Modeling the impact of early therapy for latent tuberculosis patients and its optimal control analysis

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Abstract Effective tuberculosis (TB) control depends on case findings to discover infectious cases, investigation of contacts of those with TB, as well as appropriate treatment. Adherence and successful completion of the treatment are equally important. Unfortunately, due to a number of personal, psychosocial, economic, medical, and health service factors, a significant number of TB patients become irregular and default from treatment. In this paper, a mathematical model is developed to assess the impact of early therapy for latent TB and non-adherence on controlling TB transmission dynamics. Equilibrium states of the model are determined and their local stability is examined. With the aid of the center manifold theory, it is established that the model undergoes a backward bifurcation. Qualitative mathematical analysis of the model suggests that a high level of latent tuberculosis case findings, coupled with a decrease of defaulting rate, may be effective in controlling TB transmission dynamics in the community. Population-level effects of organized campaigns to improve early therapy and to guarantee successful completion of each treatment are evaluated through numerical simulations and presented in support of the analytical results.

Keywords Tuberculosis · Therapy adherence · Case findings · Reproductive number · Optimal control

Mathematics Subject Classifications (2010) 92B05 · 93A30 · 93C15

1 Introduction

Tuberculosis (TB) is a global health concern. It is a major cause of illness and death worldwide, especially in low- and middle-income countries where it is fueled by human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), by population increase where TB is most prevalent, and by increased poverty [1, 2]. For example,

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TB is the most common infection for the estimated 5.5 million South Africans living with HIV/AIDS (in a national population of some 48 million). The co-infection rate of HIV is estimated at 73% in all TB cases. The estimated incidence of TB in South Africa is 692 per 100,000 people [2, 3], a rate the World Health Organization (WHO) classifies as a serious epidemic. Even though the Directly Observed Therapy Shortcourse (DOTS) program has been active since 1995, TB remains a major health problem in South Africa and especially in the Eastern Cape [4]. The cure rate of 65% remains well below the 85% rate recommended by the WHO [2, 3]. At 41%, the Eastern Cape's cure rate lags even further behind the national average [5].

Adhering to a treatment schedule and successfully completing it are crucial to the control of any global disease [6–9]. Poor adherence to self-administration of treatment of a chronic disease is a common behavioral problem [8, 10–12] including in patient suffering from TB [11–15] and leprosy [16–18]. Health-seeking behavior and non-adherence to therapy have been cited as major barriers to the control of TB [12, 19–31]. Non-adherence is a complex, dynamic phenomenon with a wide range of interacting factors impacting treatment-taking behavior [28]. It poses a significant threat to both the individual patient and public health and is associated with higher transmission rates, morbidity, and costs of TB control programs [2, 28]. Furthermore, it leads to persistence and resurgence of TB and is regarded as a major cause of relapse and drug resistance [2, 21, 32].

The World Health Organization defines a defaulter as a patient who does not complete the stipulated course of treatment [7]. Other terms used synonymously in common parlance are absentees, or people who exhibit discontinuation, non-compliance, non-adherence, etc., each having slightly different connotations.

In a number of national programs, as many as 48% of newly detected tuberculosis patients have been considered defaulters [11, 12]. As long as defaulters continue to live in their place of residence and have yet to complete the full course of TB treatment, they remain potential sources of infection and the patients may suffer from irreversible complications such as developing multidrug resistant tuberculosis. Reasons for defaulting may be due to a number of personal, psychosocial, economic, medical, and health service factors.

In this paper, we wish to use a deterministic model to investigate the impact of early therapy for non-symptomatic tuberculosis carriers on controlling the dynamics of TB in a community where there is non-adherence. In this study, a defaulter is defined as a patient who has not received TB treatment for two consecutive months and thus who is considered to have discontinued the treatment. The paper is structured as follows. The model is formulated in Section 2 and comprehensively analyzed in Section 3. Expected population effects from improved public health practices are investigated in Section 4 through numerical simulations of the model using parameter values representative of the region. A brief discussion section concludes the paper.

2 Model formulation

Based on epidemiological status, the population is divided into six classes according to the individual's disease status: susceptible population (S), undetected non-symptomatic (latent) carriers (E), detected non-symptomatic (latent) carriers (E_D), symptomatic carriers (I), defaulters (L), and recovered (R). The total population (N) at time t is given by $N = S + E + E_D + I + L + R$. We assume a constant size population with a recruitment

and non-TB-related death rate at time t given by μ . New recruits are assumed susceptible and their recruitment rate is proportional to the population and is given by $\mu N(t)$. The model takes the form:

$$\left. \begin{aligned} S' &= \mu N - \lambda_z S - \mu S, \\ E' &= p\lambda_z S + f\sigma\lambda_z R - (\gamma + k + \mu + \delta\lambda_z)E, \\ E_D' &= \gamma E - (\mu + \alpha + r_1)E_D, \\ I' &= (1-p)\lambda_z S + (1-f)\sigma\lambda_z R + (\delta\lambda_z + k)E + \alpha E_D + \rho L - (r_2 + \mu + d_1)I, \\ L' &= (1-\phi)r_2 I - (\rho + r_3 + \mu + d_2)L, \\ R' &= r_1 E_D + \phi r_2 I + r_3 L - (\mu + \sigma\lambda_z)R. \end{aligned} \right\} \quad (1)$$

Since we are not aware if defaulters have successfully recovered, died due to disease, or are still infectious, we assume that a fraction θ of them are still infectious and can transmit the disease. Assuming homogeneous mixing of the population, susceptible individuals acquire TB infection at rates λ_z , where $\lambda_z = \beta(I + \theta L)/N$. A fraction p of susceptible individuals who acquire TB infection moves to the undetected latent class at the rate λ and the complementary proportion $(1-p)$ undergoes fast progression directly to the infectious class. To account for the level of case findings, we define γ as the rate at which TB cases are detected at the latent stage. These individuals move into the detected latent class where they may receive chemoprophylaxis. Individuals who receive effective chemoprophylaxis are assumed to recover at a rate r_1 while those who do not receive treatment become infectious at a rate α . Undetected non-symptomatic individuals progress to active TB at rate k and can be re-infected at a reduced rate $\delta\lambda$ ($\delta < 1$). Infectious individuals are enrolled in therapy, some of them (a fraction ϕ) complete their treatment and successfully recover at rate r_2 while the rest $(1-\phi)$ default. Some of the individuals who would have defaulted will return to the hospital with the disease (at a constant rate ρ) while others are assumed to have recovered (at rate r_3). Here, we assume that an individual is more susceptible to TB infection as a result of the previous active disease [33–35]. Thus, the parameter $\sigma > 1$ accounts for the increase in susceptibility to re-infection of individuals who have recovered from TB. Natural mortality occurs in all classes at a constant rate μ with infectious and loss of sight individuals suffering additional mortality at rates d_1 and d_2 , respectively, due to the disease.

Figure 1 below depicts the model flow diagram.

