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TUBERCULOSIS TRANSMISSION MODEL WITH CASE DETECTION AND TREATMENT†

C. P. BHUNU*, S. MUSHAYABASA, G. MAGOMBEDZE, L.-I. ROEGER

Abstract. A deterministic tuberculosis model for theoretically assessing the potential impact of the combined effects of case detection in the presence of treatment is formulated. The qualitative features of its equilibria are analyzed and it is found that the disease-free equilibrium may not be globally asymptotically stable when the reproduction number is less than unity. This disease threshold number is further used to assess the impact of active TB case finding alone and in conjunction with treatment. A critical threshold parameter Θ, say for which case detection will have a positive impact is derived. Using the Centre Manifold theory, the model may exhibit the phenomenon of backward bifurcation (coexistence of a locally stable endemic equilibrium with a stable disease-free equilibrium) when the reproduction number is less than unity. It is shown that the possibility of backward bifurcation occurring decreases with increase case detection. Graphical representations suggest that increase in case finding accompanied by treatment of detected TB cases, result in a marked decrease of TB cases (both latent and active TB).

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Key words and phrases : Tuberculosis, Case finding, Reproduction number, Treatment.

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (Mtb). It affects about 2 billion people (one third of the world population) and is the second greatest contributor of adult mortality among infectious diseases, causing approximately more than two million deaths a year worldwide [45]. Mtb is one of the oldest human pathogens; evidence of tubercles has been found even in Egyptian mummies [11]. An estimated 3 million (one

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third of the global total of that year) new cases of TB occurred in the South-East Asia region in 2004 [45]. However, the estimated incidence per capita in sub-Saharan Africa is nearly twice that of the South-East Asia at 356 cases per 100,000 individuals in that same year. At least 1.5 million TB cases are diagnosed every year in Africa. Also, some European countries are facing a serious epidemic. For instance, there were estimated 166,000 new cases in Russia alone in 2004 [45]. According to the World Health Organisation (WHO) and the Global Fund for Fight against HIV/AIDS, not less than one-third of all humanity harbour the bacillus that causes TB. Under certain conditions, the latent TB form gets activated, with the capacity to infect others. The predominant mode of person-to-person transmission is through inhalation of bacilli released during coughing by infected persons. At least, 8 million individuals become sick with TB every year. WHO estimates that by 2020, one billion people will contract TB and 35 million will die [27]. TB greatly contributes to numerous deaths of people leaving with HIV/AIDS worldwide. Low income countries account for almost 90% of all TB cases and deaths, which are common among the economically active segment of the population, ages 15 through 54 [45].

TB incidence can be reduced by 5-10% per year by detecting at least 70% of TB cases and successfully treating 85% of the cases detected [41]. Based largely on these initial projections which were subsequently supported by further theoretical study [21], WHO adopted a 70% case detection rate (CDR) for new sputum-smear positive cases and a treatment success rate of 85% as its primary targets for TB control [25]. These targets have remained a constant benchmark for over 15 years and are currently the basis of the TB control strategy outlined in the international Stop TB strategy [42], and the United Nations Millennium Development Goals [18]. However, despite dramatic progress in TB case detection [2] and treatment under the Directly Observed Treatment, Short-course (DOTS) strategy [19], estimated global TB incidence has remained relatively stable over the past decade [20]. Among the 22 countries with the highest TB burden worldwide, only two (Kenya and Zimbabwe) achieved a 5% reduction in TB incidence (as estimated by WHO) between 2005 and 2006 [28].

Various authors have incorporated different infection pathways from primary progressive disease, reactivation, and reinfection into mathematical models of the transmission dynamics of tuberculosis [3, 4, 5, 12, 8, 9, 10, 17, 30, 15, 24, 40, 44], to name a few as this list is not exhaustive. TB models with treatment have been studied in [24, 40], and the references therein. Exogenous and endogenous re-infections, relapse and treatment have been addressed in [8, 9, 10, 24], just to mention a few. However, in order to provide further insight into key factors governing the spread of TB in poor-resource settings such as those of sub-Saharan Africa, we herein propose and develop a comprehensive model to describe the transmission of tuberculosis incorporating case finding/detection and treatment. Our model extend the one proposed in [33], in various ways. We derive conditions under which case detection will have a positive impact, no impact and possibly a negative impact on TB transmission dynamics, while

uncertainty and sensitivity analysis is carried out in [33]. We note however the structure of our models are different, herein, we have one latent class and two infective classes, and assume that recovered individuals can either become latently infected upon reinfection [35] or may with some small probability directly become actively infected (without treatment, infectious individuals move into the recovered non-state [35]). This is basically due to some degree of acquired immunity from primary infection [36].

TB poses a serious health threat to the survival of mankind as major infection outcomes in humans are latent infection (persistent infection, $\sim 90\%$ of infected) and active TB ($\sim$ 5% of infected) [1]. We are specifically interested in the following question: What is the impact of increasing active TB detection rate (Figure 3) on the dynamics of the latently infected and the total number of active TB cases in the presence or absence of treatment? Gerberry [26] propose a dynamical systems model for the population-level dynamics of TB in order to assess the trade-off which occurs between vaccination and detection/treatment of latent TB, assume that latent infection in vaccinated individuals is completely undetectable. As definitive estimates for some of the model parameters do not exist, mathematical modeling provides an effective means to approach the issue, by assuming within some fairly reasonable range those parameter values for the purpose of illustration. Nevertheless, in this study, some parameter estimates from real data of TB epidemic were graciously provided, courtesy of the Central Statistics Office of Zimbabwe (CSOZ).

In the next section, we formulate and analyze the model while numerical simulations are carried out in Section 3. The last section concludes the paper.

