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Optimal control analysis of a tuberculosis model with drug-resistant population

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Abstract Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, stands as one of the most infectious diseases globally, predominantly affecting the lungs (known as pulmonary tuberculosis). It manifests in two primary forms based on bacterial drug sensitivity: drug-sensitive TB (DS-TB) and drug-resistant TB (DR-TB). DS-TB remains susceptible to medication, whereas DR-TB has developed resistance. This study explores a mathematical model explaining the spread of tuberculosis within a drug-resistant population, proposing optimal control strategies to curb its dissemination through educational initiatives and enhancements in healthcare facilities. The stability analysis reveals that disease-free equilibrium points are locally asymptotically stable when $R_0 < 1$, while endemic equilibrium points prevail and are locally asymptotically stable if $R_0 > 1$. Additionally, sensitivity analysis identifies important parameters within the model. By using the Pontryagin Maximum Principle, control variables are integrated and numerically solved. Through simulations and cost assessments, we illustrate the efficacy of employing both control strategies concurrently, effectively reducing the populations susceptible to exposure, DS-TB, and DR-TB infections.

Keywords Mathematical Model, Stability, Optimal Control, Tuberculosis, Drug-sensitive Tuberculosis, Drug-resistant Tuberculosis.

AMS 2010 subject classifications 34A34, 34A45, 92C60, 92D30, 93C15

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1. Introduction

Tuberculosis (TB) spreads through the air when the sufferer coughs, sneezes, or spits. Infection can occur simply by inhaling some bacteria [1]. The main symptom of TB disease is coughing up phlegm for 2 weeks or more. TB healing is carried out by undergoing routine treatment until it is complete during $6-9$ of the month with TB drugs [2]. Drug-resistant TB (DR-TB) spreads in the same way as drug-sensitive TB (DS-TB) spreads, but DR-TB treatment requires a longer time, $9-24$ months, with strict *follow-up* from medical personnel. In general, DR-TB is indeed more dangerous than DS-TB because tuberculosis drugs that are usually given to TB patients can no longer kill TB bacteria in the patient's body [3]. According to the CDC, DR-TB can occur due to errors in the use and management of drugs in people with DS-TB.

It is estimated that a quarter of the world's population is exposed to TB, but only approximately $5-15\%$ of them will exhibit symptoms of active TB disease. The remainder harbor latent TB infections, which are asymptomatic and non-transmissible, though they may progress to active TB if the immune system weakens. According to global reports, around 10 million individuals contract TB annually, resulting in 1.5 million deaths. DR-TB cases are on the rise, with 157,903 cases detected, including 132,222 MDR/RR-TB cases and 25,681 pre-XDR-TB/XDR-TB cases.

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TB control aligns with the Sustainable Development Goals (SDGs), a key global initiative. While annual TB case numbers are declining, there remains a significant disparity compared to estimates. The WHO Global TB Report 2021 identifies India, Indonesia, and Philippines as having the largest gaps between estimated and reported cases, with reported numbers accounting for only 24%, 11%, and 8.3% of estimated cases, respectively. Ten countries, including China, Democratic Republic Congo, and Nigeria, contribute to approximately 70% of the global gap in DR-TB cases. This gap arises due to underreporting by TB patients and underdiagnosis, often due to limited access to healthcare or misdiagnosis [1]. Given this substantial gap, a considerable reservoir of undetected TB cases poses a significant transmission risk. Thus, several TB control strategies can be implemented: administering the BCG vaccine [4], conducting educational programs to enhance public understanding and mitigate misconceptions about TB, and improving treatment success rates [5, 6].

In recent decades, mathematical models have played an important role in disease control. There are already several studies focused on TB that have studied many factors. Agusto et al. [7] have discussed the mathematical model of the spread of MDR-TB and XDR-TB by paying attention to factors such as loss of follow-up and isolation. Gao and Huang [8] have discussed optimal control strategies to overcome TB transmission with three forms of control: vaccination, successful treatment rate, and treatment rate in vulnerable, latent humans and infected with active TB. Furthermore, Rocha et al. [9] studied the impact of immigrant populations from high-incidence TB areas on a host country. Das et al. [10] investigated the influence of media awareness programs on the dynamics of TB transmission. In the same year, Das et al. [11] discussed TB transmission in the presence of reinfection. Baba et al [12] present a tuberculosis model with saturated incidence rate and time dependent control strategy. Incorporated in the model is the therapeutic treatments given to infected individuals. Then, Ullah et al. [13] discussed the application of optimal control in the form of vaccination and treatment in the mathematical model of TB spread. In the same year, Liu et al. [14] investigated the impact of DOTS (*directly observed treatment and short course*) strategies on TB transmission in China and proposed optimal control strategies in the form of treatment for latent and infected humans. In addition, Abimdame et al. [15] demonstrated a mathematical model of TB that accounts for exogenous re-infection and incomplete treatment. The analysis reveals that the model exhibits a backward bifurcation phenomenon, primarily driven by exogenous re-infection. Interestingly, it was shown that removing incomplete treatment could significantly reduce the backward bifurcation range. In another study, fractional calculus was applied to model TB transmission dynamics, incorporating the memory effects associated with the disease spread. Olaniyi et al. [16] use Banach fixed-point theory to prove the existence and uniqueness of a solution. The fractional-order model also exhibits backward bifurcation, demonstrating the co-existence of stable TB-free and TB-present equilibria when the reproduction number is below one.

From the above discussion, the persistent efforts are imperative to combat TB, particularly DR-TB, given the ongoing emergence of new resistance variants. Hence, the authors are motivated to delve into mathematical modeling and control strategies to curb TB transmission within drug-resistant populations, drawing inspiration from the framework proposed by Liu et al. [14]. The authors differentiate the infected human population into two compartments based on bacterial drug sensitivity: DS-TB and DR-TB. Additionally, the authors incorporate various control variables into the mathematical model to address TB spread among drug-resistant populations, including educational initiatives and efforts to improve TB treatment efficacy.