Fig. 1 Flow diagram of TB transmission

It is helpful to re-scale system 1 so that we have dimensionless variables. We let

$$s = \frac{S}{N}, \quad e = \frac{E}{N}, \quad e_d = \frac{E_D}{N}, \quad i = \frac{I}{N}, \quad l = \frac{L}{N}, \quad i = \frac{I}{N}, \quad l = \frac{L}{N}, \quad w = \frac{R}{N}.$$

By defining $\lambda = \beta(i + \theta l)$, we have the following re-scaled system

$$\left. \begin{aligned} s' &= \mu - \lambda s - \mu s, \\ e' &= p\lambda s + f\sigma\lambda w - (\gamma + k + \mu + \delta\lambda)e, \\ e_d' &= \gamma e - (\mu + \alpha + r_1)e_d, \\ i' &= (1 - p)\lambda s + (1 - f)\sigma\lambda w + (\delta\lambda + k)e + \alpha e_d + \rho l - (r_2 + \mu + d_1)i, \\ l' &= (1 - \phi)r_2 i - (\rho + r_3 + \mu + d_2)l, \\ w' &= r_1 e_d + \phi r_2 i + r_3 l - (\mu + \sigma\lambda)w. \end{aligned} \right\} \quad (2)$$

3 Analytical results

3.1 Basic properties of the model

Since model system (2) monitors human populations, all its associated parameters are nonnegative. Further, the following non-negativity results hold.

Lemma 1 *The variables of model system (2) are always nonnegative. In other words, solutions of the model system (2) with positive initial data will remain positive for all time $t > 0$.*

Proof Let $t_1 = \sup\{t > 0: s > 0, e > 0, e_d > 0, i > 0, l > 0, z > 0 \in [0, t]\}$. Thus, $t_1 > 0$. It follows from the first equation of system (2) that

$$\dot{s} = \mu - \lambda_z s \geq \mu - (\lambda_z + \mu)s,$$

which can be rewritten as

$$\frac{d}{dt} \left(s(t) \exp \left\{ \mu t + \int_0^t \lambda(\tau) d\tau \right\} \right) \geq \mu \exp \left\{ \mu t + \int_0^t \lambda(\tau) d\tau \right\}.$$

Hence,

$$s(t_1) \exp \left\{ \mu t_1 + \int_0^{t_1} \lambda(\tau) d\tau \right\} - s(0) \geq \int_0^{t_1} \mu \exp \left\{ \mu y + \int_0^y \lambda(\tau) d\tau \right\} dy,$$

so that

$$s(t) \geq s(0) \exp \left\{ -\mu t_1 - \int_0^{t_1} \lambda(\tau) d\tau \right\} \left(\exp \left\{ -\mu t_1 - \int_0^{t_1} \lambda(\tau) d\tau \right\} \right) \quad (3)$$

$$\times \left(\int_0^{t_1} \mu \exp \left\{ \mu y + \int_0^y \lambda(\tau) d\tau \right\} dy \right) > 0. \quad (4)$$

Similarly, it can be shown that $e > 0, e_d > 0, i > 0, l > 0$ and $w > 0$ for all time $t > 0$. $\square$

It can easily be shown that the closed set

$$\Phi = \{(s, e, e_d, i, l, w) \in \mathbb{R}_+^6 : s + e + e_d + i + l + w \leq 1\} \quad (5)$$

is invariant and attracting for system (2), that is, solutions that start in Φ will remain there.

3.2 Disease-free Equilibrium (DFE)

Model system (2) has an evident DFE given by

$$\begin{aligned}\varepsilon^0 &= (s^0, e^0, e_d^0, i^0, l^0, w^0) \\ &= (1, 0, 0, 0, 0, 0).\end{aligned}$$

The linear stability of ε^0 is obtained using the next-generation matrix [36] for system (2). In order to compute the reproductive number, we will classify the subgroups in system (2) into two categories, namely the susceptible group (these are classes whose individuals do not have the disease, the S and R classes) and the infected group (these are components that constitute individuals infected with TB, that is E , E_D , I and L). Using the notation in [36], the nonnegative matrix F that denotes the generation of new infection terms and the non-singular matrix V that denotes the remaining transfer terms are respectively given (at the disease-free equilibrium) by

$$\begin{aligned}F &= \begin{bmatrix} 0 & 0 & p\beta & p\beta\theta \\ 0 & 0 & 0 & 0 \\ 0 & 0 & (1-p)\beta & (1-p)\beta\theta \\ 0 & 0 & 0 & 0 \end{bmatrix}, \\ V &= \begin{bmatrix} M_1 & 0 & 0 & 0 \\ -\gamma & M_2 & 0 & 0 \\ -k & -\alpha & M_3 & 0 \\ 0 & 0 & -M_4 & M_5 \end{bmatrix},\end{aligned}\tag{6}$$

with

$$\begin{aligned}M_1 &= k + \gamma + \mu, \quad M_2 = r_1 + \alpha + \mu, \quad M_3 = r_2 + d_1 + \mu, \\ M_4 &= (1 - \phi)r_2, \quad M_5 = \rho + r_3 + d_2 + \mu.\end{aligned}$$

From this, it follows that the reproductive number of model system (2) is given by

$$\mathcal{R}_A = \frac{\beta(p\alpha\gamma + (kp + (1-p)M_1)M_2)(\theta M_4 + M_5)}{M_1 M_2 (M_3 M_5 - \rho M_4)},\tag{7}$$

with $M_3 M_5 > \rho M_4$. The threshold quantity, $\mathcal{R}_A$, measures the average number of new secondary cases generated by a single individual in a population where the aforementioned control measures are in place. An associated epidemiological threshold is the *basic reproductive number* $\mathcal{R}_0$, obtained using the same technique of the next-generation operator [36], by considering model system (2) in the absence of tuberculosis control measures and is given by

$$\mathcal{R}_0 = \frac{\beta(k + (1-p)\mu)}{(k + \mu)(\mu + d_1)}.\tag{8}$$

This disease threshold quantity $\mathcal{R}_0$ measures the average number of new infections generated by a single infected individual in a completely susceptible population where there

are no tuberculosis intervention strategies. Using Theorem 2 from van den Driessche and Watmough [36], the following result is established.

Lemma 2 *The disease-free equilibrium ε^0 of system (2) is locally asymptotically stable (LAS) if $\mathcal{R}_A < 1$ and unstable if $\mathcal{R}_A > 1$.*

3.3 Sensitivity analysis

We study the sensitivity of the reproductive numbers to some intervention parameters and use the results to investigate the relative importance of the aforementioned tuberculosis intervention strategies.

3.3.1 Impact of case findings in TB control

Here, the reproductive number $\mathcal{R}_A$ is qualitatively analyzed to determine whether improvement in case findings (modeled by the rate γ) can lead to effective control or elimination of TB in the community. Using the approach by Chitnis et al. [37, 38], it follows that

$$\begin{aligned} \frac{\gamma}{\mathcal{R}_A} \frac{\partial \mathcal{R}_A}{\partial \gamma} &= - \frac{p\gamma [(k - \alpha)\mu + kr_1]}{(k + \mu + \gamma) [(k + \mu(1 - p))(\alpha + \mu + r_1) + \gamma(\alpha + (1 - p)(\mu + r_1))]} \\ &= - \frac{p\gamma k(\mu + r_1)(1 - \Theta)}{(k + \mu + \gamma) [(k + \mu(1 - p))(\alpha + \mu + r_1) + \gamma(\alpha + (1 - p)(\mu + r_1))]}, \end{aligned} \quad (9)$$

where $\Theta = \frac{\alpha\mu}{k(\mu + r_1)}$.

