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OPTIMAL CONTROL STRATEGIES FOR THE POPULATION DYNAMICS OF TUBERCULOSIS IN RESOURCE-POOR COUNTRIES

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Abstract

In this paper, optimal control theory was applied to a mathematical model describing the transmission dynamics of tuberculosis (TB) with variability in susceptibility due to difference in awareness level. Seeking to minimize the number of high-risk susceptible (and latently-infected) individuals with low level of TB awareness as well as persons with infectious TB, and to maximize the number of isolated actively-infected individuals placed under the Directly Observed Treatment Short-Course (DOTS), we incorporated time-dependent control functions to represent the fraction of susceptible (and latently-infected) individuals who benefited from TB awareness message and are now aware in a population where there is limited-resources for carrying out such enlightenment campaign programmes about TB, as well as case finding techniques for detecting and isolating active TB cases for effective treatment. The optimal controls were characterized in terms of the optimality systems, which were solved numerically for several scenarios using an iterative method with Runge-Kutta fourth order scheme. From this work, we presented a new optimal control model that examines the impact of limited-resources on TB awareness campaign programs, which ultimately affects the transmission dynamics of the disease in a population. The optimal control model presented in this work can be implemented in resource-poor countries. Numerical simulations were performed for various setting to illustrate the effect of the controls on the transmission dynamics of the disease in a population.

Keywords: Tuberculosis, mathematical model, awareness campaign, case finding techniques, limited-resources, optimal control theory, numerical simulations.

1.0 Introduction

In several developed countries of the world, TB is already considered as a disease of the past. However, in most developing countries (especially in sub-Sahara Africa and South-East Asia), the impact of TB is still devastating till date. This is especially the case in resource-poor countries affected with high disease burdens of both TB and HIV [1]. There was an estimated 10.4 million new TB cases globally in 2015, with six high burden countries (HBC) accounting for 60% of the new cases, namely: India, Indonesia, China, Nigeria, Pakistan and
South Africa [2]. This confirms the fact that TB is still a major health problem in resource-poor countries. Poverty is a significant factor influencing the current TB epidemic in countries with limited-resources for effective TB control. TB transmission is closely linked to unhealthy and crowded living conditions, malnutrition, unavailability of free or affordable health care services, as well as dependence on traditional healers for treatment which encourage the spread of TB in the community [3].

In resource-poor countries, there exists unmet need for modern diagnostic procedures. The few available smear microscopy laboratories are understaffed, poorly maintained, and they lack adequate infrastructure, reliable power supply and clean water [1]. Moreover, in such resource-limited setting, there exist few opportunities for training and retraining of staff on modern diagnostic procedures for both latent and active TB cases. The above situation is further compounded with unavailability of qualified personnel as well as limited financial resources in such countries. From the foregoing, it is obvious that the scarcity of adequate laboratory facilities in resource-poor countries makes the laboratory diagnosis (and treatment) of chronic TB cases very challenging [1].

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The epidemics of TB and HIV have continued to grow in resource-poor countries. Even with the introduction of effective and efficient treatment strategies, such as DOTS, for active TB cases, the incidence of TB will continue to increase if HIV epidemic is not urgently checked [4]. Unfortunately, in most resource-poor countries with high TB and HIV burden, antiretroviral therapy is often not commenced on persons infected with HIV until such patients have advanced HIV. As a result, most persons with HIV infection are already infected with TB without knowing so [4].

Furthermore, based on the natural history of TB, it has been shown that early detection of active TB cases, quick and effective delivering of anti-TB drugs, coupled with prevention of TB through vaccination and prophylaxis therapy can lead to effective control of TB in a resource-poor setting [5]. In spite of the gains achieved by DOTS, the treatment strategy has however been limited by the cost-effectiveness of the programme, the high unpredictability of DOTS interventions combined in TB control programmes, and the suitability of the treatment strategy to patients and health care workers in various setting [5].

The aim of this paper is to modify the mathematical model for TB in Okuonghae and Ikhimwin [6] by incorporating time-dependent control functions and to apply optimal control theory in the resulting model. The control functions represent the impact of limited-resources on intensive mass media enlightenment campaign and case finding techniques, as they impact on the population dynamics of TB. This paper is organized as follows. In Section 2, we formulate the optimal control model as an optimal control problem, and characterize the problem using the Pontryagin's Maximum Principle, and the optimality system is derived. In Section3, the optimality system is solved numerically using the Runge-Kutta method in a forward-backward fashion. Section 4 contains a brief discussion of the results from this work.

2.0 Formulation of optimal control model

The mathematical model for TB in Okuonghae and Ikhimwin [6] is modified by incorporating time-dependent control functions.

2.1 TB model in Okuonghae and Ikhimwin [6]

In this section, we describe the model in [6]. The authors in [6] extended the TB model in Okuonghae and Omosigho [7]. Instead of partitioning only the susceptible individuals according to their level of TB awareness (i.e., S_1 and S_2 as described in [7]), the authors also partitioned the latently-infected individuals according to their level of TB awareness in [6]. This assumption is reasonable because latently-infected individuals show no signs and symptoms of TB and they also do not transmit the disease. Hence, according to their level of TB awareness, the latently-infected subpopulation is split into high risk (low level of TB awareness) group, E_1, and the educated low risk (high level of awareness) group, E_2. Persons in the E_1 compartment are made up of individuals from the S_1 class as well as some from the treated class (T) who have a low level of TB awareness after their recovery. Individuals in the latent class with low level of awareness $(E_1)$are educated at a per capita rateψ, and are thereafter moved to the E_2 compartment. Individuals who recovers after successful treatment can become re-infected, with a fraction $0 \le \omega \le$ lof such persons entering the class of latent TB infections with low level of TB awareness (E_1), while the remaining fraction, 1 - ω, are moved into the E_2 compartment.