2. Model formulation

We develop a mathematical model of the transmission dynamics of TB incorporating the effects of case detection and treatment between the following five mutually exclusive compartments: individuals susceptible to the disease $S(t)$, those exposed to TB or latently infected $E(t$, these individuals are infected but are yet to develop active TB (asymptomatic); infectives unaware of their TB status $I_1(t)$, these are infectious individuals harbouring active TB; infectives who know their TB status after being detected $I_2(t)$ and are on treatment; recovered $R(t)$, who were previously infected and "successfully" treated. The total population size is $N(t)$, given by

$$N(t) = S(t) + E(t) + I_1(t) + I_2(t) + R(t). \tag{1}$$

Individuals enter the susceptible class at a constant rate Λ through birth and/or migration. This class becomes infected with Mtb at a time-dependent rate $\lambda(t)$, given by

$$\lambda(t) = \frac{\beta c(I_1(t) + \gamma I_2(t))}{N(t)}, \tag{2}$$

where β is the probability of infection; c is the per capita (or effective contact) rate; $\gamma \leq 1$ models the fact that individuals who have been detected as having

active TB and put on treatment are less infectious (assuming treatment reduces infectiousness and hence transmissibility) than their corresponding counterparts (that is, γ is an implicit function of the treatment rate r, with the constraint $\gamma(0) = 1$). Individuals in the different compartments experience natural death at a constant rate μ. A proportion f of the Mtb-infected individuals move to the latently infected state $E(t)$, while the remaining proportion of the infected $(1 - f)$ develop fast TB and progress into the $I_1(t)$ class. It is important to note that we use the popular two way paths $f\lambda$ and $(1 - f)\lambda$. However, this may not reproduce the observed exponential progression pattern which can be achieved using two latent classes [4, 6, 46], since we are considering one latent class and two infectious classes. Individuals in the $E(t)$ class progress to active TB at rates k and $\delta\lambda$ for endogenous reactivation and exogenous re-infection (of $\sim 510\%$ of latently infected [1]), respectively with $\delta < (1 - f) < 1$ (this is consistent with the observation in [31]) since latent individuals have acquired partial immunity, which reduces the risk of subsequent infection, but does not completely prevent it [29]. Some individuals in the $I_1(t)$ class are detected as having active TB at a rate ρ and move into the $I_2(t)$ class which is the class for the detected active TB cases on treatment. Individuals in $I_2(t)$ are treated at a rate r. Of the individuals on treatment, a proportion p completes treatment and moves into the recovered class $R(t)$. The remainder $(1 - p)$ will stop taking on the medication and move back to the latently infected class. Individuals in the active TB classes $I_1(t)$ and $I_2(t)$) suffer from disease-induced death at a rate d. Those who would have recovered from TB as a result of treatment in class $R(t)$ are not totally immune from re-infection, and are thus, re-infected at a rate $\sigma\lambda$, with $\sigma < 1$ accounting for partial immunity as a result of previous infection. Most people are assumed to mount an effective immune response to the initial infection that limits proliferation of the bacilli and leads to long-lasting *partial immunity* both to further infection and to reactivation of latent bacilli remaining from the original infection [24, 39]. Nevertheless, some few individuals (however small) in this category may still develop active TB as a consequence of exogenous reinfection, i.e., acquiring a new infection from another infectious individual [24]. A proportion $(1 - f)$ of those in $R(t)$ will develop fast TB and move into $I_1(t)$, while the complementary proportion f will move into the latent state, $E(t)$ due to re-infection. We note that some individuals in this class are reinfected and remain latent, and consequently, we do not account for such since their disease status remains unchanged.

The structure of the model is depicted in Figure 1, and based on our model description and assumptions, we establish the following model equations.

$$\begin{aligned} S'(t) &= \Lambda - \lambda S - \mu S, \\ E'(t) &= f\lambda(S + \sigma R) + (1 - p)rI_2 - (k + \mu + \delta\lambda)E, \\ I_1'(t) &= \lambda(1 - f)(S + \sigma R) + (k + \delta\lambda)E - (\mu + \rho + d)I_1, \\ I_2'(t) &= \rho I_1 - (\mu + d + r)I_2, \quad R'(t) = prI_2 - (\mu + \sigma\lambda)R. \end{aligned} \tag{3}$$

The first octant of system (3) is positively invariant and attracting, and solutions starting in there where all the variables are non-negative stay there. Thus, system (3) will be analyzed in a suitable region $\Omega \subset \mathbb{R}^5_+$, given by

$$\Omega = \left\{ (S, E, I_1, I_2, R) \in \mathbb{R}^5_+ : N \leq \frac{\Lambda}{\mu} \right\}, \tag{4}$$

which is positively invariant and attracting. Existence, uniqueness and continuation results for system (3) hold in this region. Furthermore, in the absence of case detection (ρ) and treatment (γ), we have $\rho = 0$ and $\gamma = 0$ respectively.

2.1. Disease free-equilibrium and stability analysis. The disease-free equilibrium of model system (3) is given by

$$\mathbf{E^0} = (S^0, E^0, I_1^0, I_2^0, R^0) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0 \right). \tag{5}$$

Following van den Driessche and Watmough [43], the reproduction number for model system (3) is given by

$$\mathbf{R_{D_T}} = \frac{\beta c(k+(1-f)\mu)(\mu+d+r+\gamma\rho)}{(k+\mu)[d^2+\mu(r+\mu)+d(\rho+r+2\mu)]+\rho(\mu(\mu+r)+k(pr+\mu))}. \tag{6}$$

This disease threshold number is defined as the number of new infections produced by a typical infectious individual introuced into a totally naive population where there is detection and treatment of active TB. From Theorem 2 in [43], the following result is established.