2. Formulation of a Tuberculosis Model with a Drug-Resistant Population

In this section, a mathematical model of tuberculosis with a drug-resistant population is formulated. The assumptions used for the model construction are as follows:

1. The vaccinated population (V) consists individuals who have received successful BCG vaccination, primarily newborns.
2. The duration of vaccine protection is finite, implying that previously vaccinated individuals can revert to a susceptible state (S).
3. Individuals exposed to TB cannot transmit the disease; only those infected with TB have the potential for transmission.
4. The recovered population (R) may become exposed (E) again, as dormant (inactive) MTB bacteria persist in the body.

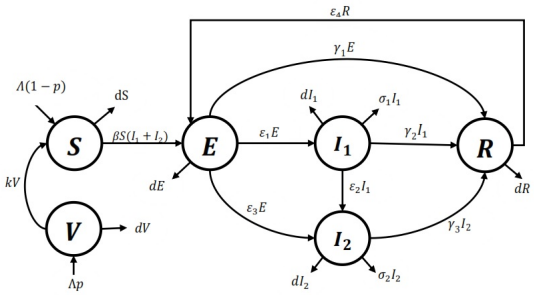

Figure 1. Transmission diagram. Mathematical model diagram of tuberculosis with a drug-resistant population.

The human population is divided into six compartments, which are the susceptible population (S), the vaccinated population (V), the exposed population (E), the infected DS-TB population (I_1), the infected DR-TB population (I_2), and human populations recovering from tuberculosis (R). The defining parameters can be seen in Table 1. Based on the assumptions, we can set up the transmission diagram that is shown in Figure 1. From the diagram in Figure 1, transmission models can be formulated as follows:

$$\frac{dS}{dt} = \Lambda\,(1-p) - \beta S(I_1+I_2) + kV - dS, \tag{1}$$

$$\frac{dV}{dt} = \Lambda p - (k+d)V, \tag{2}$$

$$\frac{dE}{dt} = \beta S\,(I_1+I_2) - aE + \varepsilon_4 R, \tag{3}$$

$$\frac{dI_1}{dt} = \varepsilon_1 E - bI_1, \tag{4}$$

$$\frac{dI_2}{dt} = \varepsilon_3 E + \varepsilon_2 I_1 - cI_2, \tag{5}$$

$$\frac{dR}{dt} = \gamma_1 E + \gamma_2 I_1 + \gamma_3 I_2 - (d+\varepsilon_4)R. \tag{6}$$

where

$a = (\varepsilon_1 + \varepsilon_3 + d + \gamma_1)\,,$
$b = (d + \sigma_1 + \gamma_2 + \varepsilon_2)\,,$
$c = (d + \sigma_2 + \gamma_3)\,.$

Furthermore, for reason of simplicity, $S(t), V(t), E(t), I_1(t), I_2(t), R(t)$ are written into S, V, E, I_1, I_2, R with $S, V, E, I_1, I_2, R \geq 0$. Then defined $N(t)$ as total population at t, with $N = S + V + E + I_1 + I_2 + R \geq 0$. Then, all parameters are positive, with $\Lambda > 0$ and $0 < d, \beta, \sigma_1, \sigma_2, k, \varepsilon_1, \varepsilon_2, \varepsilon_3, \gamma_1, \gamma_2, \gamma_3 < 1$.

The disease-free equilibrium of tuberculosis is a condition in which there is no disease of tuberculosis. This equilibrium is attainable when there is no infected population ($I_1 = 0$ and $I_2 = 0$). Thus, a disease-free equilibrium is obtained by

$$E_0 = (S, V, E, I_1, I_2, R) = \left(\frac{\Lambda(k + d(1-\ p))}{d(k+d)}, \frac{\Lambda p}{k+d}, 0, 0, 0, 0\right).$$

Then the effective reproduction number (R_0) will be determined, which represents the expectation of the average number of new infected individuals due to contact between infected populations and suspected individuals. In this study, we applied the Next Generation Matrix (NGM) method to get R_0 which has been developed by [17] to obtain

$$R_0 = \left[\beta\left(\frac{\Lambda(k + d(1-p))}{d(k+d)}\right)\left(\frac{\varepsilon_1\varepsilon_2 + \varepsilon_3 b + \varepsilon_1 c}{abc}\right)\right].$$

Table 1. Parameters. Description of parameters in the model of drug abuse reduction.

Parameter	Description
Λ	Natural birth rate
d	Natural death rate
β	Transmission rate
σ_1	Disease-induced death rate due to DS-TB
σ_2	Disease-induced death rate due to DR-TB
k	Rate of immunity acquisition
p	The fraction of BCG vaccinated successfully
ε_1	Rate of progression from E to I_1
ε_2	Rate of progression from I_1 to I_2
ε_3	Rate of progression from E to I_2
ε_4	Rate of progression from R to E
γ_1	Recovery rate of the exposed
γ_2	Recovery rate of the infectious with DS-TB
γ_3	Recovery rate of the infectious with DR-TB

The drug-free equilibrium E_0 will be locally asymptotically stable if $R_0 < 1$ and will be unstable when $R_0 > 1$. While the endemic equilibrium is the condition that there is a tuberculosis patient, as well as the spread of that disease. Endemic equilibrium $E^* = (S^*, V^*, E^*, I_1^*, I_2^*, R^*)$ is obtained when $S \neq 0, V \neq 0, E \neq 0, I_1 \neq 0, I_2 \neq 0, R \neq 0$.