The authors also assumed that the enlightenment programmes produces temporary 'immunity' at a per capita rate θ_1 (for the susceptible individuals, S_1 and S_2) and at a rate θ_2 (for the latently-infected individuals, E_1 and E_2). The case $\theta_1(\theta_2)=\infty$ corresponds to the situation where there is absolutely no immunity (resulting from the enlightenment programme), whereas $\theta_1(\theta_2)=0$ corresponds to the situation where there is life-long immunity. Hence, $\theta_1(\theta_2)$ measures the rate at which individuals from the $S_2(E_2)$ group returns to the $S_1(E_1)$ group as a result of continuous education from the TB awareness programmes while the disease remains in the population. It was further assumed that β is TB transmission rate.

In addition, the authors assumed that $0 < p_1(p_2) < 1$ represent the fraction of individuals with new TB infections who developed the disease fast per unit of time from the class of latent TB infections with low level of TB awareness (high level of TB awareness). Due to the benefits accruing from the awareness programmes, the authors assumed that $p_1 > p_2$ since new TB infections are promptly detected and as such fewer cases of fast progressions from latent to active TB will be recorded amongst individuals with a high level of TB awareness (low risk group).

It was further assumed that the modifications parameters, $b_1(b_2)$, accounts for exogenous reinfection of latently-infected individuals in the $E_1(E_2)$ class, with $0 \le b_2 \le b_1 \le 1$ and $k_1(k_2)$represent the progression rate of individuals from the latent class, $E_1(E_2)$, to active TB. In addition to the impact of active cough identification (α_2) and the cost factor (v), on improving the case detection (and identification) rates, apparent from the number of active TB cases in the J compartment, the authors also assumed that π is the rate at which an active-case finding strategy is used in searching for chronic TB cases for treatment, with r being the treatment rate. The remaining parameter in the model are as defined in [7].

Based on the above assumptions, the modified model in [6] is given by the following system of non-linear ordinary differential equations:

$$
\begin{aligned}
\frac{dS_1}{dt} &= \Lambda - \alpha_1 S_1 - \beta S_1 \frac{(I+\eta J)}{N} + \theta_1 S_2 - \mu S_1,\\
\frac{dS_2}{dt} &= \alpha_1 S_1 - \sigma\beta S_2 \frac{(I+\eta J)}{N} - \theta_1 S_2 - \mu S_2,\\
\frac{dE_1}{dt} &= (1-p_1)\left(\beta S \frac{(I+\eta J)}{N} + \omega \in \beta T \frac{(I+\eta J)}{N}\right) - b_1\beta E_1 \frac{(I+\eta J)}{N}\\
&\quad -(k_1+\mu+\psi)E_1 + \theta_2 E_2,\\
\frac{dE_2}{dt} &= (1-p_2)\left(\sigma\beta S_2 \frac{(I+\eta J)}{N} + (1-\omega)\in \beta T \frac{(I+\eta J)}{N}\right) - b_2\beta E_2 \frac{(I+\eta J)}{N}\\
&\quad -(k_2+\mu+\theta_2)E_2 + \psi E_1,\\
\frac{dI}{dt} &= p_1\beta(S_1 + \omega\in T)\frac{(I+\eta J)}{N} + p_2\beta(\sigma S_2 + (1-\omega)\in T)\frac{(I+\eta J)}{N}\\
&\quad + \beta(k_1E_1 + b_2E_2)\frac{(I+\eta J)}{N} + k_1E_1 + k_2E_2 + (\nu\alpha_2 + \mu + d + \pi)I,\\
\frac{dJ}{dt} &= (\pi + \nu\alpha_2)I - rJ - \mu J,\\
\frac{dT}{dt} &= rJ - \in \beta T \frac{(I+\eta J)}{N} - \mu T,
\end{aligned}
\tag{1}
$$

with $N = S_1 + S_2 + E_1 + E_2 + I + J + T$ as the total population.

The effective reproduction corresponding to the model (1) denoted by R_T, is given by

$$
\Re_T = \frac{\beta(\mu + \eta\pi + r + \eta\nu\alpha_2)(K_1 + K_2 + K_3)}{K_4} \tag{2}
$$

where

$$
\begin{aligned}
K_1 &= k_1[(\mu+\sigma\alpha_1+\theta_1)(k_2+\theta_2) + \mu(\mu+\sigma\alpha_2+\theta_1)],\\
K_2 &= \mu(\mu+\theta_2+\psi)[\sigma\alpha_1 p_2 + p_1(\mu+\theta_1)],\\
K_3 &= k_2(\mu+\theta_1)(\mu p_1 + \psi) + k_2\sigma\alpha_1(\mu+\psi),\\
K_4 &= (\mu+r)(d+\mu+\pi+\nu\alpha_2)(\mu+\alpha_1+\theta_1)[(\mu+k_1)(\mu+k_2+\theta_2) + (\mu+k_2)\psi].
\end{aligned}
\tag{3}
$$

The qualitative and quantitative study as well as the TB control measures gleaned from the analysis of the TB model (1) are given in [6].The definition of state variables and parameters in the model (1) are presented in Tables 1 and 2.

Table 1: Description of state variables in the TB model (1).

Variable	Description
$S_1(t)$	Population of 'uneducated' susceptible individuals
$S_2(t)$	Population of 'educated' susceptible individuals
$E_1(t)$	Population of 'uneducated' latently-infected individuals
$E_2(t)$	Population of 'educated' latently-infected individuals
$I(t)$	Population of infectious individuals
$J(t)$	Population of infectious (identified) individuals
$T(t)$	Population of treated individuals

Table 2: Description of parameters in the TB model (1).