Theorem 1. *The disease-free equilibrium* $\mathbf{E^0}$ *is locally asymptotically stable whenever* $\mathbf{R_{D_T}} < 1$*, and unstable otherwise.*

2.1.1. Analysis of the reproduction number, $\mathbf{R_{D_T}}$. In the absence of case detection ($\rho = 0$) and treatment ($r = 0$), we have

$$\lim_{(\rho,r)\to(0,0)} \mathbf{R_{D_T}} = \mathbf{R_0} = \frac{\beta c(k+(1-f)\mu)}{(k+\mu)(\mu+d)}, \tag{7}$$

which is the basic reproduction number (threshold number in the absence of any of the control measures). If case detection alone is introduced, then,

$$\lim_{r\to 0} \mathbf{R_{D_T}} = \mathbf{R_D} = \frac{\beta c(k+(1-f)\mu)(\mu+d+\gamma\rho)}{(k+\mu)(\mu+d)(\mu+d+\rho)} = \frac{\mu+d+\gamma\rho}{\mu+d+\rho}\mathbf{R_0} = \mathbf{H_1 R_0}. \tag{8}$$

Since $\mathbf{H_1} = \frac{\mu+d+\gamma\rho}{\mu+d+\rho} < 1$, TB case detection alone will help in reducing initial disease transmission. Differentiating $\mathbf{R_D}$ with respect to the case finding parameter ρ, we have

$$\frac{\partial \mathbf{R_D}}{\partial \rho} = -\frac{(\mu+d)(1-\gamma)}{(\mu+d+\rho)^2}\mathbf{R_0} < 0. \tag{9}$$

The above inequality (9) further confirms that increasing the rate of case finding of active TB patients has a positive impact on TB control [33], and thus enhance efforts to curtail the epidemic. Effects of active TB treatment alone have been

shown to have a positive impact on TB control (see Bhunu et al. [8]) and will not be discussed here. Rewriting $\mathbf{R_{D_T}}$ as

$$\mathbf{R_{D_T}} = \frac{\mu + d + r + \gamma\rho}{\mu + d + r + \rho - \frac{\mu\rho}{d+\mu} + \rho\frac{\mu(\mu+r)+k(pr+\mu)}{(k+\mu)(d+\mu)}}\mathbf{R_0} = \mathbf{H_2}\mathbf{R_0},$$

where

$$\mathbf{H_2} = \frac{\mu + d + r + \gamma\rho}{\mu + d + r + \rho - \frac{\mu\rho}{d+\mu} + \rho\frac{\mu(\mu+r)+k(pr+\mu)}{(k+\mu)(d+\mu)}} < 1,$$

It can be shown after some little algebraic manipulations that $\mathbf{H_2} - \mathbf{H_1} < 0$, implying that concurrently combining case finding and treatment has a greater impact in reducing initial disease transmission than taking these measures one at a time.

Impact of the case detection in TB control
Equation (9) can be re-written as

$$\frac{\partial \mathbf{R_D}}{\partial \rho} = -\frac{\beta c}{(\mu+d+\rho)^2}(1-\Theta) < 0, \tag{10}$$

where $\Theta = \frac{f\mu}{k+\mu}$. The impact of case detection is dependent on the sign of this threshold quantity, Θ. Since $\mathbf{R_D}$ is a decreasing function of ρ, then, case detection will have a positive impact if $\Theta < 1$, no impact if $\Theta = 1$ and a negative impact if $\Theta > 1$. The last two cases are biologically unrealistic as case detection will always have a positive impact on TB control. This is consistent with the simulations shown in Figure 3. With some reasonable TB parameter values, the quantity Θ is always less than unity, suggesting that case detection will always have a positive impact on TB dynamics.

We now investigate the effects of case detection in the presence of treatment by differentiating $\mathbf{R_{D_T}}$ with respect to ρ, which yields,

$$\frac{\partial \mathbf{R_{D_T}}}{\partial \rho} = -\frac{\beta c(k+(1-f)\mu)(\mu+d+r)[(\mu+k)(\mu+d)(1-\gamma)+r(\mu+kp)]}{((k+\mu)[d^2+\mu(r+\mu)+d(\rho+r+2\mu)]+\rho(\mu(\mu+r)+k(pr+\mu)))^2} < 0, \tag{11}$$

implying that increase of case finding will have a greater impact if accompanied by treatment. In general not all detected TB cases are put on treatment, meaning $\rho \geq r$. What happens when all people who have been detected as having active TB are put on treatment? To answer this question we have to consider what happens when $\rho = r$. Letting $\rho = r$, $\mathbf{R_{D_T}}$ reduces to

$$\mathbf{R_{D_{T_1}}} = \frac{\beta c(k+(1-f)\mu)(\mu+d+\rho+\gamma\rho)}{(k+\mu)[d^2+\mu(\rho+\mu)+d(\rho+\rho+2\mu)]+\rho(\mu(\mu+\rho)+k(p\rho+\mu))}. \tag{12}$$

Subtracting $\mathbf{R_{D_{T_1}}}$ from $\mathbf{R_{D_T}}$, we obtain

$$\begin{aligned}\Delta &= \mathbf{R_{D_T}} - \mathbf{R_{D_{T_1}}} \\ &= \frac{\gamma\rho\beta c(k+(1-f)\mu)(\rho-r)[\gamma\rho(\mu+kp)+(\mu+d)(k(p-\rho)+\theta_1\gamma p)]}{(\theta_1(d^2+(\mu+2d)\theta_2)+\rho(\mu\theta_2+\theta_4))(\theta_1(d^2+\mu\theta_3+d(\theta_2+\theta_3))+\rho(\mu\theta_3+\theta_5))} > 0,\end{aligned} \tag{13}$$

where $\theta_1 = k+\mu$, $\theta_2 = \rho+\mu$, $\theta_3 = r+\mu$, $\theta_4 = k(p\rho+\mu)$, $\theta_5 = k(pr+\mu)$. Since equation (13) is positive, putting all detected TB cases on treatment will have

a greater positive impact on TB control than treating a portion of the detected cases. This suggests that increasing case finding accompanied by treatment of all the the detected cases may achieve better TB control (albeit no development of resistance).
The disease-free equilibrium may not be globally asymptotically stable owing to the model exhibiting the phenomenon of backward bifurcation where a stable disease-free equilibrium co-exists with a stable endemic equilibrium, for a certain range of the associated reproduction number less than unity.