Setting the right-hand sides of the model (1)-(6) equals zero. The endemic equilibrium point of the model is

$$S^* = \frac{abcd + \varepsilon_4\left(c\varepsilon_1\left(d+\sigma_1\right) + (d+\sigma_2)(\varepsilon_1\varepsilon_2 + b\varepsilon_3) + bcd\right)}{\beta\left(c\varepsilon_1 + b\varepsilon_3 + \varepsilon_1\varepsilon_2\right)\left(d+\varepsilon_4\right)},$$

$$V^* = \frac{\Lambda p}{k+d},$$

$$E^* = (R_0 - 1)\left(1 + \frac{\varepsilon_4(bc\gamma_1 + c\gamma_2\varepsilon_1 + \gamma_3 b\varepsilon_3 + \gamma_3\varepsilon_1\varepsilon_2)}{abc\left(d+\varepsilon_4\right)(R_0-1)}\right)\frac{ad\left(bc\right)^2\left(d+\varepsilon_4\right)}{\beta(abcd + \varepsilon_4\left(c\varepsilon_1\left(d+\sigma_1\right) + (d+\sigma_2)(\varepsilon_1\varepsilon_2 + b\varepsilon_3 + bcd\right)},$$

$$I_1^* = \frac{\varepsilon_1 E^*}{b},$$

$$I_2^* = \frac{E^*}{bc}\left(b\varepsilon_3 + \varepsilon_1\varepsilon_2\right),$$

$$R^* = \frac{E^*\left(bc\gamma_1 + c\gamma_2\varepsilon_1 + \gamma_3 b\varepsilon_3 + \gamma_3\varepsilon_1\varepsilon_2\right)}{bc\left(d+\varepsilon_4\right)}.$$

by the value of a, b and c refer to the equation 1-6.

From the results of analytical calculations the terms are sufficient and the conditions need a non-endemic equilibrium point E_0 will be stable local asymptotic if and only if $R_i < 1$, with $i = 0, 1, 2, 3, 4$.

$$R_1 = \beta\left(\frac{\Lambda(k + d(1-p))}{d(k+d)}\right)\left(\frac{(\varepsilon_1 b - \varepsilon_1\varepsilon_2 + c\varepsilon_3)}{abc}\right),$$

$$R_2 = \beta\left(\frac{\Lambda(k + d(1-p))}{d(k+d)}\right)\left(\frac{(\varepsilon_1+\varepsilon_3)\left(\varepsilon_4+d\right)}{bc\left(\varepsilon_4+d\right) + d\left(ab+ac\right) + \varepsilon_1\varepsilon_4\left(d+\sigma_1+\varepsilon_2\right) + \varepsilon_1\varepsilon_3\left(d+\sigma_2\right)}\right),$$

$$R_3 = \frac{\left(1 + \frac{K_2}{abc(1-R_0)}\right)(b+c)}{\left((a+b+c+d+\varepsilon_4)\left(1 + \frac{K_1}{abc(1-R_0)}\right)\right)},$$

$$R_4 = \frac{\left(\frac{A_1^2(\varepsilon_4+d)}{abc(1-R_0)}\left(1 - \frac{K_3}{(1-R_0)}\right)\right) + \left(1 + \frac{K_2}{abc(1-R_0)}\right)^2}{A_1\left(\frac{1}{b+c}\left(1 + \frac{K_1}{abc(1-R_0)}\right)\right)\left(\left(1 + \frac{K_2}{abc(1-R_0)}\right)\right)},$$

Table 2. Parameter value of the spread of tuberculosis with drug-resistant population model

Parameter	Unit	Value	Source
Λ	$\frac{person}{year}$	$450862,2$	[19]
d	$year^{-1}$	$\frac{1}{73,5}$	Assumed
β	$year^{-1}$	$0,0000003$	Assumed
σ_1	$year^{-1}$	$0,365$	[7]
σ_2	$year^{-1}$	$0,009$	Assumed
k	$year^{-1}$	$0,25$	[14]
p	-	$0,6$	[13]
ε_1	$year^{-1}$	$0,2351$	[13]
ε_2	$year^{-1}$	$0,08$	Assumed
ε_3	$year^{-1}$	$0,013$	[7]
ε_4	$year^{-1}$	$0,5$	[11]
γ_1	$year^{-1}$	$0,6683$	[14]
γ_2	$year^{-1}$	$1,5$	[7]
γ_3	$year^{-1}$	$0,075$	Assumed

where

$$A_1 = a + b + c + d + \varepsilon_4,$$

$$A_2 = ab + ac + ad + a\varepsilon_4 + bc + bd + b\varepsilon_4 + cd + c\varepsilon_4 - \gamma_1\varepsilon_4 - \beta\left(\frac{\Lambda(k + d(1 - p))}{d(k + d)}\right)(\varepsilon_1 + \varepsilon_3),$$

$$A_3 = abc + abd + ab\varepsilon_4 + acd + ac\varepsilon_4 + bcd + bc\varepsilon_4 - b\gamma_1\varepsilon_4 - c\gamma_1\varepsilon_4 - \gamma_2\varepsilon_1\varepsilon_4 - \gamma_3\varepsilon_3\varepsilon_4 - \beta\left(\frac{\Lambda(k + d(1 - p))}{d(k + d)}\right)(c\varepsilon_1 + b\varepsilon_3 + d\varepsilon_1 + d\varepsilon_3 + \varepsilon_1\varepsilon_2 + \varepsilon_1\varepsilon_4 + \varepsilon_3\varepsilon_4),$$

$$A_4 = abcd + abc\varepsilon_4 - bc\gamma_1\varepsilon_4 - b\gamma_3\varepsilon_3\varepsilon_4 - c\gamma_2\varepsilon_1\varepsilon_4 - b\gamma_3\varepsilon_2\varepsilon_4 - \beta\left(\frac{\Lambda(k + d(1 - p))}{d(k + d)}\right)(bd\varepsilon_3 + b\varepsilon_3\varepsilon_4 + cd\varepsilon_1 + d\varepsilon_1\varepsilon_2 + \varepsilon_1\varepsilon_2\varepsilon_4 + c\varepsilon_1\varepsilon_4),$$

$$K_1 = \frac{\varepsilon_4}{abc\,(\varepsilon_4 + d)}\left(bc\gamma_1 + b\gamma_3\varepsilon_3 + c\gamma_2\varepsilon_1 + \gamma_3\varepsilon_1\varepsilon_2\right),$$

$$K_2 = ab^2 + (ac + ad + c\varepsilon_4 + bc + bd + b\varepsilon_4 + cd + (\varepsilon_1 + \varepsilon_3 + d))\,(b + c) - \beta\left(\frac{\Lambda(k + d(1 - p))}{d(k + d)}\right)(\varepsilon_1\,(d + \sigma_1 + \gamma_2) + c\varepsilon_3),$$

$$K_3 = bc\,(\varepsilon_4 + d) + d\,(ab + ac) + \varepsilon_1\varepsilon_4\,(d + \sigma_1 + \varepsilon_2) + \varepsilon_1\varepsilon_3\,(d + \sigma_2) - \beta\left(\frac{\Lambda(k + d(1 - p))}{d(k + d)}\right)(\varepsilon_1 + \varepsilon_3)\,(\varepsilon_4 + d).$$

by the value of a, b and c refer to the equations 1-6.