Parameter	Description
μ	Natural death rate
Λ	Recruitment rate
β	Transmission rate
b_1, b_2	Transmission rate (exogenous re-infection)
p_1, p_2	Fraction of fast progression
k_1, k_2	Progression rate
r	Recovery rate
d	TB – induced death rate

v	Cost factor
η	Modification parameter for reduced infectiousness of isolated persons
α_1, ψ	Awareness rate
α_2	Cough identification rate
$\in$	Modification parameter for infectiousness of previously treated individuals
θ_1, θ_2	'Immunity' measure
σ	Effect of program
ω	Fraction of treated with high awareness
π	Active case–finding rate

2.2 Formulation and analysis of optimal control problem

The TB model in [6] is modified by incorporating time-dependent control functions, $w_1(t)$ and $w_2(t)$. The control functions are bounded and *Lebesgue* integrable, with $w_1(t)$ being a control that represent the fraction of susceptible (and latently-infected) individuals who received TB awareness message and are now aware in a population where there is limited-resources for carrying out such enlightenment campaign programmes about TB. The case $w_1(t) \to 1$ implies that limited resources has a strong negative impact on TB awareness campaign programmes, and thus unable to educated high-risk susceptible $(S_1(t))$ and latently-infected $(E_1(t))$ individuals with a low level of TB awareness. Whereas, the case $w_1(t) \to 0$ indicates that limited resources does not negatively impact on TB awareness campaign programmes, thus available enlightenment programmes are able to educate a large fraction of high-risk susceptible (and latently-infected) individuals with a low level of TB awareness. The function $w_2(t)$, is a case finding control that represent the proportion of infectiouspersons who are identified and isolated in health-care facilitiesfor proper treatment and prevention of contacts with susceptibleand latently-infected individuals.The term $1+w_2$ represent the effort that supports the case findingtechniques and isolation policy in 'holding down' the isolated infectious individuals for proper treatment.

Based on the above assumptions, the optimal control model is given by

$$
\begin{aligned}
\frac{dS_1}{dt} &= \Lambda - (1-w_1(t))\alpha_1 S_1 - \beta S_1 \frac{(I+\eta J)}{N} + \theta_1 S_2 - \mu S_1,\\
\frac{dS_2}{dt} &= (1-w_1(t))\alpha_1 S_1 - \sigma\beta S_2 \frac{(I+\eta J)}{N} - (\theta_1 - \mu) S_2,\\
\frac{dE_1}{dt} &= (1-p_1)\left(\beta S_1 \frac{(I+\eta J)}{N} + \omega \in \beta T \frac{(I+\eta J)}{N}\right) - b_1 \beta E_1 \frac{(I+\eta J)}{N}\\
&\quad - \theta_2 E_2 - (1-w_1(t))\psi E_1 - (k_1+\mu)E_1,\\
\frac{dE_2}{dt} &= (1-p_2)\left(\sigma\beta S_2 \frac{(I+\eta J)}{N} + (1-\omega) \in \beta T \frac{(I+\eta J)}{N}\right) - b_2 \beta E_2 \frac{(I+\eta J)}{N}\\
&\quad - (k_2+\mu+\theta_2)E_2 + \psi E_1,\\
\frac{dI}{dt} &= p_1\beta(S_1 + \omega \in T)\frac{(I+\eta J)}{N} + p_2\beta(\sigma S_2 + (1-\omega) \in T)\frac{(I+\eta J)}{N}\\
&\quad + \beta(b_1 E_1 + b_2 E_2)\frac{(I+\eta J)}{N} + k_1 E_1 + k_2 E_2 - (1+w_2(t))v\alpha_2 I + (\pi + d + \mu)I,\\
\frac{dJ}{dt} &= (1+w_2(t))v\alpha_2 I + \pi I - (r+\mu)J,\\
\frac{dT}{dt} &= rJ - \in \beta T \frac{(I+\eta J)}{N} - \mu T,
\end{aligned}
\tag{4}
$$

The objective functional to be minimized is given by

$$
G(w_1^*, w_2^*) = \int_0^{t_f} \left(S_1(t) + E_1(t) + I(t) - J(t) + \frac{B_1}{2} w_1^2(t) + \frac{B_2}{2} w_2^2(t) \right) dt \tag{5}
$$

In (5), we minimize the number of high-risk susceptible and latent TB infections with low level of TB awareness through intensive mass media campaign efforts, and also minimize the number of persons in the undetected infectious persons through case finding techniques. At the same time, we seek to maximize the number of individuals in the identified infectious group (placed on a treatment regime under DOTS programme). Hence, our interest is to minimize an objective functional that shows a trade-off needed in minimizing the number of high-risk susceptible *(S_1)* and latently-infected *(E_1)* individuals with low level of TB awareness, as well as undetected infectious individuals *(I)*, while maximizing the number of detected infectious individuals*(J)*, with minimal associated relevant cost of achieving these interventions. The associated cost of carrying the intensive mass TB awareness campaign as well as the cost of implementing case finding techniques (which uses active cough as a marker for identifying a potential active TB case) in a population are nonlinear and hence take a quadratic form.

It assumed that that the associated cost of carrying out such an intensive TB awareness campaign, and the cost of conducting active cough identification are nonlinear and thus take a quadratic form. The parameters B_1 and B_2 signifies the weights on the benefit and cost (and they balance the cost factors due to the size and significance of the terms constituting the objective functional).Consequently, we seek to find an optimal pair, w_1*and w_2*, such that

$$G(w_1^*, w_2^*) = \min\{G_2(w_1, w_2): w_1, w_2 \in \Omega\}, \quad (6)$$

where Ω is the control set defined by:

$$\Omega = \left\{(w_1, w_2) \in L^1(0, t_f) \times L^1(0, t_f) \mid a_i \le w_i \le b_i\right\} \quad (7)$$

with a_i, b_i, i = 1,2being non-negative constants.