If all detected non-symptomatic latent carriers are successfully treated, it implies that $\alpha = 0$ and $\Theta = 0$ and thus (9) will be strictly less than zero, suggesting that detected non-symptomatic latent TB carriers will have a positive impact on tuberculosis control. However, if treatment of detected non-symptomatic latent TB carriers is not 100%, that is $\alpha \neq 0$, then case findings of latently infected TB individuals will have a positive impact on TB dynamics if $\Theta < 1$, no impact if $\Theta = 1$ and a negative impact if $\Theta > 1$. We summarize the result in the following Lemma 3.

Fig. 2 Relationship between the reproductive number ($\mathcal{R}_A$) and rate of tuberculosis case findings at the latent stage (γ)

Table 1 Model parameters and their interpretations

Parameter	Symbol	Value	Source
Proportion of defaulters who are still infectious	θ	0.9	Assumed
Relative susceptibility of the recovered people	σ	1.05	Assumed
Relative susceptibility of the latent TB cases	δ	0.7	[35]
Rate of returning to hospital for defaulters	ρ	0.01 years ⁻¹	[39]
Disease-related mortality rate for active TB	d_1	0.02 years ⁻¹	[35]
Disease-related mortality rate for defaulters	d_2	0.2 years ⁻¹	[39]
Rate of progression to active TB for detected and unsuccessfully treated latent TB cases	α	0.001 years ⁻¹	Assumed
Natural rate of progression to active TB	k	0.005 years ⁻¹	[39]
Rate of recovery for detected latent TB	r_1	0.55 years ⁻¹	Assumed
Rate of recovery for individuals in class I	r_2	0.45 years ⁻¹	Assumed
Rate of recovery for detected defaulters	r_3	0.005 years ⁻¹	Assumed
Rate of detection for latent TB cases	γ	0.2 years ⁻¹	Assumed
Proportion of newly infected recovery individuals with latent tuberculosis	f	0.99	[40]
Proportion of newly infected susceptible individuals with latent tuberculosis	p	0.99	[40]
Proportion of infectious defaulters	$1 - \phi$	0.2	Assumed
Natural mortality rate	μ	0.01 years ⁻¹	[41]
Effective contact rate	β	0.35 years ⁻¹	[41]

Lemma 3 *Tuberculosis case findings at the latent stage for model system (2) only, will have*

- *a positive impact in tuberculosis control if $\Theta < 1$,*
- *no impact in tuberculosis control if $\Theta = 1$,*
- *a negative impact in tuberculosis control if $\Theta > 1$.*

The above mathematical analysis is consistent with the simulation shown in Figs. 2 and 7. With parameter values taken from the literature and others assumed within realistic ranges for illustrative purposes (see Table 1), the quantity Θ is always less than unity, suggesting that case findings at the latent stage will have a positive impact on tuberculosis control in the community. This is in agreement with Fig. 2 and in accordance with a recent *Detec TB* study conducted in Harare (Zimbabwe), which showed that active screening for tuberculosis (TB) can uncover a very large number of TB cases in settings with a high prevalence of HIV and reduces (within a couple of years) the community's burden of TB [42].

3.3.2 Impact of non-compliance with tuberculosis treatment

Sensitivity analysis is numerically carried out on the reproductive number $\mathcal{R}_A$ in order to investigate the impact of non-compliance with tuberculosis treatment (parameter $1 - \phi$) of infectious individuals under a treatment regime on the transmission dynamics of TB in the community. It follows that

$$\lim_{\phi \rightarrow 1} \mathcal{R}_A = \frac{\beta [(k + (1 - p)\mu)(\alpha + \mu + r_1) + \gamma(\alpha + (1 - p)(\mu + r_1))]}{(k + \mu + \gamma)(\alpha + \mu + r_1)(\mu + d_1 + r_2)}. \quad (10)$$

Thus, a sufficiently effective program with the goal of reducing or discouraging individuals from defaulting, i.e., $\phi \rightarrow 1$, may be successful in eliminating tuberculosis in the community,

Fig. 3 Relationship between $\mathcal{R}_A$ and ϕ (the proportion of individuals who receive effective therapy)

provided the right-hand side of (10) is less than unity. The profile of $\mathcal{R}_A$, as a function of ϕ , is depicted in Fig. 3 and the set of parameters used in these simulations is in Table 1.

Figure 3 suggests that an increase in the proportion of infectious individuals who receive effective therapy through reducing or discouraging defaulting will have a positive impact on controlling tuberculosis in the community. Letting $\eta = 1 - \phi$, we note however that

$$\frac{\eta}{\mathcal{R}_A} \frac{\partial \mathcal{R}_A}{\partial \eta} = \frac{r_2 \eta}{\theta M_4 + M_5} \left(\theta + \frac{r_2}{\xi (4M_3 M_5 - \rho M_5)} \right) > 0, \quad (11)$$

where $\xi = \beta(p\alpha\gamma + (kp + (1 - p)M_1)M_2)$. Thus, an increase in the defaulting rate leads to an increase in the initial disease transmission (in which case values of $\mathcal{R}_A$ are above one and cause a persistent TB epidemic). We now numerically investigate the impact of varying the case finding rate (γ) and the defaulting rate $\eta = 1 - \phi$.

Figure 4 demonstrates that a case finding rate below a baseline level ($\gamma = 0.2$) seems to have no significant impact on controlling tuberculosis cases in a community where there is non-adherence to TB treatment. These results are in agreement with the results in Figs. 2 and 3.

Impact of non-compliance with tuberculosis treatment Here we wish to investigate the impact of the effective contact rate β , as well as the impact of the absence of TB control

Fig. 4 The relationship between the reproductive number ($\mathcal{R}_A$, versus case finding rate (γ)) and defaulting rate $\eta = 1 - \phi$

Fig. 5 Graphical representation of the relationship between the reproductive numbers ($\mathcal{R}_A$ and $\mathcal{R}_0$) and the contact rate (β)

strategies in the community by comparing the two reproductive numbers $\mathcal{R}_A$ and $\mathcal{R}_0$ while varying β using parameter values in Table 1.

It is evident from Fig. 5 that the aforementioned TB intervention strategies may have a positive impact on controlling the transmission dynamics of TB in the community. Further, analysis of the figure suggests that an increase in the contact rate may increase the magnitude of the associated reproductive number.

3.4 Endemic Equilibrium (EE)

Due to its complex nature, the endemic equilibrium for system (2) denoted by $\varepsilon^* = (s^*, e^* > 0, e_d^* > 0, i^* > 0, l^* > 0, w^* > 0)$ is given in terms of the force of infection $\lambda^* = \beta(i^* + \theta l^*)$, with

$$s^* = \frac{\mu}{\lambda^* + \mu},$$

$$e^* = \frac{p\lambda^*\mu}{(\lambda^* + \mu)(\delta\lambda + M_1)} + \frac{f\delta\lambda[(1-p)\lambda^*\mu(\delta\lambda^* + M_1)g_1 + p\lambda^*\mu(g_3 - g_1g_2)]}{(\lambda^* + \mu)(f\delta\lambda^*(g_3 - g_1g_2) + (\delta\lambda^* + M_1)(\sigma(1-f)g_1 + (\mu + \delta\lambda)g_3))},$$

$$e_d^* = \frac{\gamma}{M_2} \left(\frac{p\lambda^*\mu}{(\lambda^* + \mu)(\delta\lambda + M_1)} + \frac{f\delta\lambda[(1-p)\lambda^*\mu(\delta\lambda^* + M_1)g_1 + p\lambda^*\mu(g_3 - g_1g_2)]}{(\lambda^* + \mu)(f\delta\lambda^*(g_3 - g_1g_2) + (\delta\lambda^* + M_1)(\sigma(1-f)g_1 + (\mu + \delta\lambda)g_3))} \right)$$