Moreover, the endemic equilibrium point will be analyzed through numerical simulation by using a phase field because it is difficult to do analytically, The parameter values and initial values are presented in Tables 2 and 3. Modeling and verification are crucial processes as they ensure the model's accuracy and assess whether it possesses the desired characteristics [18].

Based on Figure 2, it is seen that at the moment when the initial value is given, the population graph tends to converge to a single point $I_1; I_2 = (5,61 \times 10^5; 1,081 \times 10^6)$. This means that the overall dynamics of each population on the mathematical model of TB spread in the presence of drug-resistant populations move close to the endemic equilibrium point $E_1 = (8,813 \times 10^5; 2,381 \times 10^6; 4,669 \times 10^6; 5,61 \times 10^5; 1,081 \times 10^6; 7,87 \times 10^5)$. In addition, using the given parameter values, the effective reproduction number $R_0 = 3,4885 > 1$, which is greater than 1, is obtained.

Table 3. Initial value

Variable	Initial value		
	1	2	3
$S(0)$	9×10^6	6×10^4	9×10^3
$V(0)$	4×10^6	$2,5 \times 10^4$	1×10^4
$E(0)$	$1,2 \times 10^6$	1×10^5	$1,3 \times 10^4$
$I_1(0)$	5×10^5	$1,2 \times 10^5$	5×10^3
$I_2(0)$	1×10^5	$5,5 \times 10^4$	2×10^3
$R(0)$	1×10^5	8×10^3	$9,5 \times 10^3$

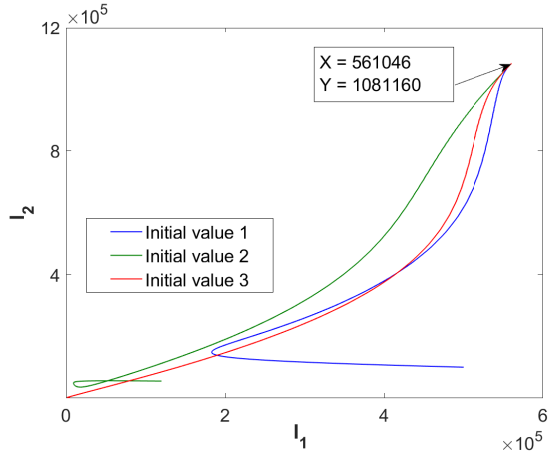

Figure 2. The phase field of mathematical model of the spread of tuberculosis with drug-resistant population

3. Parameter Sensitivity Analysis

We analyze parameter sensitivity to investigate the role of each parameter in terms of the stability of the non-endemic and endemic equilibrium points through the sensitivity index (e_m) of each parameter. The parameter values used to calculate the sensitivity index refer to the Table 2. We chose to use parameter values from established references instead of deriving them from real-world data to maintain the accuracy and reliability of our model. By relying on widely accepted and validated values from the literature, we can confidently develop a model that accurately represents the dynamics of drug-resistant tuberculosis. This approach allowed us to gain a better understanding of the stability characteristics of the endemic equilibrium in the context of drug-resistant TB. Then, the parameter sensitivity index is formulated as follows, and the calculation results can be seen in Table 4,

$$e_m = \left(\frac{\partial R_0}{\partial m}\right) \frac{m}{R_0},$$

m : Parameter to be analyzed
e_m : Sensitivity index of parameter m.

Table 4 presents positive or negative values for the sensitivity index. A positive sensitivity index signifies that the R_0 value increases following an increase in the parameter value, while a negative sensitivity index indicates a decrease in the R_0 value post parameter increase. For instance, the sensitivity index of β is 1, implying that a 10% increase in the transmission rate of tuberculosis disease leads to a corresponding 10% increase in the R_0 value, and conversely, a 10% decrease in β results in a 10% decrease in R_0. Similarly, a 10% increase or decrease in the value of γ_3 corresponds to a similar change in R_0. However, if the recovery rate of the exposed (γ_1) increases by 10%, the R_0 value decreases to 4.76%. The analysis also applies to other parameters.