The Pontryagin's Maximum Principle [8] provides the necessary conditions that an optimal pair must satisfy. This principle converts (4), (5) and (6) into a problem of minimizing an Hamiltonian, H, pointwisely with respect to w_1 and w_2:

$$H = S_1(t) + E_1(t) + I(t) + \frac{B_1}{2} w_1^2(t) + \frac{B_2}{2} w_2^2(t) + \sum_{i=1}^{7} \lambda_i f_i \quad (8)$$

where f_i (i=1, …, 7) is the right-hand side of the system of differential equations of the i-th state variable. When the Pontryagin's Maximum Principle is applied and the existence result for optimal control from [9], we claim the following result:

Theorem1: There exists an optimal control pair w_1^*, w_2^* and the corresponding solution S_1*, S_2*, E_1*, E_2*, I*, J*and T* that minimizes $G(w_1, w_2)$ over Ω. Furthermore, there exist adjoint functions: $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6$ and λ_7 such that

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -1 + \lambda_1\left(\frac{\beta(I^*+\eta J^*)}{N^*} + \alpha_1(1-w_1^*(t)) + \mu\right) - \lambda_2\alpha_1(1-w_1^*(t)) \\
&\quad - \lambda_3\left(\frac{\beta(1-p_1)(I^*+\eta J^*)}{N^*}\right) - \lambda_5\left(\frac{\beta p_1(I^*+\eta J^*)}{N^*}\right) \\
\frac{d\lambda_2}{dt} &= -\lambda_1\theta_1 + \lambda_2\left(\frac{\beta\sigma(I^*+\eta J^*)}{N^*} + \theta_1 + \mu\right) - \lambda_4\left(\frac{\beta\sigma(1-p_2)(I^*+\eta J^*)}{N^*}\right) \\
&\quad - \lambda_5\left(\frac{\beta\sigma p_2(I^*+\eta J^*)}{N^*}\right) \\
\frac{d\lambda_3}{dt} &= -1 + \lambda_3\left(\frac{\beta b_1(I^*+\eta J^*)}{N^*} + \psi(1-w_1^*(t)) + k_1 + \mu\right) - \lambda_2\psi(1-w_1^*(t)) \\
&\quad - \lambda_5\left(\frac{\beta b_1(I^*+\eta J^*)}{N^*} + k_1\right) \\
\frac{d\lambda_4}{dt} &= -\lambda_3\theta_2 + \lambda_4\left(\frac{\beta b_2(I^*+\eta J^*)}{N^*} + k_2 + \theta_2 + \mu\right) - \lambda_5\left(\frac{\beta b_2(I^*+\eta J^*)}{N^*} + k_2\right) \\
\frac{d\lambda_5}{dt} &= -1 + \lambda_1\left(\frac{\beta S_1^*}{N^*}\right) + \lambda_2\left(\frac{\beta S_2^*}{N^*}\right) \\
&\quad - \lambda_3\left((1-p_1)\left(\frac{\beta \in \omega T^*}{N^*} + \frac{\beta S_1^*}{N^*}\right) - \frac{\beta b_1 E_1^*}{N^*}\right) \\
&\quad - \lambda_4\left((1-p_2)\left(\frac{\beta \in (1-\omega)T^*}{N^*} + \frac{\beta\sigma S_2^*}{N^*}\right) - \frac{\beta b_2 E_2^*}{N^*}\right) \\
&\quad - \lambda_5\left(\beta p_1\left(\frac{\in \omega T^* + S_1^*}{N^*}\right) + \beta p_2\left(\frac{\in (1-\omega)T^* + \sigma S_2^*}{N^*}\right) + \beta\left(\frac{b_1E_1^* + b_2E_2^*}{N^*}\right) - \alpha_2 v(1+u_2^*(t)) - (\pi + d + \mu)\right) \\
&\quad - \lambda_6(\pi + \alpha_2 v(1+u_2^*(t))) + \lambda_7\left(\frac{\beta \in T^*}{N^*}\right) \\
\frac{d\lambda_6}{dt} &= -1 + \lambda_1\left(\frac{\beta\eta S_1^*}{N^*}\right) + \lambda_2\left(\frac{\beta\eta\sigma S_2^*}{N^*}\right) \\
&\quad - \lambda_3\left((1-p_1)\left(\frac{\beta\eta \in \omega T^*}{N^*} + \frac{\beta\eta S_1^*}{N^*}\right) - \frac{\beta\eta b_1 E_1^*}{N^*}\right) \\
&\quad - \lambda_4\left((1-p_2)\left(\frac{\beta\eta \in (1-\omega)T^*}{N^*} + \frac{\beta\eta\sigma S_2^*}{N^*}\right) - \frac{\beta\eta b_2 E_2^*}{N^*}\right) \\
&\quad - \lambda_5\left(\beta\eta p_1\left(\frac{\in \omega T^* + S_1^*}{N^*}\right) + \beta\eta p_2\left(\frac{\in (1-\omega)T^* + \sigma S_2^*}{N^*}\right) + \beta\eta\left(\frac{b_1E_1^* + b_2E_2^*}{N^*}\right)\right) \\
&\quad + \lambda_6(r+\mu) + \lambda_7\left(\frac{\beta\eta \in T^*}{N^*} - r\right)
\end{aligned} \quad (10a)$$

$$\frac{d\lambda_7}{dt} = -\lambda_3\left(\frac{\beta \in \omega(1-p_1)(I^*+\eta J^*)}{N^*}\right) + \lambda_4\left(\frac{\beta \in (1-\omega)(1-p_2)(I^*+\eta J^*)}{N^*}\right) \quad (10b)$$
$$-\lambda_5\left(\frac{\beta \in \omega(1-p_1)(I^*+\eta J^*)}{N^*}\right) - \lambda_4\left(\frac{\beta \in (1-\omega)(1-p_2)(I^*+\eta J^*)}{N^*}\right)$$
$$-\lambda_5\left(\frac{\beta \in \omega p_1(I^*+\eta J^*)}{N^*} + \frac{\beta \in (1-\omega)p_2(I^*+\eta J^*)}{N^*}\right)$$
$$-\lambda_7\left(\frac{\beta \in (I^*+\eta J^*)}{N^*} + \mu\right),$$

with transversality conditions

$$\lambda_i(t_f) = 0, \qquad i = 1,...,7 \quad (11)$$

and

$$N^* = S_1^* + S_2^* + E_1^* + E_2^* + I^* + J^* + T^*.$$

Moreover, the following characterization for the control function holds

$$w_1^*(t) = \min\left(\max\left(\alpha_1, \frac{1}{B_1}\left[\alpha_1 S_1^*(\lambda_1 - \lambda_2) + \psi E_1(\lambda_3 - \lambda_4)\right]\right), b_1\right), \quad (12a)$$

and

$$w_2^*(t) = \min\left(\max\left(\alpha_2, \frac{1}{B_2}\left[\alpha_2 v I^*(\lambda_5 - \lambda_6)\right]\right), b_2\right). \quad (12b)$$