2.2. Endemic equilibrium and stability analysis. The endemic equilibrium (EE) of system (3) is given by $\mathbf{E}^* = (S^*, E^*, I_1^*, I_2^*, R^*)$ where in terms of the force of infection λ^*,

$$\begin{aligned}
&S^* = \tfrac{\Lambda}{\mu+\lambda^*},\ I_1^* = \tfrac{\Lambda a_4 a_5 \lambda^*(a_2-\mu f)}{a_1\rho\{\rho p r(\sigma\lambda^*(a_2-\mu f)+a_5(-a_2a_3a_4+(1-p)r(k+\delta\lambda^*)\rho)\}},\\
&I_2^* = \tfrac{\rho}{\mu+d+r} I_1^*,\ E^* = \tfrac{(\mu+\rho+d)I_1^* - \lambda^*(1-f)(S^*+\sigma R^*)}{k+\delta\lambda^*},\\
&R^* = \tfrac{pr\rho}{(\mu+\sigma\lambda^*)(\mu+d+r)} I_1^*.
\end{aligned} \tag{14}$$

with

$$\begin{aligned}
&a_1 = \mu+\lambda^*,\ a_2 = k+\mu+\delta\lambda^*,\ a_3 = \mu+\rho+d,\\
&a_4 = \mu+d+r,\ a_5 = \mu+\sigma\lambda^*.
\end{aligned} \tag{15}$$

By making the following change of variables $S = x_1,\ E = x_2,\ I_1 = x_3,\ I_2 = x_4,\ x_5 = R$, so that $N(t) = \sum_{n=1}^{5} x_n$ and using the vector notation $X = (x_1, x_2, x_3, x_4, x_5)^T$, model system (3) under these conditions can be rewritten in the form $\frac{dX}{dt} = (f_1, f_2, f_3, f_4, f_5)$, such that

$$\begin{aligned}
x_1'(t) &= f_1 = \Lambda - \tfrac{\beta c(x_3+\gamma x_4)x_1}{\sum_{n=1}^{5} x_n} - \mu x_1,\\
x_2'(t) &= f_2 = \tfrac{f\beta c(x_3+\gamma x_4)(x_1+\sigma x_5)}{\sum_{n=1}^{5} x_n} - (\mu+k)x_2 - \delta\tfrac{\beta c(x_3+\gamma x_4)x_2}{\sum_{n=1}^{5} x_n} + (1-p)rx_4,\\
x_3'(t) &= f_3 = \tfrac{\beta c(1-f)(x_3+\gamma x_4)(x_1+\sigma x_5)}{\sum_{n=1}^{5} x_n} + kx_2 + \delta\tfrac{\beta c(x_3+\gamma x_4)x_2}{\sum_{n=1}^{5} x_n} - (\mu+d+\rho)x_3,\\
x_4'(t) &= f_4 = \rho x_3 - (\mu+d+r)x_4,\\
x_5'(t) &= f_4 = prx_4 - \mu x_5 - \sigma\tfrac{\beta c(x_3+\gamma x_4)x_5}{\sum_{n=1}^{5} x_n}.
\end{aligned} \tag{16}$$

To analyze the stability of this equilibrium point we make use of the Centre Manifold theory [14] as described in Theorem 4.1 of Castillo-Chavez and Song [16]. The Jacobian matrix of system (16) at $\mathbf{E^0}$ is given by

$$J(\mathbf{E^0}) = \begin{bmatrix}
-\mu & 0 & -\beta c & -\gamma\beta c & 0\\
0 & -(\mu+k) & f\beta c & \gamma f\beta c + (1-p)r & 0\\
0 & k & (1-f)\beta c - (\mu+d+\rho) & (1-f)\gamma\beta c & 0\\
0 & 0 & \rho & -(\mu+d+r) & 0\\
0 & 0 & 0 & pr & -\mu
\end{bmatrix}. \tag{17}$$

From matrix (17), it follows that the reproduction number is $\mathbf{R_{D_T}}$ as defined in (6). If β is taken as a bifurcation parameter, then, bifurcation takes place at $\beta = \beta^*$. Let $\mathbf{R_{D_T}} = 1$, solving for β we have

$$\beta = \beta^* = \frac{(k+\mu)[d^2+\mu(r+\mu)+d(\rho+r+2\mu)]+\rho(\mu(\mu+r)+k(pr+\mu))}{c(\mu(1-f)+k)(\mu+d+r+\gamma\rho)}. \tag{18}$$

The linearized system of the transformed equation (16) with $\beta = \beta^*$ has a simple zero eigenvalue, hence the Centre Manifold theory [14], can be used to analyze the dynamics of (16) near $\beta = \beta^*$. It can be shown that the Jacobian of (16) at $\beta = \beta^*$ has a right eigenvector associated with the zero eigenvalue given by $w = [w_1, w_2, w_3, w_4, w_5]^T$ where,

$$\begin{aligned} &w_1 = -\frac{\{(\mu+d+r+\gamma\rho)\beta^* c\}w_3}{\mu(\mu+d+r)},\ w_2 = \frac{\{(\mu+d+r+\gamma\rho)f\beta^* c+(1-p)\rho r\}w_3}{(\mu+k)(\mu+d+r)},\\ &w_3 = w_3 > 0,\ w_4 = \frac{\rho w_3}{\mu+d+r},\ w_5 = \frac{pr\rho w_3}{\mu(\mu+d+r)}. \end{aligned} \tag{19}$$

The left eigenvector of $J(\mathbf{E^0})$ associated with the eigenvalue at $\beta = \beta^*$ is given by $z = [z_1, z_2, z_3, z_4, z_5]^T$ where,

$$z_1 = 0,\ z_2 = \frac{kz_3}{\mu+k},\ z_3 = z_3 > 0,\ z_4 = \frac{\{\gamma\beta c(\mu(1-f)+k)+(1-p)rk\}z_3}{(\mu+k)(\mu+d+r)},\ z_5 = 0. \tag{20}$$

Note that by treating latently infected individuals and moving them to the recovered class we actually subject them to higher rates of reinfection, thus, a strong possibility exists that the treatment of latent individuals may increase disease prevalence in some settings despite increasing the stability of the disease-free equilibrium [26]. One way in which such behavior could be observed analytically would be by proving the existence of a backwards bifurcation in which the disease persists despite having $\mathbf{R_{D_T}} < 1$. In order to establish the conditions for the existence of backward bifurcations, we use the approach in Castillo-Chavez and Song [16] (Theorem 4.1).