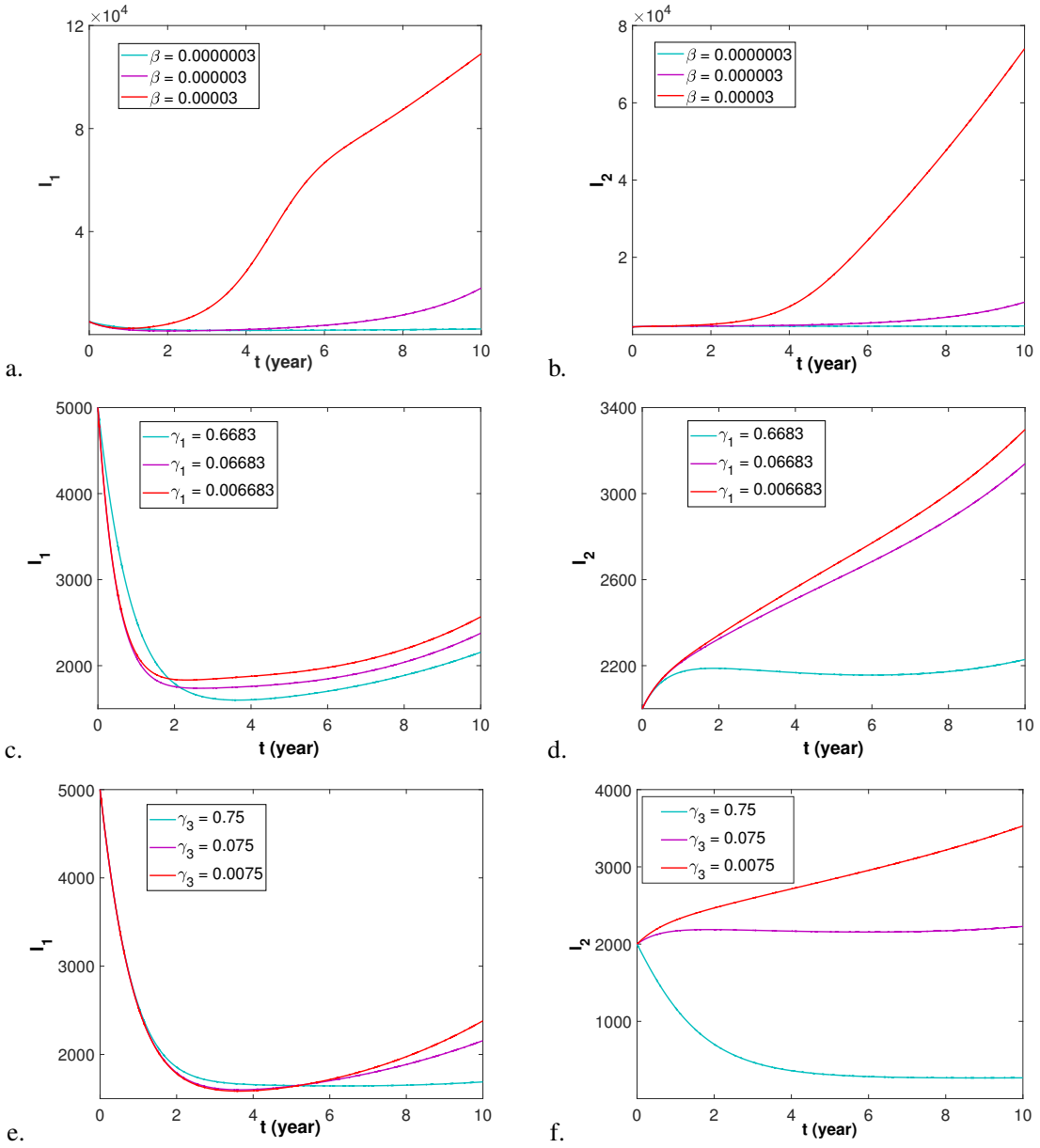

Figure 3. The effect of transmission rate (β), treatment success rate for DS-TB (γ_1), and treatment success rate for DR-TB (γ_3) on the population of DS-TB infected (I_1) and the population of DR-TB infected (I_2). The variations in these parameters illustrate their impact on the dynamics of TB infection. Other parameter values are provided in Table 2

.

Figure 3 illustrates the impact of changes in the parameters β, γ_3, and γ_1 on the populations of humans infected with drug-sensitive tuberculosis (DS-TB), denoted as I_1, and drug-resistant tuberculosis (DR-TB), denoted as I_2. An increase in the values of the transmission rate, β, and the progression rate from latent to active DR-TB, γ_3, is observed to correlate with a rise in the number of individuals infected with both DS-TB and DR-TB. This correlation can be attributed to the positive sensitivity indexes associated with β and γ_3, indicating that higher values of these parameters tend to drive an increase in the infected populations. The positive sensitivity index

Table 4. Index of Parameter Sensitivity

Parameter (m)	Sensitivity Index	$R_0 = 3,4885$			
		$m-10\%$	$m-5\%$	$m+5\%$	$m+10\%$
Λ	1	3,1396	3,3141	3,6629	3,8374
d	$-1,1789$	3,9466	3,7053	3,2929	3,1156
β	1	3,1397	3,3141	3,6629	3,8374
σ_1	$-0,1158$	3,5297	3,5089	3,4685	3,4488
σ_2	$-0,0607$	3,50989	3,4992	3.4779	3.46752
k	0,0681	3,4624	3,4761	3,4999	3.5104
p	$-0,0774$	3,5155	3,5020	3,4750	3,4615
ε_1	0,3684	3,3566	3,4234	3,5519	3,6138
ε_2	0,2544	3,3994	3,4440	3,5328	3,5769
ε_3	0,3648	3,3611	3,4248	3,5521	3,6156
ε_4	$-0,7186$	3,7586	3,6185	3,3675	3,2546
γ_1	$-0,4757$	3,6682	3,5748	3,4086	3,3344
γ_2	$-0,5060$	3,67975	3,5803	3,4035	3,3246
γ_3	1	3,1396	3,3141	3,6629	3,8374

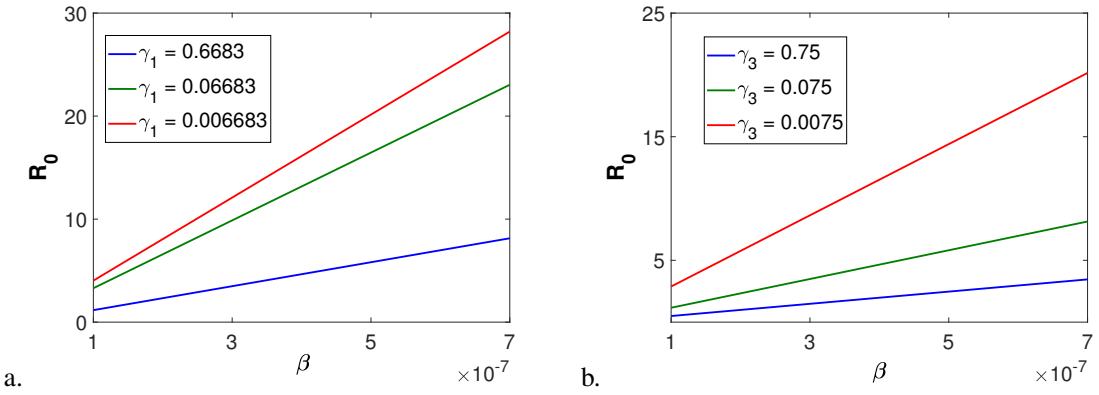

Figure 4. Sensitivity analysis of the transmission rate (β) with respect to the effective reproduction number (R_0). (a) Sensitivity of R_0 to β for three different values of the treatment success rate for DS-TB (γ_1). (b) Sensitivity of R_0 to β for three different values of the treatment success rate for DR-TB (γ_3). These analyses highlight the influence of treatment success rates on TB transmission dynamics. All parameter values are provided in Table 2.

implies that the populations of I_1 and I_2 are directly proportional to the magnitude of β and γ_3; thus, as these parameters increase, the number of infections rises accordingly.