Proof: By Corollary 4.1 in [9], the convexity of the integrand of *G* in (5) with respect to (u_1, u_2) guarantees the existence of an optimal pair, a priori boundedness of the state variables, and the Lipschitz property of the state system with respect to the state variables. The adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle [8] such that:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_1}, \quad \lambda_1(t_f) = 0,$$
$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial S_2}, \quad \lambda_2(t_f) = 0,$$
$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial E_1}, \quad \lambda_3(t_f) = 0,$$
$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial E_2}, \quad \lambda_4(t_f) = 0, \quad (13)$$
$$\frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial I}, \quad \lambda_5(t_f) = 0,$$
$$\frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial J}, \quad \lambda_6(t_f) = 0,$$
$$\frac{d\lambda_7}{dt} = -\frac{\partial H}{\partial T}, \quad \lambda_7(t_f) = 0.$$

Considering the optimality conditions

$$\frac{\partial H_2}{\partial \omega_1} = 0 \text{ and } \frac{dH_2}{d\omega_2} = 0, \quad (14)$$

the optimal control pair (w_1^*, w_2^*) can be solved for, subject to the state variables. Taking into account the bounds on the control, the characterization in (12) can be obtained. This yield, for the optimal control, $w_1^*(t)$,

$$\frac{\partial H}{\partial w_1} = B_1 w_1 + \alpha_1 S_1(\lambda_1 - \lambda_2) + \psi E_1(\lambda_3 - \lambda 4) = 0 \quad (15)$$

which implies that

$$w_1^*(t) = \frac{1}{B_1}\left[\alpha_1 S_1^*(\lambda_2 - \lambda_1) + \psi E_1^*(\lambda_4 - \lambda_3)\right] \quad (16)$$

on the control set $\{t : a_1 < w_1^*(t) < b_1\}$.

Similarly, for the optimal control function $w_2^*(t)$, we have

$$\frac{\partial H}{\partial w_2} = B_2 w_2 + \alpha_2 v I(\lambda_6 - \lambda_5) = 0 \quad (17)$$

which implies that

$$w_2^*(t) = \frac{1}{B_2} v \alpha_2 I(\lambda_5 - \lambda_6) \quad (18)$$

on the control set $\{t : a_2 < w_2^*(t) < b_2\}$.

We note that the optimality conditions (i.e., taking derivatives of the Hamiltonian with respect to the controls) only hold in the interior of the control set.

3.0 Numerical simulations

The optimal strategy for effective control of TB, consisting of intensive mass media enlightenment campaign coupled with some case finding techniques (for identifying chronic TB cases), in a population with limited-resources are obtained by solving the optimality systems which is made up of the system of controlled ordinary differential equations for the state system and their corresponding adjoint equations.

Consequently, the state system, together with an initial condition, are solved forward in time using a guess for the controls over the simulated time, while the adjoint system, with values at the final time t_f, is solved backward in time using the current iterative solution of the state system. The controls are then updated using a convex combination of the controls coupled with the value from the characterization (12).

The process, as well as the iteration is stopped if the values of unknowns at the previous iteration are very close to the ones at the present iteration [10]. It is important to note that the optimal control analysis carried out in this work, as well the simulations do not depend on the specific parameter values used for the simulation.

Table 3: Baseline value and ranges of the parameters of the optimal control model (4)

Parameters	Baseline values	Range	References
μ	0.02041year^{-1}	(0.0143, 0.04)	[11]
Λ	μ x 10^5 year^{-1}	—	[12]
β	8.557 year^{-1}	(4.4769, 15.1347)	[13]
b_1, b_2	1.5 year^{-1}	(0, 1)	[13]
p_1, p_2	0.1 year^{-1}	(0.05, 0.3)	[14]
k_1, k_2	0.0005 year^{-1}	(0.005, 0.05)	[15]
r	1.5 ind^{-1} year^{-1}	(1.5, 2.5)	[7]
d	0.365 year^{-1}	(0.22, 0.39)	[16]
ν	0.5 year^{-1}	(0, 1)	[6]
η	0.4 year^{-1}	(0, 1)	[6]
α_1, ψ	5 year^{-1}	(0, 40)	[6]
α_2	5 year^{-1}	(0, 40)	[6]
$\in$	1.2 year^{-1}	(1, 2)	[17]
θ_1, θ_2	1 year^{-1}	(0, 40)	[6]
σ	0.5 year^{-1}	(0, 1)	[6]
ω	0.5 year^{-1}	(0, 1)	[6]
π	0.5 year^{-1}	(0, 30)	[6]

The parameters used in numerically solving the optimal control problem in this chapter are given in Table 3, and for the initial conditions, we made use of the following values: $S_1(0)=(65/120)N, S_2(0)=(30/120)N$, $E_1(0)=(20/120)N$, $E_2(0)=(4/120)N$, $I(0)=(35/1200)N$, $J(0)=(20/1200)N, T(0)=(0/1200)N$, where $N=100,000$

[2, 18]. For the weights on the control functions, we have made use of the values: $B_1 = 50$ and $B_2 = 100$. And for the bounds on the control functions, we made use of $0 \le u_1 \le 0.95$ and $0 \le u_2 \le \frac{1}{\alpha_2 \nu}$