$$i^* = \frac{\lambda^*}{(\lambda^* + \mu)g_1} \times \left(\frac{f\delta\lambda^*[(1-p)\lambda^*\mu(\delta\lambda + M_1)g_1 + p\lambda^*\mu(g_1g_2 - g_3)]}{(\delta\lambda^* + M_1)[(\delta\lambda^* + M_1)((1-f)\lambda^*\delta g_1 + (\mu + \delta\lambda^*)g_3) + f\delta\lambda^*(g_1g_2 - g_3)]} \right) + \frac{\mu + \delta\lambda[p\lambda^*\mu(g_1g_2 - g_3) + (\delta\lambda^* + M_1)]}{\lambda^* + \mu},$$

$$\begin{aligned}
I^* &= \frac{\eta r_2}{M_5} \left(\frac{\lambda^*}{\lambda^* + \mu} g_1 \right. \\
&\quad \times \frac{(f \delta \lambda^* [(1-p) \lambda^* \mu (\delta \lambda + M_1) g_1 + p \lambda^* \mu (g_1 g_2 - g_3)])}{(\delta \lambda^* + M_1) [(\delta \lambda^* + M_1)((1-f) \lambda^* \delta g_1 + (\mu + \delta \lambda^*) g_3) + f \delta \lambda^* (g_1 g_2 - g_3)]} \\
&\quad \left. + \frac{\eta r_2}{M_5} \left(\frac{\mu + \delta \lambda [p \lambda^* \mu (g_1 g_2 - g_3) + (\delta \lambda^* + M_1)]}{\lambda^* + \mu} \right) \right), \\
w^* &= \frac{(1-p) \lambda^* \mu (\delta \lambda^* + M_1) g_1 + p \lambda^* \mu (g_1 g_2 - g_3)}{(\lambda^* + \mu) [f \delta \lambda^* (g_3 - g_1 g_2) (\delta \lambda^* + M_1) (\sigma (1-f) g_1) + (\mu + \delta \lambda^*) g_3]},
\end{aligned}$$

where parameters M_1, M_2, M_3, M_4, M_5 and η have been defined earlier on in (7) and (11), respectively, and

$$g_1 = r_2 \left(\phi + \frac{\eta r_3}{M_5} \right), \quad g_2 = k + \delta \lambda^* + \frac{\alpha \gamma}{M_2}, \quad g_3 = \frac{\gamma r_1}{M_2} \left(\frac{\eta \rho r_2}{M_5} - M_3 \right). \quad (12)$$

3.4.1 Existence of backward bifurcation

The epidemiological implication of Lemma 2 is that TB can be eliminated from the community when $\mathcal{R}_A < 1$, provided the initial sizes of the sub-populations of system (2) are in the basin of attraction of ε^0 . In other words, an influx of a small number of infected individuals into the community will not generate large outbreaks if $\mathcal{R}_A < 1$. Models of TB dynamics with exogenous re-infection are known to exhibit the phenomenon of backward bifurcation [43–45] where a stable disease-free equilibrium (DFE) co-exists with a stable endemic equilibrium (EE) when $\mathcal{R}_A < 1$. The public health implication of backward bifurcation is that the classical requirement of having the basic reproduction number less than unity, although necessary, is not (or no longer) sufficient for disease control. For more details on the influence of backward bifurcation on interpretation of the disease threshold parameter in a model of epidemic tuberculosis with re-infection, see Singer and Kirschner [44]. The existence of backward bifurcation in model system (2) is explored below using centre manifold theory [46], as described in Castillo-Chavez and Song [45]. Before starting our main results, we provide the following theorem and lemma that will be useful in the subsequent section.

Theorem 1 (See Castillo-Chavez and Song [45]) *Consider the following general system of ordinary differential equations with a parameter ϕ ,*

$$\frac{dx}{dt} = f(x, \phi), \quad f: \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R}^n \text{ and } f \in C^2(\mathbb{R}^n \times \mathbb{R}). \quad (13)$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (13) for all values of the parameter ϕ , that is $f(0, \phi) = 0$ for all ϕ and we assume

- A1 $A = D_x f(0, 0) = \left(\frac{\partial f_i}{\partial x_j}(0, 0) \right)$ is the linearization of system (13) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;
- A2 Matrix A has a right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.

Let f_k be the k th component of f and

$$\begin{aligned} a &= \sum_{k,i,j=1}^n v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0), \\ b &= \sum_{k,i=1}^n v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0). \end{aligned} \quad (14)$$

The local dynamics of (13) around 0 are totally governed by a and b .

- i $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;
- ii $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, asymptotically stable and there exists a positive unstable equilibrium;
- iii $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;
- iv $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly, a negative equilibrium becomes positive and locally asymptotically stable.

To apply this method, the following change of variables is required. Let $s = x_1, e = x_2, e_d = x_3, i = x_4, l = x_5$ and $w = x_6$. So that $\lambda^* = \beta(x_4 + \theta x_5)$. Further, by using the vector notation $\mathbf{x} = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, model system (2) can be written in the form $\frac{d\mathbf{x}}{dt} = F(\mathbf{x})$, with $F = (f_1, f_2, f_3, f_4, f_5, f_6)^T$.

$$\begin{aligned} x'_1 &= f_1 = \mu - \lambda x_1 - \mu x_1, \\ x'_2 &= f_2 = p\lambda x_1 + f\sigma\lambda x_6 - (\gamma + k + \mu + \delta\lambda)x_2, \\ x'_3 &= f_3 = \gamma x_2 - (\mu + \alpha + r_1)x_3, \\ x'_4 &= f_4 = (1 - p)\lambda x_1 + (\delta\lambda + k)x_2 + (1 - f)\sigma\lambda x_6 + \alpha x_3 + \rho x_5 - (r_2 + \mu + d_1)x_4, \\ x'_5 &= f_5 = (1 - \phi)r_2 x_4 - (\rho + \mu + r_3 + d_2)x_5, \\ x'_6 &= f_6 = r_1 x_3 + \phi r_2 x_4 + r_3 x_5 - (\sigma\lambda + \mu)x_6, \end{aligned} \quad (15)$$

The method entails evaluating the Jacobian of system (15) at the disease-free (ε^0) denoted by $J(\varepsilon^0)$. This gives

$$J(\varepsilon^0) = \begin{bmatrix} -\mu & 0 & 0 & -\beta & -\beta\theta & 0 \\ 0 & -M_1 & 0 & p\beta & p\beta\theta & 0 \\ 0 & \gamma & -M_2 & 0 & 0 & 0 \\ 0 & k & \alpha & (1-p)\beta - M_3 & (1-p)\beta\theta + \rho & 0 \\ 0 & 0 & 0 & M_4 & -M_5 & 0 \\ 0 & 0 & r_1 & \phi r_2 & r_3 & -\mu \end{bmatrix},$$

from which it can be shown that the dominant eigenvalue of $J(\varepsilon^0)$ is $\mathcal{R}_A$, which is given by (7). For $\mathcal{R}_A = 1$, solving for $\beta = \beta_*$, we have

$$\beta = \beta_* = \frac{M_1 M_2 (M_3 M_5 - \rho M_4)}{(p\alpha\gamma + (kp + (1-p)M_1)M_2)(\theta M_4 + M_5)}.$$

Thus, the linearized system of the transformed (15) with $\beta = \beta_*$ chosen as the bifurcation parameter has a simple zero eigenvalue. Hence, it can be shown that the Jacobian of (15) at $\beta = \beta_*$ has right and left eigenvectors (associated with the zero eigenvalue) given below.