Computations of the bifurcation parameters a and b

For system (16), the non-zero partial derivatives of $F = (f_1, f_2, f_3, f_4, f_5)$ associated with b at $\beta = \beta^*$ are

$$\frac{\partial^2 f_2}{\partial x_3 \partial\beta} = fc,\ \frac{\partial^2 f_2}{\partial x_4 \partial\beta} = \gamma fc,\ \frac{\partial^2 f_3}{\partial x_3 \partial\beta} = (1-f)c,\ \frac{\partial^2 f_3}{\partial x_4 \partial\beta} = \gamma(1-f)c. \tag{21}$$

It follows from (21) that

$$b = c(w_2 + \gamma w_3)(fz_2 + (1-f)z_3) > 0. \tag{22}$$

Similarly, the non-zero partial derivatives of F associated with a can be computed and we obtain

$$\begin{aligned} a = &-\frac{2(k+(1-f)\mu)\beta^* c\mu}{(\mu+k)\Lambda}\left[w_3^2 + (1+\gamma)w_3w_4 + (1-\sigma)w_3w_5 + \gamma w_4^2 + \gamma(1-\sigma)w_4w_5\right]z_3\\ &-\frac{2(\mu+k-(\delta+f)\mu)\beta^* c\mu}{(\mu+k)\Lambda}\left[w_2w_3 + \gamma w_2w_3\right]z_3. \end{aligned} \tag{23}$$

Therefore, $a < 0$ whenever $\mu + k > \mu(\delta + f)$ and for some $\mu + k < \mu(\delta + f)$, we have $a > 0$. Let $\phi = \beta - \beta^*$, then, using items (i) and (iv) of Theorem 4.1 in [16], we establish the following results.

Theorem 2. *For some parameter values, if $\mu+k < \mu(\delta+f)$, then model system (3) has a backward bifurcation at $\mathbf{R_{D_T}} = 1$. If $\mu + k > \mu(\delta + f)$, the endemic equilibrium $\mathbf{E}^*$ is locally asymptotically stable for $\mathbf{R_{D_T}}$ close to 1.*

For $a, b > 0$ system (3) can have multiple endemic equilibria (which basically depends on the model structure and the qualitatively properties of its parameters, eg. models with imperfect vaccine [32, 38], exogenous re-infection [30, 33]) for $\mathbf{R_{D_T}} < 1$. Seemingly subtle differences in model assumptions can have significant effects on biological conclusions [17]. This type of behaviour has been observed in epidemiological models in various contexts, driven by the choice of the two way paths $f\lambda$ and $(1 - f)\lambda$ (as backward bifurcation also seems to depend of this choice). The phenomenon of backward (subcritical) bifurcation in disease models, where a stable endemic equilibrium coexists with a stable disease-free equilibrium when the associated reproduction number is less than unity, has important public health implications for disease control [37]. In such a scenario, the classical requirement of the reproduction number being less than unity is only necessary, but not a sufficient condition for disease elimination. Consequently, extra control strategies such as educational campaigns, treatment compliance, poverty eradication, quitting smoking and vaccination to name a few are concurrently needed to curtail the TB epidemic. For $a < 0$, the model exhibits a forward or transcritical bifurcation.

Role of case detection and treatment on the backward bifurcation
$\hbar_1 = -\frac{2(k+(1-f)\mu)\beta^* c\mu}{(\mu+k)\Lambda}$, $\hbar_2 = -\frac{2(\mu+k-(\delta+f)\mu)\beta^* c\mu}{(\mu+k)\Lambda}(1+\gamma)w_3 z_3$. Then, differentiating a partially with respect to the case detection rate, ρ, we obtain

$$\begin{aligned} \frac{\partial a}{\partial \rho} &= -\frac{\hbar_1 w_3^2 z_3}{\mu+d+r}\left[(1+\rho)+(1-\sigma)p\frac{r}{\mu}+\frac{2\gamma\rho}{\mu+d+r}\left\{1+(1-\sigma)p\frac{r}{\mu}\right\}\right] \\ &\quad -(1+\gamma)\hbar_2 w_3^2 z_3 \frac{c\gamma f\beta^*+(1-p)r}{(\mu+k)(\mu+d+r)} < 0. \end{aligned} \tag{24}$$

The bifurcation coefficient a is a decreasing function of ρ, and the possibility of this phenomenon occurring decreases with increases in case detection. The more we detect people harbouring any form of TB (with the assuming that they will eventually have access to treatment), the less likely it is that backward bifurcation can arise. Also,

$$\begin{aligned} \frac{\partial a}{\partial r} &= -\rho z_3 \hbar_1 \frac{w_3^2}{(\mu+d+r)^2}\left[(1-\sigma)\frac{p}{\mu}\left(\mu+d+\frac{\mu+d-r}{\mu+d+r}r\gamma\right)-(1+\gamma)\right] \\ &\quad -(1-\gamma)\rho\hbar_2\frac{z_3}{\mu+k}\left(\frac{w_3}{\mu+d+r}\right)^2\{pr-(\mu+d+r)(p+\gamma-1)\}. \end{aligned} \tag{25}$$

We note that the expression in the square brackets is negative. Therefore, let $B_1 := (1+\gamma) - (1-\sigma)\frac{p}{\mu}\left(\mu + d + \frac{\mu+d-r}{\mu+d+r}r\gamma\right)$, $B_2 := pr - (\mu+d+r)(p+\gamma-1)$, then,
after some little manipulation and re-arrangement, equation (25) is negative provided the following inequality holds:

$$\frac{k+(1-f)\mu}{k+(1+f-\delta)\mu}B_1 < \frac{1-\delta}{k+\mu}B_2. \tag{26}$$

Consequently, if inequality (26) holds, then, the backward bifurcation coefficient a will be a decreasing function of the treatment rate r, and its possibility occurring decreases with increasing r. This result is solely driven by the fact that treatment is assumed 100% effective.
bf Remark: The condition $\mu + k < \mu(\delta + f)$ for which the model undergoes backward bifurcation can be rewritten as $\delta > (1-f) + \frac{k}{\mu}$. The consensual view that infection induces partial immunity to subsequent infections implies that $\delta < (1-f)$, therefore, backward bifurcation may not be biologically realistic. Consequently, the higher the susceptibility to reinfection the easier it will be to achieve control and/or eradication of TB[13].