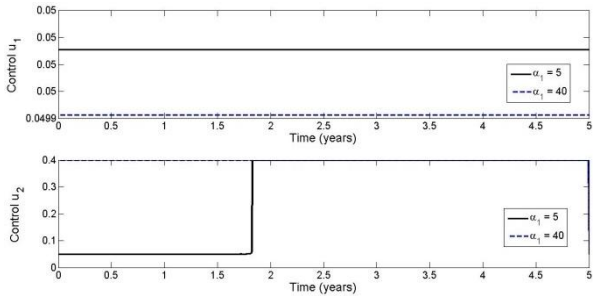

Figure 1: The controls u_1 and u_2 for the case $\mu = 0.0241$, $\Lambda = \mu \times 10^5$, $b_1 = 0.2$, $b_2 = 0.2$, $p_1 = 0.1$, $p_2 = 0.1$, $k_1 = 0.05$, $k_2 = 0.05$, $r = 1.5$, $d = 0.365$, $\nu = 0.5$, $\eta = 0.4$, $\psi = 5$, $\alpha_1 = 5$, $\alpha_2 = 5$, $\in = 1.2$, $\theta_1 = 1$, $\theta_2 = 1$, $\sigma = 0.5$, $\omega = 0.4$, $\pi = 5$, $B_1 = 50$, $B_2 = 100$, *when* α_1 *is varied.*

Figure 1 shows the controls plotted as a function of time when the awareness rate (α_1) is varied. For both values of α_1, it is observed (in the first frame) that the control (u_1), which represents the fraction of susceptible (and latently-infected) individuals who benefited from the enlightenment message, remained close to the lower bound for the entire 5-year period of simulation. It is worth noting that even a huge increase in the awareness rate did not impact positively on the control (u_1), since u_1 remained close to the lower bound. This implies that limited-resources for effective TB control had a strong negative impact on intensive mass media enlightenment campaign about TB.The second frame shows that for a low value of α_1, the second control (u_2), which presents the proportion of infectious persons who are identified and isolated in health-care facilitiesfor proper treatment and prevention of contacts with susceptibleand latently-infected individuals, remained close to the lower bound for nearly 2 years before rising (sharply) to its upper bound for the remaining period of the simulation. On the other hand, with higher value of α_1, the control (u_2) remained at the upper bound for the entire 5-year period of simulation. This indicates that maintaining the case finding at the upper bound is required in order to achieve optimal control of TB, in the setting described here.

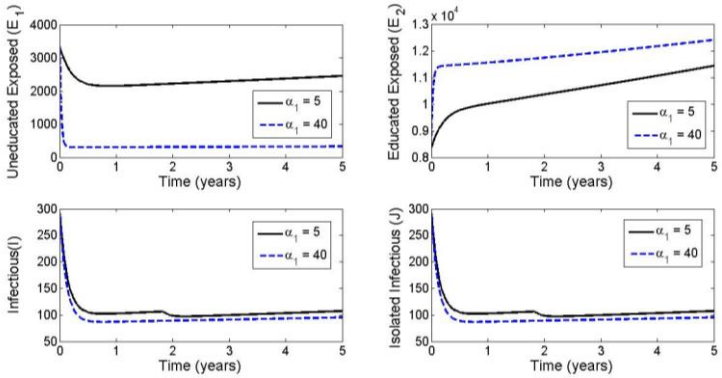

Figure2: Optimal controls strategies for the case u_1 and u_2 for the case $\mu = 0.0241$, $\Lambda = \mu \times 10^5$, $b_1 = 0.2$, $b_2 = 0.2$, $p_1 = 0.1$, $p_2 = 0.1$, $k_1 = 0.05$, $k_2 = 0.05$, $r = 1.5$, $d = 0.365$, $\nu = 0.5$, $\eta = 0.4$, $\psi = 5$, $\alpha_1 = 5$, $\alpha_2 = 5$, $\in = 1.2$, $\theta_1 = 1$, $\theta_2 = 1$, $\sigma = 0.5$, $\omega = 0.4$, $\pi = 5$, $B_1 = 50$, $B_2 = 100$, *when* α_1 *is varied.*

Figure 2 represent the impact of implementing the optimal control strategy (presented in Figure 1) with an increase in the awareness rate (α_1) on some of the epidemiological classes. The plots show that increasing the value of α_1 leads to a reduction in the number of 'uneducated' (high risk) latently-infected individuals, and a corresponding increase in the number of 'educated' (low risk) latently-infected persons. However, implementation of this optimal control strategy will only result in a slight reduction of chronic TB cases. After implementing this optimal control strategy for a simulation period of 5 years, it will result in the aversion of about *2,127/100,000* latent TB infections, and *72/100,000* active TB cases.

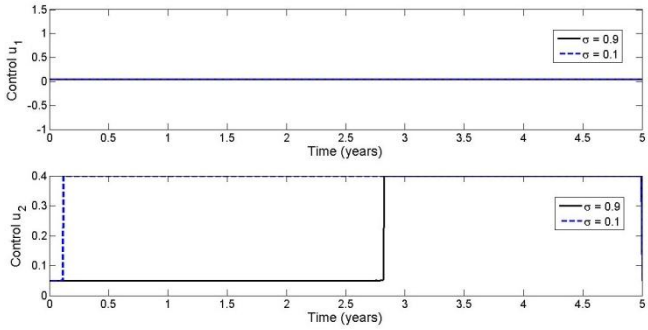

Figure3: Thecontrols u_1 and u_2 for the case $\mu = 0.0241$, $\Lambda = \mu \times 10^5$, $b_1 = 0.2$, $b_2 = 0.2$, $p_1 = 0.1$, $p_2 = 0.1$, $k_1 = 0.05$, $k_2 = 0.05$, $r = 1.5$, $d = 0.365$, $\nu = 0.5$, $\eta = 0.4$, $\psi = 5$, $\alpha_1 = 5$, $\alpha_2 = 5$, $\in = 1.2$, $\theta_1 = 1$, $\theta_2 = 1$, $\sigma = 0.5$, $\omega = 0.4$, $\pi = 5$, $B_1 = 50$, $B_2 = 100$, *when* σ *is varied.*

Figure 3 depicts the controls plotted as functions of time when the effect of the enlightenment program is varied. We recall that the TB awareness programme is assumed to reduce the chances of TB infection of susceptible individuals (with high level of TB awareness) by a factor, $\sigma (0 \le \sigma \le 1)$. The case $\sigma = 0$ signifies that the awareness programme is completely

effective, whereas $\sigma = 1$ implies that the programme is completely ineffective in reducing TB incidence. The first frame in Figure 3 shows that for both values of σ, the control (u_1) remained very close to the lower bound for the entire 5-year period of simulation; indicating that limited-resources had a negative impact on the effectiveness of the awareness programme. Hence, regardless of the effectiveness of the enlightenment programme, the control will remain close to the lower bound if resources are limited.The second frame shows that for $\sigma = 0.9$, the second control (u_2) remained close to the lower bound for nearly 3 years before rising (sharply) to its upper bound for the remaining period of the simulation. However, for $\sigma = 0.1$ the control (u_2) remained close to the lower bound for about 1 month, before a steep increase to the upper bound for the remaining period of simulation.