Eigenvectors of $J(\varepsilon^0)$ It can be shown that the Jacobian $J(\varepsilon^0)$ of system (15) at $\beta = \beta_*$ has a right eigenvector (corresponding to the zero eigenvalue) given by $\mathbf{w} = (w_1, w_2, w_3, w_4, w_5, w_6)^T$, where

$$\begin{aligned} w_1 &= \frac{-\beta_*(w_4 + \theta w_5)}{\mu}, & w_2 &= \frac{p\beta_*}{k + \gamma + \mu} \left[1 + \frac{(1 - \phi)r_2}{\mu + \rho + r_3 + d_2} \right] w_4, \\ w_3 &= \frac{\gamma w_2}{\mu + \alpha + r_1}, & w_4 &> 0, & w_5 &= \frac{(1 - \phi)r_2 w_4}{\mu + \rho + r_3 + d_2}, \\ w_6 &= \frac{r_1 w_3 + \phi r_2 w_4 + r_3 w_5}{\mu}. \end{aligned}$$

Further, the Jacobian $J(\varepsilon^0)$ has a left eigenvector (associated with the zero eigenvalue) given by $\mathbf{v} = (v_1, v_2, v_3, v_4, v_5, v_6)^T$, where

$$\begin{aligned} v_1 &= 0, & v_2 &= \frac{[k(\alpha + \mu + r_1) + \alpha\gamma] v_4}{(\alpha + \mu + r_1)(k + \gamma + \mu)}, & v_5 &= \frac{p\beta_*\theta v_2 + [(1 - p)\beta_*\theta + \rho] v_4}{\mu + \rho + r_3 + d_2}, \\ v_6 &= 0, & v_3 &= \frac{\alpha v_4}{\alpha + \mu + r_1}, & v_4 &> 0. \end{aligned}$$

Computations of the bifurcation coefficients a and b For the sign of b , it can be shown that the associated non-vanishing partial derivatives of F are

$$\begin{aligned} \frac{\partial^2 f_2}{\partial x_4 \partial \beta_*} &= p, & \frac{\partial^2 f_2}{\partial x_5 \partial \beta_*} &= p\theta, \\ \frac{\partial^2 f_4}{\partial x_4 \partial \beta_*} &= 1 - p, & \frac{\partial^2 f_4}{\partial x_5 \partial \beta_*} &= (1 - p)\theta. \end{aligned} \quad (16)$$

It follows from (16) that

$$b = (w_4 + \theta w_5)(pv_2 + (1 - p)v_4) > 0. \quad (17)$$

Similarly, it can be shown after some algebraic manipulations that the bifurcation coefficient a is given by

$$\begin{aligned} a &= v_2 \sum_{i,j=1}^n w_i w_j \frac{\partial^2 f_2}{\partial x_i \partial x_j} + v_4 \sum_{i,j=1}^n w_i w_j \frac{\partial^2 f_4}{\partial x_i \partial x_j} \\ &= Z_1 + Z_2 + Z_3 + Z_4, \end{aligned} \quad (18)$$

where

$$\begin{aligned} Z_1 &= -2\beta v_4 w_4 \left[1 + \frac{(1-\phi)\theta r^2}{M_5} \right]^2 \left[(1-p) + \frac{p(kM_2 + \alpha\gamma)}{M_1 M_2} \right] \left[1 + \left(1 - \frac{\gamma}{M_2} \right) \frac{p\beta}{M_1} \right], \\ Z_2 &= -2(1-\sigma)\beta v_4 w_4 \left[\frac{p\beta\gamma r_1}{\mu} \left(1 + \frac{(1-\phi)\theta r_2}{M_5} \right) + \frac{r_2(\phi M_5 + (1-\phi)r_3)}{M_5} \right], \\ Z_3 &= -2(1-\sigma)\beta\mu v_4 w_4 \left[1 + \frac{(1-\phi)\theta r_2}{M_5} \right] \left[(1-p) + \frac{p(kM_2 + \alpha\gamma)}{M_1 M_2} \right], \\ Z_4 &= -\frac{2p\sigma\beta^2 v_4 w_4}{M_1} \left[1 + \frac{(1-\phi)\theta r_2}{M_5} \right]^2 \left[1 + \frac{kM_2 + \alpha\gamma}{M_1 M_2} \right], \end{aligned} \quad (19)$$

with M_1, M_2, M_5 as defined earlier. Thus, $b > 0$ and $a > 0$ or $a < 0$ depending on the sign $Z_1 + Z_2 + Z_3 + Z_4$. Using items (i) and (iv) of Theorem 4.1 in Castillo-Chavez and Song [45], we establish the following results.

Lemma 4 *Whenever $a > 0$, the model system (2) undergoes backward bifurcation at $\mathcal{R}_A = 1$, otherwise for $a < 0$, a unique endemic equilibrium ε^* is guaranteed for $\mathcal{R}_A > 1$, and is locally asymptotically stable in the neighborhood of 1.*

Fig. 6 Bifurcation diagrams for (2). For backward bifurcation we used the parameter values in Table 1 and β is varied in the range 0.000001 to 0.003, with $\gamma = 0.001$, $\phi = 0.23$ and $k = 0.000013$. For forward bifurcation we used the parameter values in Table 1 with β varied in the range 0.003–0.35 with $\gamma = 0.3$, $\phi = 0.8$ and $k = 0.01$

We used the C++ programming language to create the two bifurcation diagrams (backward bifurcation and forward bifurcation) for system (2), illustrated in Fig. 6. The parameter values used are in Table 1, except for ϕ , γ , k and β .

From the results in Fig. 6 we note that if $\gamma < 0.2$ and $\phi < 0.7$, i.e., ($\eta \leq 0.3$), the model system (2) undergoes a backward bifurcation and if the reverse occurs ($\gamma \geq 0.2$ and $\phi \geq 0.7$), we have a forward bifurcation. These results suggest that early therapy (of $\gamma \geq 0.2$ and above) coupled with decreasing defaulting rate ($\phi \geq 0.7$) may be effective in controlling TB in the community.