On the other hand, a reduction in the value of γ_1, which represents the recovery rate from DS-TB, results in a significant increase in both DS-TB and DR-TB infections. This trend can be attributed to the negative sensitivity index of the parameter γ_1, which indicates that a lower recovery rate leads to a higher burden of infection. The negative sensitivity index suggests that the populations of I_1 (infected with DS-TB) and I_2 (infected with DR-TB) are inversely related to γ_1. In simpler terms, when the recovery rate from DS-TB decreases, fewer individuals recover from the infection, leading to a prolonged presence of infected individuals in the population. This, in turn, causes a subsequent increase in the number of infected individuals in both DS-TB and DR-TB categories, which increases the overall transmission dynamics. The interplay among parameters such as β (transmission rate), γ_3 (recovery rate for DR-TB), and γ_1 emphasizes their critical roles in controlling the spread of tuberculosis within the population. To control the disease effectively, these parameters must stay balanced, as even small changes can greatly affect its spread.

Based on this explanation, it is evident that the β and γ_3 parameters are fundamental to the mathematical modeling of tuberculosis with drug resistance, as reflected in their notably higher absolute sensitivity index values compared to other parameters. The transmission rate (β) governs the speed at which the infection spreads among individuals, while the cure rate for DR-TB infection (γ_3) plays a crucial role in determining how quickly infected

individuals recover or transition into a non-infectious state. Both parameters are central to the dynamics of TB dissemination, and their variations have profound effects on the disease burden. The simulation results, which show the impact of β and γ_3 on the effective reproduction number (R_0), are illustrated in Figure 4. This figure highlights how changes in these parameters can either increase or decrease the likelihood of sustained transmission within the population. By understanding the dynamics of parameters with both positive and negative sensitivity indexes, we can create better and more focused intervention strategies. For instance, enhancing recovery rates for both DS-TB and DR-TB or reducing transmission rates through improved public health measures could help lower the overall burden of tuberculosis, especially within high-risk populations. Recognizing the sensitivity of these parameters is key to optimizing interventions and ensuring that control measures are both effective and sustainable in the long term.

4. Application of Optimal Control

The educational program, denoted by u_1, is designed to target susceptible individuals within the population. By raising awareness and disseminating knowledge about TB transmission, symptoms, and preventive measures, this program aims to reduce the susceptibility of individuals to TB infection. Concurrently, efforts to enhance TB treatment success, denoted by u_2, involve a multifaceted approach. This includes bolstering the infrastructure and resources dedicated to TB treatment, such as providing comprehensive facilities and improving service quality for individuals diagnosed with TB. By ensuring timely diagnosis, access to medication, and adherence to treatment protocols, these efforts seek to mitigate the spread of TB within the population.

$$\frac{dS}{dt} = \Lambda\,(1-p) - (1-u_1)\beta S(I_1+I_2) + kV - dS, \tag{7}$$

$$\frac{dV}{dt} = \Lambda p - (k+d)V \tag{8}$$

$$\frac{dE}{dt} = (1-u_1)\beta S\,(I_1+I_2) - a_1E + \varepsilon_4 R, \tag{9}$$

$$\frac{dI_1}{dt} = \varepsilon_1 E - (d+\sigma_1+\gamma_2+\varepsilon_2+u_2\omega_2)I_1, \tag{10}$$

$$\frac{dI_2}{dt} = \varepsilon_3 E + \varepsilon_2 I_1 - (d+\sigma_2+\gamma_3+u_2\omega_3)\,I_2, \tag{11}$$

$$\frac{dR}{dt} = a_2E + (u_2\omega_2+\gamma_2)I_1 + (u_2\omega_3+\gamma_3)I_2 - a_3R. \tag{12}$$

where $a_1 = (\varepsilon_1+\varepsilon_3+d+\gamma_1+u_2\omega_1)\,; a_2 = (u_2\omega_1+\gamma_1)$ and $a_3 = d+\varepsilon_4$. Then $\omega_1, \omega_2, \omega_3$ are success treatment rate of the exposed, the human population infected of DS-TB and DR-TB, respectively.

The success rate of DS-TB treatment is higher than the success rate of DR-TB treatment. Then, the treatment success rate of individuals exposed to TB is higher than the success rate of DR-TB treatment. It can be assumed

$$\omega_2 > \omega_3 \quad \text{and} \quad \omega_1 > \omega_3. \tag{13}$$

Moreover, treatment for individuals exposed to TB is not yet available evenly in some developing countries, so it can be assumed

$$\omega_2 > \omega_1. \tag{14}$$

From 13 and 14, we derive

$$\omega_2 > \omega_1 > \omega_3.$$

For the optimal control in this study, a cost function was devised to minimize the human population exposed to TB, as well as those infected with DS-TB and DR-TB, while also minimizing the cost associated with implementing control measures. Therefore, the cost function can be formulated as follows:

The performance index $(MinJ\,(u_1,u_2))$ that can be formed based on the above explanation is as follows:

$$\int_0^{t_f} \left(A_1E + A_2I_1 + A_3I_2 + \frac{B_1}{2}\,(u_1)^2 + \frac{B_2}{2}\,(u_2)^2 \right) dt$$

where $0 \leq u_1, u_2 \leq 1$ and $A_1, A_2, A_3, B_1, B_2 > 0$. A_1, A_2, A_3 are a weighting constant of $E,\ I_1$,I_2. Meanwhile, B_1 and B_2 are weighting constants of u_1 and u_2 that have a range of $0 \leq u_1, u_2 \leq 1$ indicating that the control administration effort has a chance of success between 0 and 1. Optimal control time out is at an interval $t_0 \leq t \leq t_f$ that expresses the time of observation made, which is the time when the control is given to the end time of the control. The quadratic function of the control cost is adopted, as stated in [20, 21, 22].