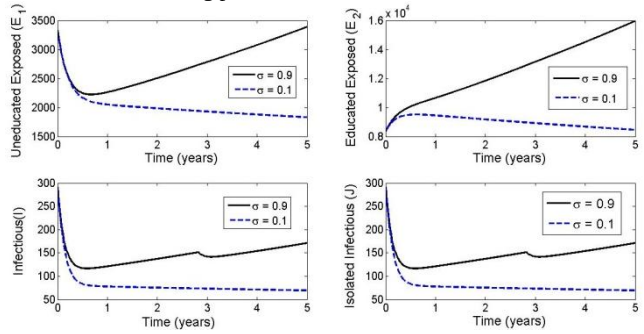

Figure 4: Optimal controls strategies for the case $\mu = 0.0241$, $\Lambda = \mu \times 10^5$, $b_1 = 0.2$, $b_2 = 0.2$, $p_1 = 0.1$, $p_2 = 0.1$, $k_1 = 0.05$, $k_2 = 0.05$, $r = 1.5$, $d = 0.365$, $\nu = 0.5$, $\eta = 0.4$, $\psi = 5$, $\alpha_1 = 5$, $\alpha_2 = 5$, $\in = 1.2$, $\theta_1 = 1$, $\theta_2 = 1$, $\sigma = 0.5$, $\omega = 0.4$, $\pi = 5$, $B_1 = 50$, $B_2 = 100$, *when* σ *is varied.*

Figure 4 shows some epidemiological classes when the optimal control strategy (presented in Figure 3) is implemented with an improvement in the effectiveness of the educational programme (σ), in a population with limited with resources. The plots show that as the effectiveness of the TB enlightenment programme is improved, it resulted in significant reduction in both latent and active TB cases. In fact, after implementing of this optimal control strategy for a period of 5 years, it will result in the aversion of about *9,055/100,000* latent TB infections and some *601/100,000* active TB cases.

Figure 5 shows the controls plotted as a function of time with a variation in the cough identification rate (α_2). The first frame shows that for both values of α_2, the control (u_1) remained close to the lower bound. However, the second frame shows that for both values of α_2, the control (u_2) initially remained close to the lower bound before a steep increase to the upper bound for almost the entire 5-year period of simulation.

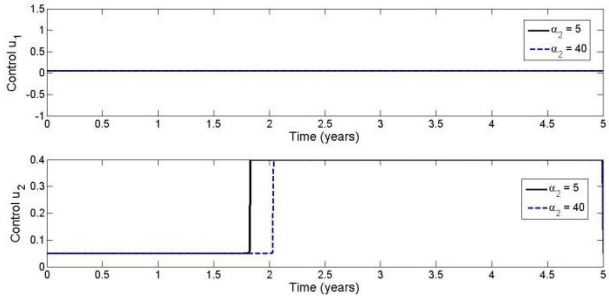

Figure5: The controls u_1 and u_2 for the case $\mu = 0.0241$, $\Lambda = \mu \times 10^5$, $b_1 = 0.2$, $b_2 = 0.2$, $p_1 = 0.1$, $p_2 = 0.1$, $k_1 = 0.05$, $k_2 = 0.05$, $r = 1.5$, $d = 0.365$, $\nu = 0.5$, $\eta = 0.4$, $\psi = 5$, $\alpha_1 = 5$, $\alpha_2 = 5$, $\in = 1.2$, $\theta_1 = 1$, $\theta_2 = 1$, $\sigma = 0.5$, $\omega = 0.4$, $\pi = 5$, $B_1 = 50$, $B_2 = 100$, *when* α_2 *is varied.*

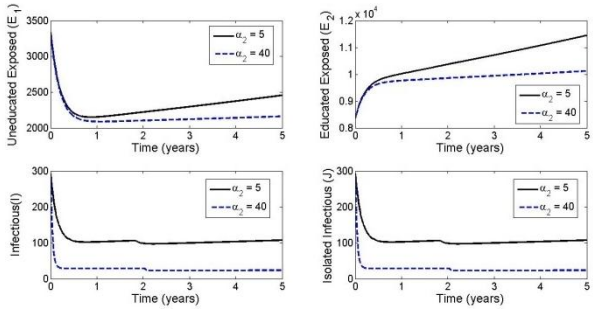

Figure 6: Optimal controls strategies for the case u_1 and u_2 for the case $\mu = 0.0241$, $\Lambda = \mu \times 10^5$, $b_1 = 0.2$, $b_2 = 0.2$, $p_1 = 0.1$, $p_2 = 0.1$, $k_1 = 0.05$, $k_2 = 0.05$, $r = 1.5$, $d = 0.365$, $\nu = 0.5$, $\eta = 0.4$, $\psi = 5$, $\alpha_1 = 5$, $\alpha_2 = 5$, $\in = 1.2$, $\theta_1 = 1$, $\theta_2 = 1$, $\sigma = 0.5$, $\omega = 0.4$, $\pi = 5$, $B_1 = 50$, $B_2 = 100$, *when* α_2 *is varied.*

Figure 6 shows the impact of implementing the optimal control strategy (presented in Figure 5) on some of the epidemiological classes, with an increase in the cough identification rate (α_2). The plots show that an increase in the value of α_2 will result in significant decrease in the number of latent and active TB cases in the population. However, more effect is seen on the infectious subpopulations. After implementing the optimal control strategy for a 5-year period of simulation, it will result in the aversion of about 1,624/100,000 latent TB infections, and about 164/100,000 active TB cases.