3. Numerical simulations

To numerically assess the effectiveness of therapy for detected tuberculosis infections (both latent and active) in reducing the prevalence of the disease, we use the standard fourth-order Runge-Kutta numerical scheme (coded in C++ programming language), and parameter values in Table 1.

In Table 1, CSOZ means Central Statistics Office of Zimbabwe. Figure 2 is a graphical representation showing the impact case findings of individuals harbouring active TB has on TB transmission dynamics in the absence of treatment. The graphs suggest that TB case detection of active TB have some partial positive degree in the control of TB as noted by a small reduction in the latently infected class (Figure 2 (b)) and small rate of decrease in the susceptible class (Figure 2 (a)) as case detection rates are increased. This tends to suggest that case detection alone is not enough in the fight against the TB epidemic. Next, we illustrate the effect active TB case findings has on TB transmission dynamics when it is accompanied with active TB treatment (this is shown in Figure 3). It is noted that increasing active TB detection rate (Figure 3) when accompanied with treatment is most beneficial to the community as noted by an increase of the susceptibles (Figure 3 (a)), decrease of the latently infected (Figure 3 (b)) and decrease of the total number of TB cases (Figure 3 (c)). Case detection is a necessary step towards reducing disease burden and should be accompanied by adequate measures such as treatment, counselling patients on treatment compliance and completion (to avoid development of resistance). Finally, we illustrate the effect of treatment compliance and completion (of their medication course) on the transmission dynamics of TB. Figure 4 is a graphical representation showing the effect of ensuring that TB patients on treatment fully complete

their medication course. All the graphs in Figure 4 show that an increase in the number of TB patients who complete their treatment has a positive effect on TB control. This is noted by a decrease of latently infected and active TB cases as the number of people who complete their medication course increases.

4. Conclusion

A deterministic TB model which captures the effects of case finding and treatment strategy is formulated and analysed. The model is shown to undergo the phenomenon of backward bifurcation at $\mathbf{R_{D_T}} = 1$. Below, we summarize some of the main theoretical and epidemiological findings of the study: While Okuonghae and Korobeinikov [34] obtained a critical detection level below which the disease-free equilibrium is unstable even with such a very high probability of successful treatment (88%), we derived a critical threshold parameter Θ, say for which case detection will have positive, negative or no impact on the disease dynamics. Analysis of the reproduction number suggests that concurrently increasing active TB case finding accompanied by treatment (if sustained and well implemented) of detected TB cases has a greater impact on TB dynamics than applying these measures singly. The model may exhibit the phenomenon of backward bifurcation under certain conditions. It occurrence decreases with increasing case detection rate (ρ), and may increase or decrease with increasing treatment rate (r), depending on whether treatment is 100% effective, and the development of resistance. Case detection alone was analytically shown to also have positive impact on TB control. Its impact depends on the sign of a certain threshold parameter Θ, and for $\Theta \leq 1$, case detection will always have a positive or no impact. We note however that from TB epidemiology, realistic parameter values always yield $\Theta < 1$. Consequently, case detection will always have a positive impact on the control and reduction of TB burden. Numerical simulations which support the analytical results tend to suggest that increase in case finding accompanied by treatment of detected TB cases, result in a marked decrease of TB cases (both latent and active TB). Thus, the prospect of effectively controlling TB in a community increases with increased case detection. Increase in the number of people who complete their treatment is beneficial in the fight against TB (especially to avert TB resistance, this is addressed elsewhere). Thus, results from the study agrees with the conclusion in [2]. They highlight the potential effectiveness of active case finding of tuberculosis patients with limited access to DOTS facilities in the developing country setting. Thus, TB control starts with case findings, especially in resource-limited settings where there is an urgent need to increase case finding (both latent and active) efforts, place all detected TB cases on treatment and ensuring that individuals under therapy comply an complete their treatment. Consequently, educational campaigns should emphasize on treatment compliance (which should be given prominence). Also, programs such as contact tracing, which identify and treat contacts of persons infected with Mtb, may have a substantial effect on controlling tuberculosis epidemics

[46]. The proposed study is not exhaustive and can be extended in various ways by incorporating; imperfect vaccine, vaccine waning immunity, treatment efficacy, resistant and sensitive TB strains to name a few. Also, treatment efficacy combined with compliance and development of resistance are viable and will be given prominence elsewhere.

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C. P. Bhunu PhD (National University of Science and Technology, Zimbabwe) His research interests include differential equations, mathematical epidemiology, and mathematical ecologyical computation.

Department of Applied Mathematics, National University of Science and Techology, AC 939 Ascot, Bulawayo, Zimbabwe.
e-mail: cpbhunu@gmail.com

Visiting Fellow, Clare Hall College University of Cambridge, CB3 9AL, UK.
e-mail: cb655@cam.ac.uk

S. Mushayabasa MSc. (National University of Science and Technology, Zimbabwe) His research interests are in biomathematics.

Department of Applied Mathematics, National University of Science and Techology, AC 939 Ascot, Bulawayo, Zimbabwe.
e-mail: steadymushaya@gmail.com

G. Magombedze PhD. (National University of Science and Technology, Zimbabwe) His research interests are in biomathematics.

University of Cape Town,Computational Biology, IIDMM. Obs, Anzio Rd, 7925, Cape Town, South Africa.
e-mail: gmagombedze@gmail.com

L.-I. Roeger PhD. (Purdue University) Her research interests are in Dynamical systems, differential equations, difference equations, nonstandard finite difference schemes, mathematical epidemiology, and mathematical ecology.