3.4.2 The impact of early therapy for non-symptomatic carriers and non-adherence on backward bifurcation

The model system (2) may exhibit the phenomenon of backward bifurcation where multiple endemic equilibria co-exist with a disease-free equilibrium. Thus, the condition for the associated reproductive number ($\mathcal{R}_A$) to be less than unity for TB reduction, albeit necessary, is not sufficient for TB eradication [47]. Consequently, extra TB control measures such as identification of poor and vulnerable groups in the community with little or no access to TB therapy, educational campaigns to inform the public about the advantages of treatment compliance, poverty eradication, quitting smoking, and evaluating the population-level impact of pro-poor measures, etc., are concurrently needed to control the TB epidemic in the community. The model system (2) will exhibit the phenomenon of backward bifurcation for the following inequalities: $a > 0$ and $b > 0$. We now proceed to investigate the role of early therapy (case findings of latently infected individuals) on the backward bifurcation, by partially differentiating the coefficient a with respect to γ (the case findings rate). Let

$$\tilde{h}_0 = \frac{2\beta\sigma(\rho + (1 - \phi) + r_2 + r_3 + d_2 + \mu)}{(\rho + r_3 + d_2 + \mu)}.$$

Then, taking the partial derivative of a with respect to γ gives

$$\begin{aligned} & -\frac{\tilde{h}_0 w_4^2 v_4}{\mu + \alpha + r_1} \left[\left\{ \frac{pn_1}{k + \mu + \gamma} \left(1 - \frac{k\gamma}{k + \mu + \gamma} \right) \right\} \right. \\ & \quad \times \left. \left\{ n_1 \left(1 + \frac{(1 + n_1)}{(n_2 - n_3 n_4)(k + \mu + \gamma)} \right) \left(1 - \frac{k\gamma}{(k + \mu + \gamma)} \right) \right\} \right], \end{aligned} \quad (20)$$

with, $n_1 = \frac{\alpha}{\mu + \alpha + r_1}$, $n_2 = (\mu + d_1 + r_2) - (1 - p)\beta$, $n_3 = (1 - p\beta\theta + \rho)$, $n_4 = \frac{(1 - \phi)r_2}{\mu + \rho + r_3 + d_2}$.

Since $\frac{k\gamma}{k + \mu + \gamma} < 1$, the bifurcation coefficient a is a decreasing function of γ , implying that the possibility of this phenomenon occurring decreases with the increasing rate of case findings (γ). Therefore, the more we detect people harboring any form of TB at the latent stage, the less likely this phenomenon (backward bifurcation) can arise. Also, let

$$\begin{aligned} \tilde{h}_1 &= 2\beta v_4 w_4, \quad \tilde{h}_2 = \left[(1 - p) + \frac{p(kM_2 + \alpha\gamma)}{M_1 M_2} \right], \\ \tilde{h}_3 &= \left[1 + \left(1 - \frac{\gamma}{M_2} \right) \frac{p\beta}{M_1} \right], \quad \tilde{h}_4 = \left[1 + \frac{kM_2 + \alpha\gamma}{M_1 M_2} \right]. \end{aligned} \quad (21)$$

Taking the partial derivative of a with respect to ϕ , after some rearrangement, gives

$$-\hbar_1 \hbar_2 \left\{ \frac{B_2(\mu + \rho + d_2)}{M_5} - \frac{r_2}{M_5} W \right\} \quad (22)$$

where $W = \left[B_2(\hbar_3 + (1 - \sigma)B_1) + \frac{2p\sigma\beta B_2 \hbar_4}{M_1} + \frac{(1 - \sigma)M_5 B_1 B_2 + (\phi M_5 + (1 - \phi)r_2 r_3)}{M_5} \right]$, $B_1 = \frac{\beta\beta\gamma r_1}{\mu}$ and $B_2 = 1 + \frac{(1 - \phi)\theta r_2}{M_5}$.

If $\frac{r_2}{M_5} < \frac{B_2(\mu + \rho + d_2)}{M_5}$, then the backward bifurcation coefficient a will be a decreasing function of ϕ and its possibility of occurring decreases with increasing treatment completion ϕ . This result is solely driven by the fact that all individuals who are on treatment will complete treatment and it is assumed that this is 100% effective. If one considers treatment efficacy and development of resistance, then the reverse may be the case, since an increase in (incomplete) treatment contributes to the development of resistance, and this in turn may increase the possibility of backward bifurcation. If the above inequality is reversed, which is the case with the parameter values in Table 1, then backward bifurcation is likely to arise as treatment increases (this is mainly due to failure of completing treatment and non-adherence to treatment compliance). This will further be investigated elsewhere. Finally, by partially differentiating the bifurcation coefficient a with the respect to the defaulting rate ($\eta = 1 - \phi$), we obtain

$$\frac{\partial a}{\partial \eta} = -\frac{2\hbar_1 \theta r_2 B_2}{M_5} \left\{ \hbar_2 \left(\hbar_3 + \frac{1 - \sigma}{2B_2} \right) + \frac{1}{2\theta B_2} \left(\frac{r_3}{r_2} - M_5 \right) \right\}. \quad (23)$$

Since $\hbar_2 \left(\hbar_3 + \frac{1 - \sigma}{2B_2} \right) + \frac{r_3}{2r_2 \theta B_2} < \frac{M_5}{2\theta B_2}$, (23) is positive. Thus, bifurcation is likely to occur as the rate of defaulting increases. This is to be expected, as these individuals will be spreading the disease where it is thought to be under control.

4 Simulation study of population-level effects

In order to illustrate the results of the foregoing analysis, we have simulated a model system (2) using the baseline parameters values summarized in Table 1 and the MATLAB ODE solver, ode45.

Simulations in Fig. 7 depict the effects of an increase in case findings of TB cases at the latent stage on the disease dynamics over a period of time. It clearly shows that when TB case findings increase, the size of the infected subpopulation (i and l) decreases significantly, which leads to a decrease in the undetected latent carriers (e_d) due to the reduction in the risk of exposure to TB. An intervention that ensures a higher rate of case findings will cause an increase in the detected latent carriers (e_d) over the initial 5–15 years after the start of the intervention. Later, it decreases due to the vanishing epidemics. A case finding rate below the baseline level ($\gamma = 0.2$) seems to have dangerous consequences for the population, leading to an increase in all infected and latent compartments. This is a result of the basic reproductive number $\mathcal{R}_A$ crossing above the threshold level of one as depicted in Fig. 2. An increase of the case finding rate also increases the recovery population.

The numerical results in Fig. 8 show the effects of a decrease in the proportion of active TB individuals who abscond (defaulters) on the disease dynamics while on treatment

Fig. 7 Simulations of model system (2) showing the effects of an increase in TB case findings at the latent stage, modeled by the parameter (γ), on the dynamics of (a) susceptible population s , (b) undetected latent carriers e , (c) detected latent carriers e_d , (d) infected I , (e) defaulters l and (f) the recovery population w , over a period of years. The rest of the parameters are fixed on their baseline values from Table 1 and the following assumed initial conditions $s = 0.5$, $e = 0.25$, $e_d = 0.05$, $i = 0.1$, $l = 0.005$, $w = 0.005$. If $\gamma = 0.1$, 0.2 , 0.3 , 0.4 , 0.5 , then $\mathcal{R}_A$ is 1.48 , 0.78 , 0.65 , 0.52 and 0.48 , respectively

over a period of time (in years). It suggests that when the defaulting rate decreases, the size of each infected and latent class also decreases. We note, however, that under the scenarios when 50% or more of the infected people do not complete their treatment ($\phi \leq 0.5$), a significant TB outbreak is expected during the next 20–30 years. This epidemic

Fig. 8 Simulations of model system (2) showing the effects of a decrease of the defaulting rate ($1 - \phi$) on the dynamics of (a) susceptible populations, (b) undetected latent carriers e , (c) detected latent carriers e_d , (d) infected I , (e) defaulters l and (f) the recovery population w , over a period of years. The rest of the parameters are fixed on their baseline values from Table 1 and the following assumed initial conditions: $s = 0.5$, $e = 0.25$, $e_d = 0.05$, $i = 0.1$, $l = 0.005$, $w = 0.005$. When $\phi = 0.1, 0.3, 0.5, 0.7, 0.9$ the reproductive number $\mathcal{R}_A$ is 2.1, 1.7, 1.52, 1.18 and 0.98, respectively

outcome is prevented if the defaulting rate is kept below 30% ($\phi \geq 0.75$). Results shown here further suggest that, apart from focusing on early therapy and adherence, tuberculosis re-infection is an important aspect that needs to be solved for effective tuberculosis control.