Based on Pontryagin's Maximum Principle [23], the first step carried out in the analysis of the optimal control problem is to form a Hamiltonian (H) function, that is:

$$H = A_1 E + A_2 I_1 + A_3 I_2 + \frac{B_1}{2}\left(u_1\right)^2 + \frac{B_2}{2}\left(u_2\right)^2 + \theta^T\left(t\right)\left(f\left(x\left(t\right), u\left(t\right), t\right)\right)$$

$\left(f\left(x\left(t\right), u\left(t\right), t\right)\right)$ is the right segment model of TB spread in the presence of a drug-resistant population accompanied by a control variable, while $\theta^T\left(t\right)$ is co-state variable.

Furthermore, in order to obtain optimal conditions, the Hamiltonian function above must meet stationary conditions, namely $\frac{\partial H}{\partial u_1} = 0$ and $\frac{\partial H}{\partial u_2} = 0$. So that the optimal controllers u_1 and u_2 are obtained

$$u_1^* = \min\left\{1, \max\left(0, \frac{\beta S(I_1 + I_2)(\theta_3 - \theta_1)}{B_1}\right)\right\},$$
$$u_2^* = \min\left\{1, \max\left(0, \frac{\omega_1 E\left(\theta_3 - \theta_6\right) + \omega_2 I_1\left(\theta_4 - \theta_6\right) + \omega_3 I_2(\theta_5 - \theta_6)}{B_2}\right)\right\}.$$

The controller forms of u_1^* and u_2^* depend on state and co-state variables. The state equations are as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \frac{\partial H}{\partial \theta_1} = \Lambda\left(1-p\right) - \left(1-u_1\right)\beta S(I_1 + I_2) + kV - dS \\
\frac{dV}{dt} &= \frac{\partial H}{\partial \theta_2} = \Lambda p - (k+d)V \\
\frac{dE}{dt} &= \frac{\partial H}{\partial \theta_3} = \left(1-u_1\right)\beta S\left(I_1 + I_2\right) - \left(\varepsilon_1 + \varepsilon_3 + d + \gamma_1 + u_2\omega_1\right)E + \varepsilon_4 R \\
\frac{dI_1}{dt} &= \frac{\partial H}{\partial \theta_4} = \varepsilon_1 E - \left(d + \sigma_1 + \gamma_2 + \varepsilon_2 + u_2\omega\right)I_1 \\
\frac{dI_2}{dt} &= \frac{\partial H}{\partial \theta_5} = \varepsilon_3 E + \varepsilon_2 I_1 - \left(d + \sigma_2 + \gamma_3 + u_2\omega\right)I_2 \\
\frac{dR}{dt} &= \frac{\partial H}{\partial \theta_6} = \left(u_2\omega_1 + \gamma_1\right)E + \left(u_2\omega + \gamma_2\right)I_1 + \left(u_2\omega + \gamma_3\right)I_2 - \left(d + \varepsilon_4\right)R.
\end{aligned} \tag{15}$$

Meanwhile, the co-state equations are as follows :

$$\begin{aligned}
\dot{\theta_1} &= -\frac{\partial H}{\partial S} = d\theta_1 - [(1-u_1)\beta(I_1 + I_2)(\theta_3 - \theta_1) \\
\dot{\theta_2} &= -\frac{\partial H}{\partial V} = \left(\theta_2 - \theta_1\right)k + d\theta_1 \\
\dot{\theta_3} &= -\frac{\partial H}{\partial E} = -A_1 + \theta_3 d + \varepsilon_1(\theta_3 - \theta_4) + \varepsilon_3(\theta_3 - \theta_5) + \gamma_1(\theta_3 - \theta_6) + u_2\omega_1(\theta_3 - \theta_6) \\
\dot{\theta_4} &= -\frac{\partial H}{\partial I_1} = -A_2 + \theta_4\left(d + \sigma_1\right) + \left(1-u_1\right)\beta S\left(\theta_1 - \theta_3\right) + \left(\theta_4 - \theta_5\right)\varepsilon_2 + u_2\omega_2(\theta_4 - \theta_6) \\
\dot{\theta_5} &= -\frac{\partial H}{\partial I_2} = -A_3 + \theta_5\left(d + \sigma_2\right) + \left(1-u_1\right)\beta S\left(\theta_1 - \theta_3\right) + u_2\omega_3(\theta_5 - \theta_6) \\
\dot{\theta_6} &= -\frac{\partial H}{\partial R} = \theta_6\left(d + \varepsilon_4\right) + \varepsilon_4\theta_3.
\end{aligned} \tag{16}$$

Based on the description above, to get the values of S, V, E, I_1, I_2 and R from the optimal form u_1^* and u_2^* then it is necessary to solve the non-linear state and co-state equations. The non-linear equation system is hard to be solved analytically, so it will be solved numerically.

5. Numerical Results

The numerical simulation involves comparing a mathematical model of tuberculosis spread without control variables to one integrating control variables. The aim is to assess the effectiveness of the control efforts in achieving the objectives outlined by the presented cost function. For solving the optimal control strategy, we employ the fourth-order Runge-Kutta (RK4) scheme. Initially, we utilize the forward RK4 technique to solve the state system. Subsequently, the backward RK4 scheme is applied to solve the co-state system. The initial values for all population compartments in this simulation are set as follows: $S(0) = 9,000$, $V(0) = 10,000$, $E(0) = 13,000$, $I_1(0) = 5,000$, $I_2(0) = 2,000$, and $R(0) = 9,500$, with the simulation conducted from $t_0 = 0$ to $t_f = 10$. Parameter values in this numerical simulation correspond to those listed in Table 2, with weighting constants set as $A_1 = A_2 = A_3 = 1$ and $B_1 = 2, B_2 = 20$. The subsequent results provide a comparison of the mathematical model of TB spread within a drug-resistant population, both with and without control variables.