Department of Mathematics and Statistics Texas Tech University, USA.
e-mail: lroeger@gmail.com

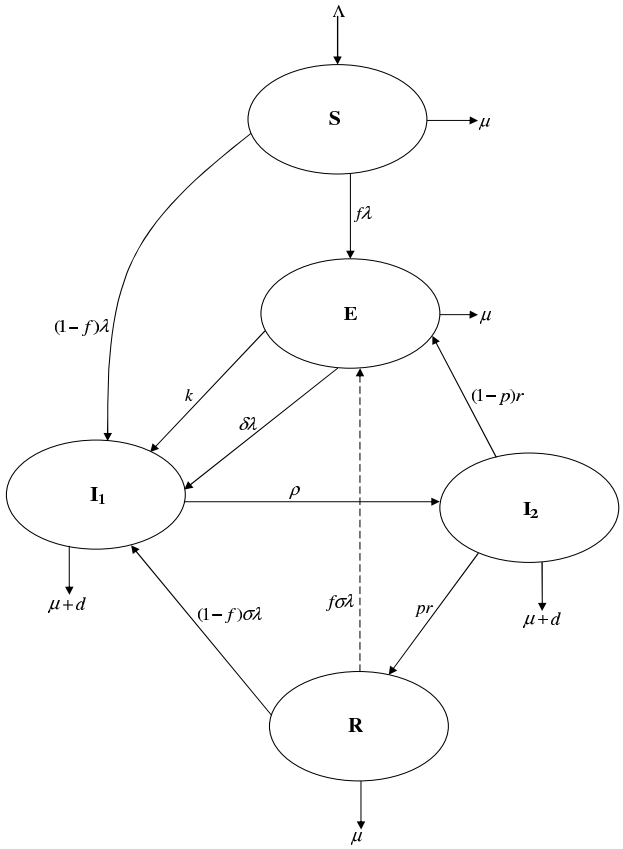

FIGURE 1. Structure of the model system (3).

TABLE 1. Model parameters and their interpretations.

Definition	**Symbol**	**Assumed(Range)($\mathbf{yr}^{-1}$)**	**Source**
Recruitment rate	Λ	0.029*3000000	CSOZ
Natural mortality rate	μ	0.02	CSOZ
Effective contact rate for TB transmission	c	3	Assumed
TB induced death rate	d	0.3	[22, 23]
Probability of TB transmission per contact	β	0.35 (0.1-0.6)	[22, 23]
Modification parameter	γ	0.4	Assumed
Proportion fully completing treatment	p	0.80	Assumed
Active TB case finding rate	ρ	0.88	Assumed
Endogenous reactivation rate	k	0.00013 (0.0001-0.0003)	[22, 23]
Treatment rate for the infectives	r	0.88	[7]
Protective factor for the exposed	δ	0.4	[8]
Protective factor for the removed	σ	0.9	[8]
Rate of developing active TB	$1-f$	0.7	[8]

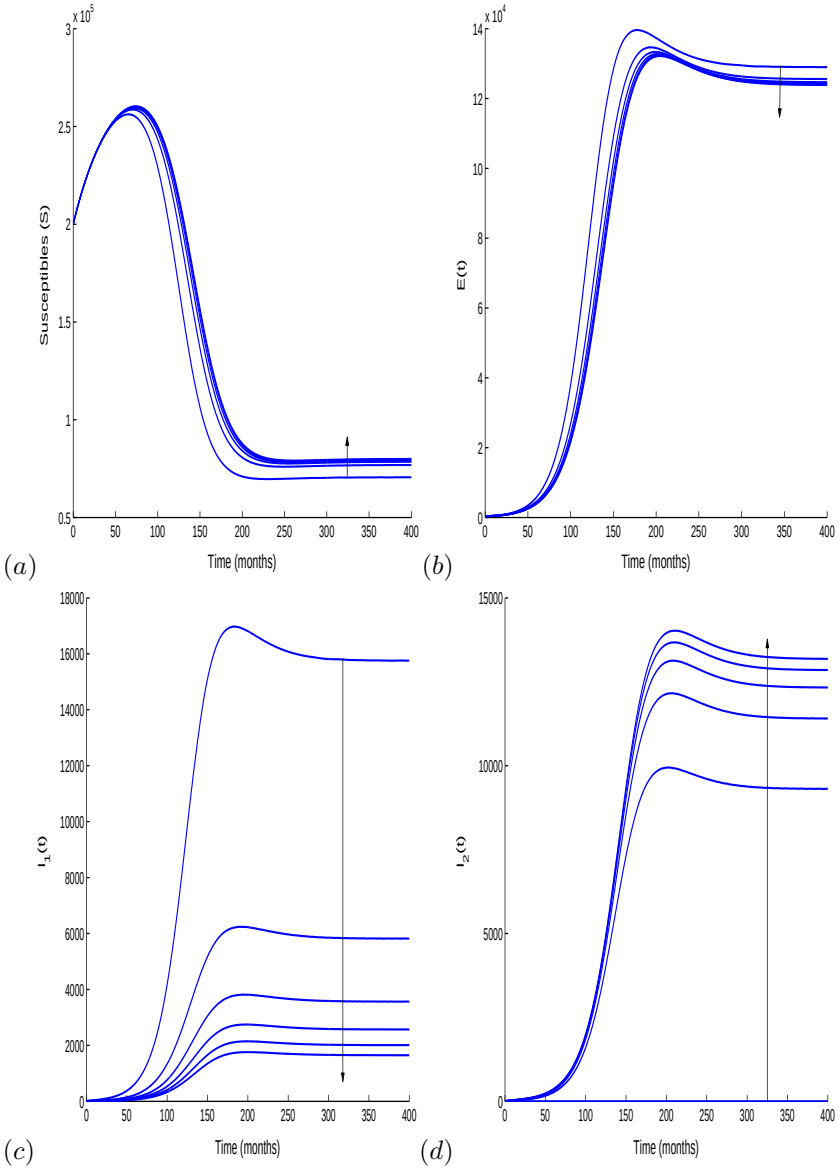

FIGURE 2. Effects of varying active TB case finding rate in the absence of treatment starting from $\rho = 0$ and increasing with a step size of 0.2 up to 1. The direction of arrow shows the increase in case finding rates. Parameter values used are in Table 1.

