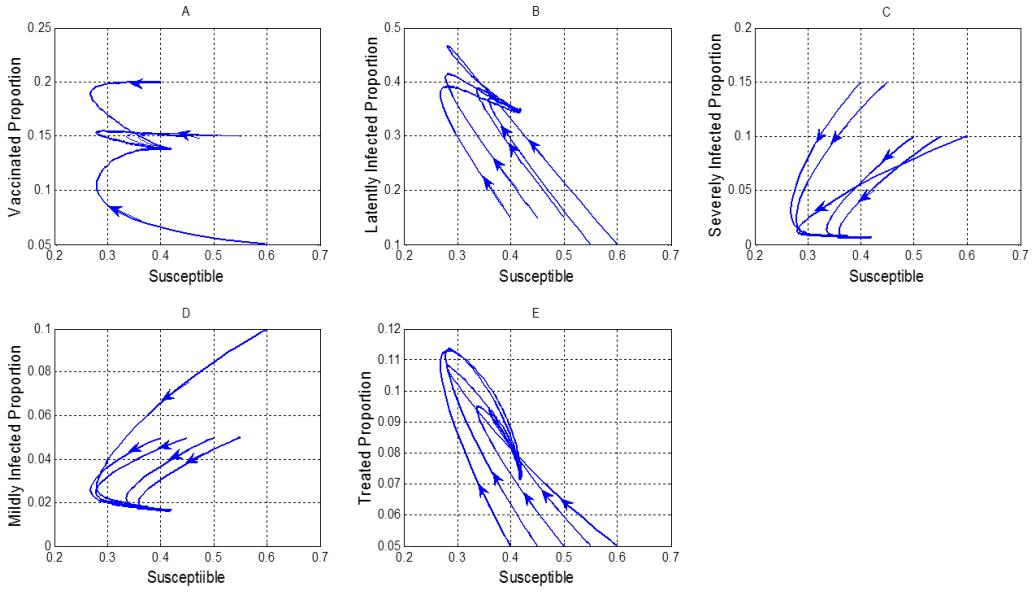

Figure 4: Shows Phase plane portraits for dynamics of susceptible population proportion and (A) vaccinated (B) latently infected (C) severely infected (D) mildly infected (E) treated population proportions showing endemic equilibrium point with varying initial values as time increases.

5. CONCLUSION

In this article, a continuous time deterministic Tuberculosis model with vaccination and treatment as intervention strategies has been formulated and the role of reinfection on transmission dynamics of TB is critically assessed. In presence of reinfection and multiple equilibria the backward bifurcation occurs at effective reproduction number $R_e = 1$. In this scenario stable disease free equilibrium coexists with two endemic equilibria: smaller unstable endemic equilibrium (with small number of infected individuals) and larger stable endemic equilibrium (with large number of infected individuals) in the neghbourhood of 1 when $R_e < 1$. This shows that even with classically reducing the threshold R_e below one the disease still persist in the community. We suggest that reinfection is a real TB feature and an important aspect to consider when modeling the complex dynamics of TB.

REFERENCES

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

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

[3] B. Buonomo, and D. Lacitignola, *On the backward bifurcation of a vaccination model with nonlinear incidence*, Nonlinear Analysis: Modelling and Control, 16(1) (2011), 30–46.

[4] J. Carr, *Applications of Center Manifold Theory*, Springer-Verlag, New York, (1981).

[5] C. Castillo-Chavez, Z. Feng, and W. Huang, *Mathematical Approaches for Emerging and Re-emerging Infectious Diseases*, An Introduction. Springer Verlag, (2002).

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

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

[8] T. Cohen, C. Colijn, B. Finklea, and 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.

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

[10] A. B. Gumel, and S. M. Moghadas, *A qualitative study of a vaccination model with non-linear incidence*, App. Math. Comput. 143 (2003), 409–419.

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

[12] S. Kim, S. Choe, J. Kim, S. Nam, Y. Shin, and S. Lee, *What Does a Mathematical Model Tell About the Impact of Reinfection in Korean Tuberculosis infection?,* Osong Public Health Res Perspect. 5(1) (2014), 40-45.

[13] A. Korobeinikov, *Lyapunov functions and global properties for SEIR and SEIS epidemic models*, Mathematical Medicine and Biology. 21(2004): 75–83.

[14] J. P. LaSalle, *The stability of dynamical systems*. CBMS-NSF in Regional Conference Series in Applied Mathematics. No. 25. SIAM, Philadelphia. (1976).

[15] C. C. McCluskey, *Lyapunov functions for tuberculosis models with fast and slow progression*, Mathematical Biosciences and Engineering, 3(4) (2006), 603–614.

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

[17] Z. Mukandavire, W. Garira, and J. M. Tchuenche, *Modelling effects of public health educational campaigns on HIV/AIDS transmission dynamics*, Appl. Math. Model. 33 (2009), 2084–2095.
[18] D. Okuonghae, and A. Korobeinikov, *Dynamics of Tuberculosis: The Effect of Direct Observation Therapy Strategy (DOTS) in Nigeria*, Mathematical Modeling of Natural Phenomena, 2 (2007), 101-113.
[19] D. Okuonghae, and 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.
[20] P. Rodriques, *Modeling tuberculosis: a compromise between biological realism and mathematical tractability*, Unpublished PhD thesis. University of Lisbon, (2009).
[21] A. Ssematimba, J. Y. T. Mugisha, and 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.
[22] P. van den Driessche, and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci. 180 (2002), 29–48.
[23] World Health Organization (WHO), *Global Tuberculosis Report (2012)*, 2010/2011 Tuberculosis Global Facts.
[24] World Health Organization (WHO), *Global Tuberculosis Report (2013)*, 2011/2012 Tuberculosis Global Facts.

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