5 Optimal case finding and treatment

In this section, we introduce controls on case findings ($u_1(t)$) and treatment ($u_2(t)$) for system (2) to obtain

$$\left. \begin{aligned} s' &= \mu - \lambda s - \mu s, \\ e' &= p\lambda s + f\sigma\lambda w - (u_1\gamma + k + \mu + \delta\lambda)e, \\ e_d' &= u_1\gamma e - (\mu + \alpha + r_1)e_d, \\ i' &= (1-p)\lambda s + (1-f)\sigma\lambda w + (\delta\lambda + k)e + \alpha e_d + \rho l - (u_2r_2 + \mu + d_1)i, \\ l' &= u_2(1-\phi)r_2i(\rho + r_3 + \mu + d_2)l, \\ w' &= r_1e_d + u_2\phi r_2i + r_3l - (\mu + \sigma\lambda)w. \end{aligned} \right\} \quad (24)$$

The controls u_1 and u_2 are bounded Lebesgue integrable functions. The control u_1 represents the effort of identifying non-symptomatic infectious individuals and u_2 represents the effort of treatment of infectious individuals. We consider the following objective function

$$J(u_1, u_2) = \int_0^{t_f} [(s + e_d) - (B_1e + B_2i) - (A_1u_1^2 + A_2u_2^2)] dt \quad (25)$$

where t_f is the final time. The coefficients B_1 and B_2 represent the weight constants of the exposed and infectious individuals while parameters A_1 and A_2 are weight and benefit costs, and they balance the size of the terms u_1^2 , and u_2^2 , respectively. We seek to find an optimal control, u_1^*, u_2^* such that

$$U = \left\{ (u_1(t), u_2(t)) \mid (u_1(t), u_2(t)) \text{ is measurable,} \right. \\ \left. a_i \leq (u_1(t), u_2(t)) \leq b_i, \quad i = 1, 2, t \in [0, t_f] \right\} \quad (26)$$

where $U = \{u_1(t), u_2(t) \mid u_1(t), u_2(t) \text{ is measurable and } a_i(u_1(t), u_2(t)) \leq b_i, i = 1, 2, t \in [0, t_f]\}$ is the control set.

5.1 Existence of an optimal control

The existence of an optimal control is proved by a result from Fleming and Rishel [48]. The boundedness of solutions of system (24) for a finite time interval is used to prove the existence of an optimal control. To determine the existence of an optimal control for our problem, we turn to Fleming and Rishel (Thm 4.1, pp. 68–69) [48], where the following properties must be satisfied:

1. The class of all initial conditions with an optimal control set u_1 and u_2 in the admissible control set along with each state equation being satisfied is not empty.
2. The control set U is convex and closed.
3. The right-hand side of the state is continuous, is bounded above by a sum of the bounded control, and can be written as a linear function of each control in the optimal control set u_1, u_2 and u_3 , with coefficients depending on time and the state variables.
4. The integrand of the functional is concave on U and is bounded above by $c_2 - c_1(|u_1|^2 + |u_2|^2)$, where $c_1, c_2 > 0$.

An existence result in Lukes (Theorem 9.2.1) [49] for system (24) for bounded coefficients is used to provide condition 1. The control set is closed and convex by definition. The right-hand side of state system (24) satisfies condition 3 since the state solutions are

a priori bounded. The integrand in the objective functional, $(s + e_d) - (B_1 e + B_2 i) - (A_1 u_1^2 + A_2 u_2^2)$, is Lebesgue integrable and concave on U . Furthermore, $c_1, c_2 > 0$ and $B_1, B_2, A_1, A_2 > 1$, hence satisfying

$$(s + e_d) - (B_1 e + B_2 i) - (A_1 u_1^2 + A_2 u_2^2) \leq c_2 - c_1 (|u_1|^2 + |u_2|^2)$$

where c_2 depends on the upper bound on $S + E_D$ and c_1 since $A_1, A_2 > 0$. Therefore the optimal control exists, since the states are bounded.

5.2 Optimality system

Since there exists an optimal control for maximizing functional (25) subject to system (24), we use Pontryagin's maximum principle to derive the necessary conditions for this optimal control. The Lagrangian is defined as

$$\begin{aligned} L_g = & [(s + e_d) - (B_1 e + B_2 i) - (A_1 u_1^2 + A_2 u_2^2)] \\ & + \lambda_1 [\mu - \lambda s - \mu s] + \lambda_2 [p\lambda s + f\sigma\lambda w - (u_1\gamma + k + \mu + \delta\lambda)e] \\ & + \lambda_3 [u_1\gamma e - (\mu + \alpha + r_1)e_d] \\ & + \lambda_4 [(1 - p)\lambda s + (1 - f)\sigma\lambda w + (\delta\lambda + k)w + \alpha e_d + \rho l - (u_2 r_2 + \mu + d_1)i] \\ & + \lambda_5 [u_2(1 - \phi)r_2 i - (\rho + r_3 + \mu + d_2)l] + \lambda_6 [r_1 e_d + u_2\phi r_2 i + r_3 l - (\mu + \sigma\lambda)w] \\ & + w_{11}(t)(b_1 - u_1(t)) + w_{12}(t)(u_1(t) - a_1) \\ & + w_{21}(t)(b_2 - u_2(t)) + w_{22}(t)(u_2(t) - a_2) \end{aligned} \quad (27)$$

where $w_{11}(t), w_{12}, w_{21}(t), w_{22}(t), w_{31}(t), w_{32}(t) \geq 0$ are penalty multipliers satisfying

$$\begin{aligned} w_{11}(t)(b_1 - u_1) &= 0, & w_{12}(t)(u_1 - a_1) &= 0, & \text{at } u_1^* \\ w_{21}(t)(b_2 - u_2) &= 0, & w_{22}(t)(u_2 - a_2) &= 0, & \text{at } u_2^* \end{aligned}$$

Theorem 2 Given optimal controls u_1^* and u_2^* and solutions of the corresponding state system (24), there exist adjoint variables $\lambda_i, i = 1, \dots, 6$ satisfying

$$\lambda'_1 = -1 + \mu\lambda_1 + \beta(i + \theta l)[p(\lambda_4 - \lambda_2) + (\lambda_1 - \lambda_4)], \quad (28)$$

$$\lambda'_2 = B_1 + \mu\lambda_2 + u_1\gamma(\lambda_2 - \lambda_3) + k(\lambda_2 - \lambda_4) + \beta\delta(i + \theta l)(\lambda_2 - \lambda_4), \quad (29)$$

$$\lambda'_3 = -1 + \mu\lambda_3 + \alpha(\lambda_3 - \lambda_4) + (\lambda_3 - \lambda_6)r_1, \quad (30)$$

$$\begin{aligned} \lambda'_4 = & B_2 + (\mu + d_1)\lambda_4 + \beta s[p(\lambda_4 - \lambda_2) + (\lambda_1 - \lambda_4)] + \beta\delta e(\lambda_2 - \lambda_4) \\ & + \beta\sigma w[f(\lambda_4 - \lambda_2) + (\lambda_6 - \lambda_4)] + r_2 u_2(\lambda_4 - (1 - \phi)\lambda_5 - \phi\lambda_6), \end{aligned} \quad (31)$$

$$\begin{aligned} \lambda'_5 = & \beta\theta s[(\lambda_1 - \lambda_4) + p(\lambda_4 - \lambda_2)] + \beta\theta\delta e(\lambda_2 - \lambda_4) + \rho(\lambda_5 - \lambda_4) + r_3(\lambda_5 - \lambda_6) \\ & + \beta\theta\sigma w[f(\lambda_4 - \lambda_2) + (\lambda_6 - \lambda_4)] + (\mu + d_2)\lambda_5, \end{aligned} \quad (32)$$

$$\lambda'_6 = \mu\lambda_6 + \beta\sigma(i + \theta l)[f\lambda_4 - \lambda_2] + (\lambda_6 - \lambda_4), \quad (33)$$

with transversality conditions $\lambda_i(t_f) = 0$ for $i = 1, \dots, 6$.