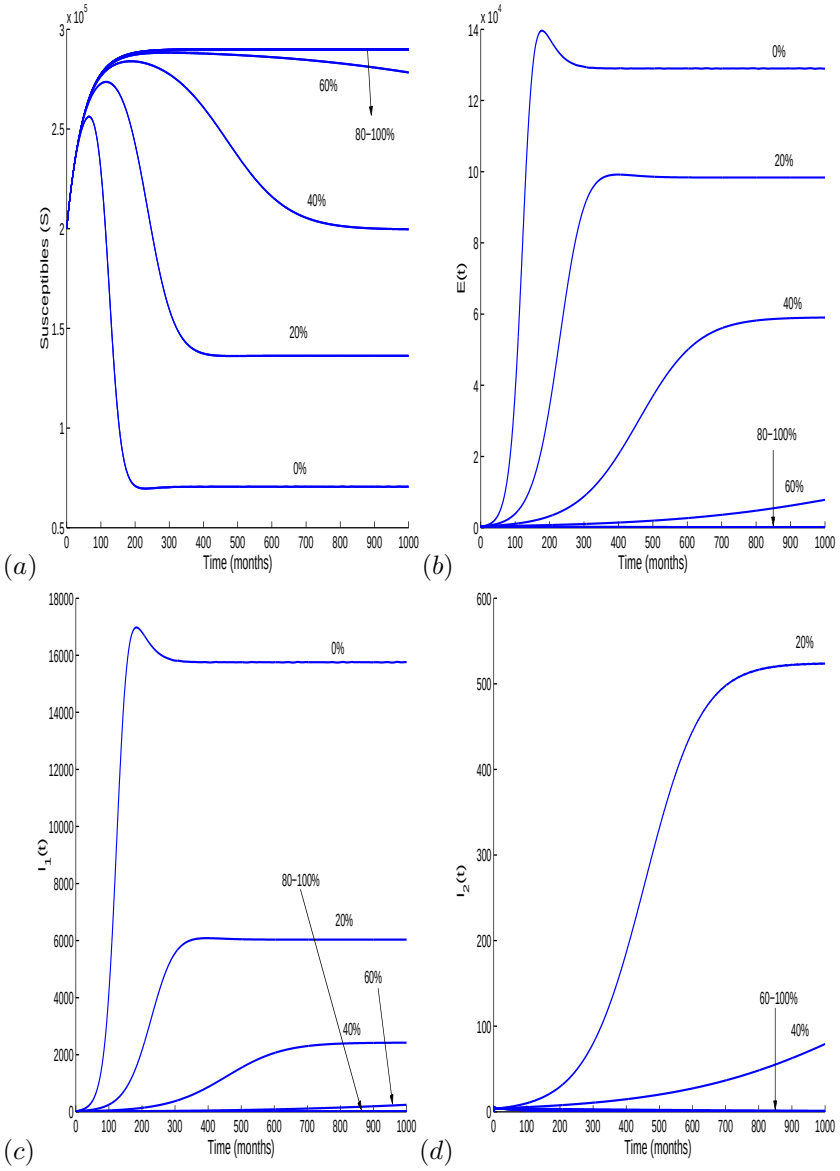

FIGURE 3. Effects of increasing the percentage of active TB detected in the presence of treatment. Parameter values used are in Table 1.

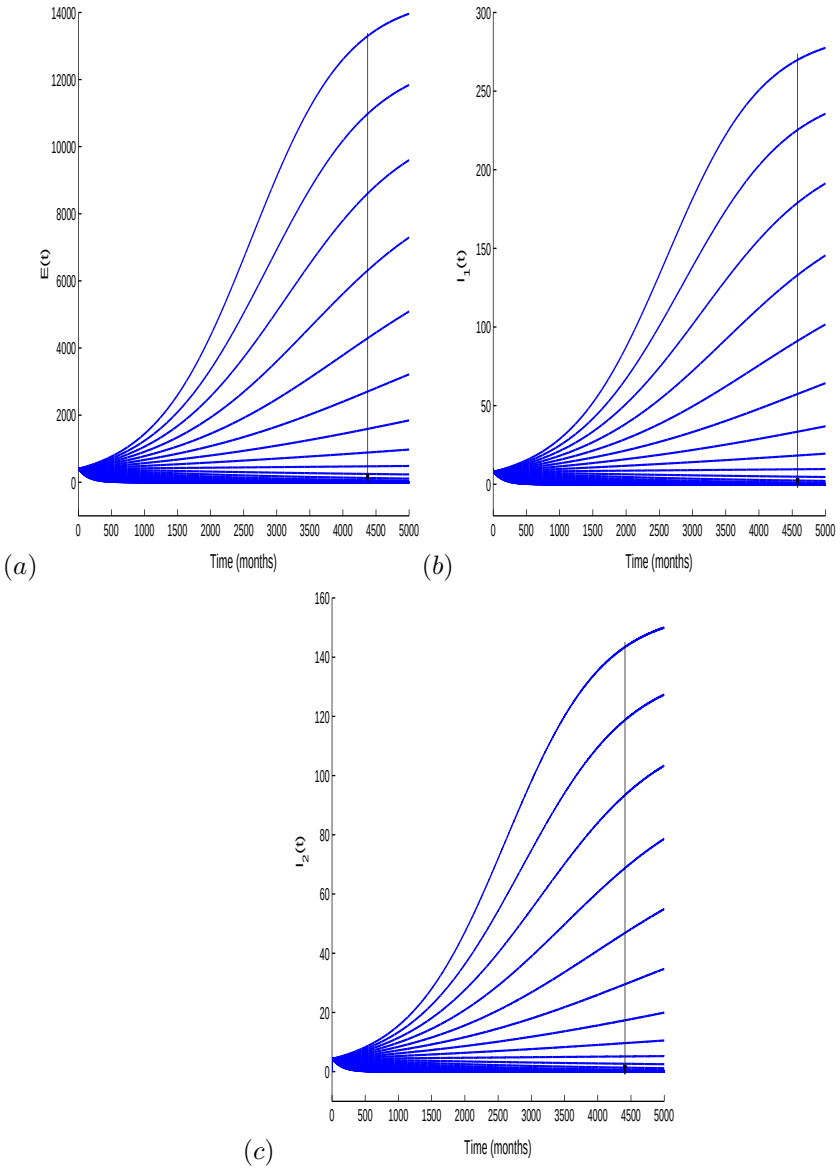

FIGURE 4. Effects of varying TB treatment completion rate starting with $p = 0.0$ and increasing with a step size of 0.01 up to 1. The direction of the arrow shows the direction of increase. Parameter values used are in Table 1.