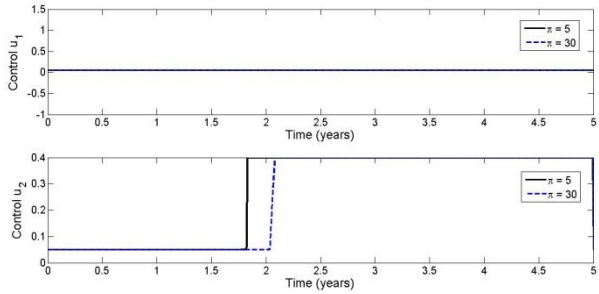

Figure 7: The controls u_1 and u_2 for the case $\mu = 0.0241$, $\Lambda = \mu \times 10^5$, $b_1 = 0.2$, $b_2 = 0.2$, $p_1 = 0.1$, $p_2 = 0.1$, $k_1 = 0.05$, $k_2 = 0.05$, $r = 1.5$, $d = 0.365$, $\nu = 0.5$, $\eta = 0.4$, $\psi = 5$, $\alpha_1 = 5$, $\alpha_2 = 5$, $\in = 1.2$, $\theta_1 = 1$, $\theta_2 = 1$, $\sigma = 0.5$, $\omega = 0.4$, $\pi = 5$, $B_1 = 50$, $B_2 = 100$, *when* π *is varied.*

In Figure 7, we have the controls plotted as a function of time with a variation in the active case finding rate (π). The first frame shows that for both values of π, the control (u_1) remained close to the lower bound. The second frame shows that for both values of π, the behavior of the control (u_2) is quite similar to that in Figure 6.5 for the entire 5-year period of simulation.

Finally, in Figure 8, we have the simulation results of implementing the optimal control strategy (presented in Figure 7) on the infected epidemiological classes. The plots show that an increase in the active case finding rate will result in reduction in number of both latent and active TB cases in the population. Just like in the Figure 6, we also observe that greater effect is felt on infectious subpopulation. After implementing the optimal control strategy for a 5-year period of simulation, it will result in the aversion of about *1,693/100,000* latent TB infections, and about *168/100,000* active TB cases.

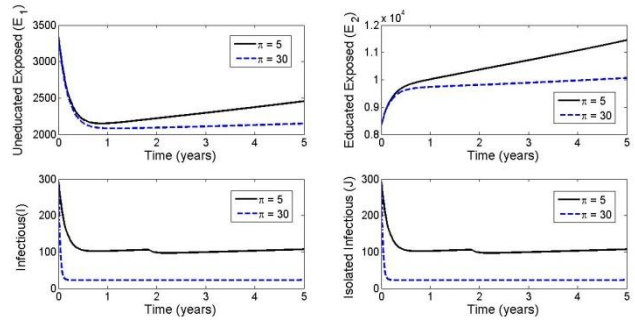

Figure 8: Optimal controls strategies for the case u_1 and u_2 for the case $\mu = 0.0241$, $\Lambda = \mu \times 10^5$, $b_1 = 0.2$, $b_2 = 0.2$, $p_1 = 0.1$, $p_2 = 0.1$, $k_1 = 0.05$, $k_2 = 0.05$, $r = 1.5$, $d = 0.365$, $\nu = 0.5$, $\eta = 0.4$, $\psi = 5$, $\alpha_1 = 5$, $\alpha_2 = 5$, $\in = 1.2$, $\theta_1 = 1$, $\theta_2 = 1$, $\sigma = 0.5$, $\omega = 0.4$, $\pi = 5$, $B_1 = 50$, $B_2 = 100$, *when* π *is varied.*

4 Discussion and conclusion

In this study, we have presented a new optimal control model that examines the impact of limited-resources on enlightenment campaign programmes for tuberculosis, which ultimately affects the population dynamics of the disease. The new optimal control model in this work is an extension of the TB model in [6]; where we incorporated time-dependent control functions which represented the fraction of susceptible (and latently-infected) individuals who benefited from TB enlightenment campaign programmes, as well as case-finding techniques for detecting and isolating active TB for effective treatment. The optimal control model presented in this paper can implemented in developing countries where there still exists limited-resources for effective TB control.

Results from the numerical simulations of our optimal control model suggest that in order to significantly reduce the incidence of latent TB infections in the population, then attention must immediately shift to improving the effectiveness of the educational programme, i.e., intensive mass media enlightenment campaign programmes about TB. On the other hand, in order to arrest cases of active TB, then attention must immediately shift to increasing the cough identification rate and the active case finding rate.

At the moment, there exists very little or no mass media enlightenment campaign about TB in Nigeria and perhaps, same in other developing countries of the world. This lack of advocacy and social mobilization about TB often keeps a large percentage of persons in the population in the dark about TB [19]. This ultimately fosters continued spread of TB in the population.

The lack of financial commitment on the part of governments in some developing countries has greatly and negatively affected effective TB control in such regions [19, 20]. The financial burden associated with TB diagnosis and treatment on TB patients in resource-poor countries continues to be one of the major problems in effectively controlling the disease in these regions. Consequently, an overall strengthening of health care system and greater funding by government of developing countries and international donor agencies is urgently needed in these regions [20].

In conclusion, the results from our optimal control model and numerical simulation has shown how an optimal combination of intensive mass media enlightenment campaign about TB, coupled with cough identification and active case finding may depend on the cost of implementing the controls as well as the parameters of the TB model, particularly, the effect of the intensive mass media awareness campaign programme (σ), cough identification rate (α_2), and active case finding rate for (π). The result from this paper provides a framework for designing cost-effective strategies for the control of TB using multiple intervention programmes in a population with limited-resources.

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