Proof The form of the adjoint equation and the transversality conditions are standard results from Pontryagin's maximum principle, [48]; therefore, solutions to the adjoint system exist and are bounded. To determine the interior maximum of our Lagrangian, we take the partial derivative of L with respect to u_1, u_2 and u_3 and set it to zero. Thus,

$$u_1^* = \frac{\gamma(\lambda_3 - \lambda_2)e}{2A_1} + \frac{w_{12} - w_{11}}{2A_1},$$

$$u_2^* = \frac{i(\phi\lambda_6 + (1 - \phi)\lambda_5 - \lambda_4)r_2}{2A_2} + \frac{w_{22} - w_{21}}{2A_2}.$$

To determine an explicit expression for the control without w_{11}, w_{12}, w_{21} and w_{22} , a standard optimality technique is utilized. The specific characterization of the optimal controls u_1^* and u_2^* is

$$u_1^* = \min \left\{ \max \left\{ a_1, \frac{\gamma(\lambda_3 - \lambda_2)e}{2A_1} \right\}, b_1 \right\}, \quad (34)$$

$$u_2^* = \min \left\{ \max \left\{ a_2, \frac{i(\phi\lambda_6 + (1 - \phi)\lambda_5 - \lambda_4)r_2}{2A_2} \right\}, b_2 \right\}. \quad (35)$$

The optimality system consists of the state system coupled with the adjoint system with the initial conditions, the transversality conditions, and the characterization of the optimal control. Substituting u_1^* and u_2^* for $u_1(t)$ and $u_2(t)$ in (28)–(33) gives the optimality system. The state system and adjoint system have finite upper bounds. These bounds are needed for the uniqueness proof of the optimality system. Due to a priori boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ordinary differential equations, we obtain the uniqueness of the optimal control for small t_f . The uniqueness of the optimal control follows from the uniqueness of the optimality system. $\square$

5.3 Numerical results

The optimality system is solved using an iterative method with a Runge–Kutta fourth-order scheme. Starting with a guess for the adjoint variables, the state equations are solved forward in time. Then these state values are used to solve the adjoint equations backward in time and the iterations continue until convergence. The simulations were carried out using the parameter values in Table 1 and the following values: $A_1 = A_2 = 1500$, $B_1 = B_2 = 30$, $u_1 = u_2 = 0.9$. The assumed initial conditions for the differential equations are $s = 0.5$, $e = 0.25$, $e_d = 0.05$, $i = 0.1$, $l = 0.005$, $w = 0.005$.

The results in Fig. 9a and f predict a lower level of susceptible and recovered populations, respectively, for the aforementioned tuberculosis intervention strategies in the absence of control, compared to a case when there is control. In Fig. 10b, we observe a sharp increase of latent tuberculosis cases for the interval 0–15 years when there is no control, versus a sharp decline on latent tuberculosis cases for the same interval when there is control. After a period of 15 years in the absence of control, we note that latent tuberculosis cases have a sharp decline. In Fig. 9c, in the presence of control, the detected population is higher than

Fig. 9 Simulations of model system (24) showing the effects of optimal case finding and treatment

in the absence of control. In Fig. 9d, we note that it takes 10 years for infectious cases to die off when there is control. In Fig. 9e, we have a slightly higher population of defaulters compared to the case when there is no control for the period 0–20 years. This is due to the fact that in this study no control has been introduced, specifically for defaulting individuals. However, after a period of 20 years, we note that the population of defaulters will be higher in the presence of control compared to a case when there is no control. It also worth noting that although we have a slightly higher population of defaulters in the presence of control, this is associated with low-latent tuberculosis cases, low-infectious cases and a high level

Fig. 10 The optimal control graphs for two controls, namely case finding control $u_1(t)$ and treatment control $u_2(t)$, $aA_1 = A_2 = 1500$, $B_1 = B_2 = 30$, (b) $A_1 = 500$, $A_2 = 1500$, $B_1 = 300$, $B_2 = 300$, (c) $A_1 = 1500$, $A_2 = 500$, $B_1 = 30$, $B_2 = 300$

of susceptible and recovery populations, implying that intervention strategies with control may be effective in controlling TB in the community.

The simulation results in Fig. 10 suggest that at the beginning of the epidemic we have to dedicate full effort to all the aforementioned intervention strategies; however, more effort should be devoted to case findings (control u_1) compared to treatment of infectious individuals (control u_2).

6 Discussion

We used a deterministic model to explore the population-level impact of case findings and non-adherence on TB transmission dynamics in sub-Saharan Africa. Comprehensive mathematical analysis of the model shows that the model undergoes a phenomenon of backward bifurcation when the reproductive number ($\mathcal{R}_A = 1$) is equal to unity. Qualitative analysis of this disease threshold number ($\mathcal{R}_A$) under the aforementioned intervention strategies shows that the intervention strategies have a positive effect on TB control, with the potential of curtailing the epidemic. Mathematical analysis and numerical simulations (Figs. 2 and 7) show that case findings of individuals harboring TB at a latent stage alone has a positive population-level impact in TB control whenever $\Theta < 1$, no impact for $\Theta = 1$ and a negative impact for $\Theta > 1$. However, we note that from TB epidemiology, realistic parameter values always yield $\Theta < 1$. Consequently, the extent to which case findings will have a positive impact on reducing the burden of global TB disease in the community when there is non-adherence is demonstrated in Fig. 4. In conclusion, our analysis highlights that intervention strategies that combine elevated levels of case findings of TB at a latent stage and treatment with a highly reduced defaulting rate will have a positive impact on TB reduction. However, the possibility of backward bifurcation is a warning sign that even more effort should be dedicated to assessing the poor and vulnerable groups who face different barriers (economic, geographical, social, and cultural) and are prone to the circulation of TB in the community. Our optimal control results suggest that more effort should be devoted to tuberculosis case findings compared to treatment of infectious individuals.

Our study has several limitations that should be acknowledged. Several studies suggest that defaulting may be associated with TB drug resistance [5, 50], which has not been captured in this study. The scenario being modeled here is more common in resource-limited settings, where HIV/AIDS is more prevalent. Thus the suggested TB treatment levels may not be the most probable levels to achieve effective TB control. Although this is a theoretical study, the scarcity and limited availability of the data limit our ability to extract accurate findings from the study. If the data were available, sensitivity analysis could have been used to determine values for the model parameters (for instance, the effective contact rate for TB transmission plays a crucial role in controlling the dynamics of TB in the community, hence its value determined from realistic data is also important).

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