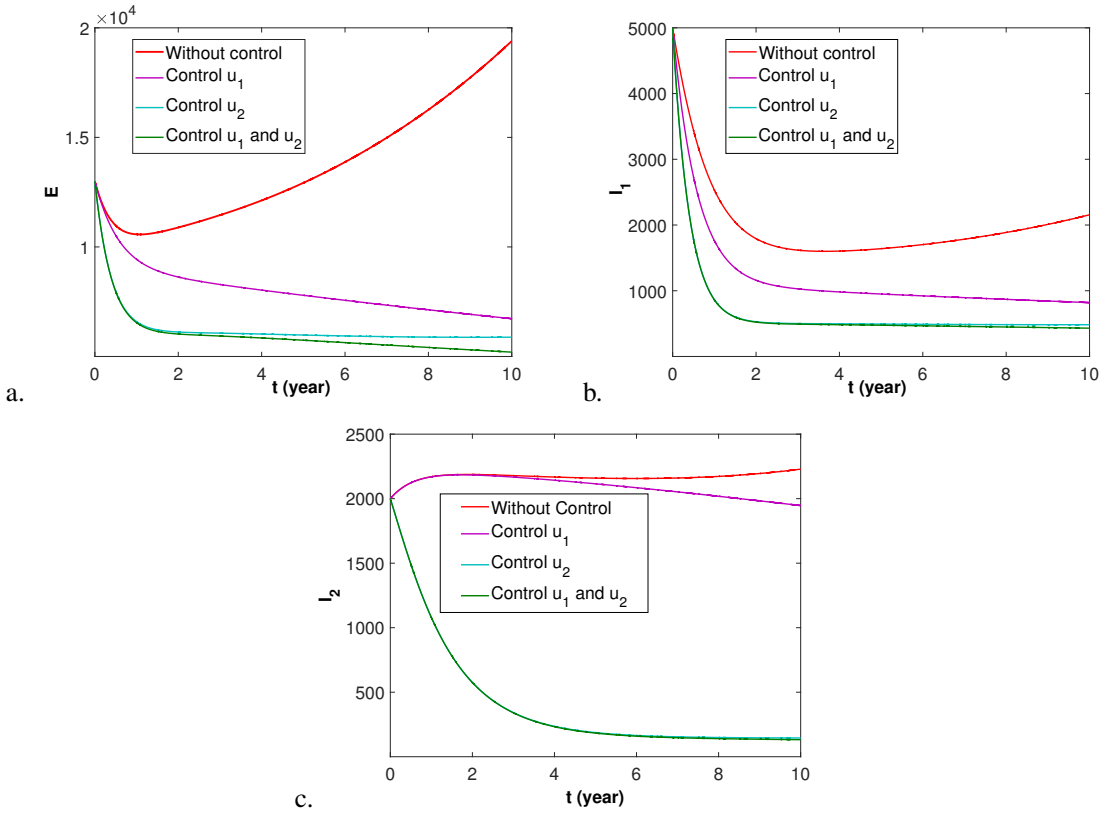

Figure 5. Comparison between the number population (a) Exposed E, (b) Infected of DS-TB I_1, (c) Infected of DR-TB I_2 without and with control. All parameter values are in Table 2. For this simulation, we imposed $\omega_1 = 0.8$, $\omega_2 = 0.9$, $\omega_3 = 0.7$ that refer to the inequality 13 and 14.

Table 5. Comparison of total population E, I_1, I_2 with and without control strategies

Condition	Total population up to year 10			Cost value
	E	I_1	I_2	
No Control	19.400	2.156	2228	–
Control u_1	6.725	819	1946	113147.34399912
Control u_2	5.880	483	145	73311.35638514
Control u_1 and u_2	5.198	430	131	70309.02795641

Figure 5 illustrates that implementing both the educational campaign (u_1) and enhancing treatment facilities (u_2) concurrently leads to a significant decrease in the populations of exposed individuals (E), those infected with DS-TB (I_1), and those infected with DR-TB (I_2) compared to scenarios without control strategies. Without control, the total populations of E, I_1, I_2 exhibit continuous increase. However, upon the application of controls u_1 and u_2, these populations show a consistent decline, gradually approaching zero.

Furthermore, it can be seen from Table 5 that the application of controls u_1 and u_2 simultaneously is the most effective in reducing the population humans were exposed (E) by 73%, the human population infected with DS-TB (I_1) by 80% and the human population infected with DR-TB (I_2) by 93%. Also, the application of both control simultaneously gives the smallest cost value compared to the application of control u_1 or u_2 alone.

6. Conclusion

This paper presents an analysis of tuberculosis spread within a drug-resistant population. The model reveals two equilibria: disease-free and endemic equilibrium. The disease-free equilibrium is locally asymptotically stable when the effective reproduction number is below one. Additionally, we conduct sensitivity analysis on model parameters to identify the most influential factors driving tuberculosis transmission.

Optimal controls are then implemented in the form of a societal education campaign and enhancements in TB treatment facilities. Results from numerical simulations demonstrate a significant reduction in the populations of exposed individuals (E), those infected with drug-susceptible tuberculosis (DS-TB) (I_1), and those infected with drug-resistant tuberculosis (DR-TB) (I_2) when both controls are applied simultaneously. This suggests that a comprehensive approach, combining public awareness and improved healthcare infrastructure, is crucial for effectively controlling the spread of tuberculosis in drug-resistant populations.

In future studies, the mathematical model of tuberculosis could be expanded to include the smoker population as well as fractional-order dynamics [24]. With smoking habits on the rise globally, there is a growing concern about their impact on the dynamics of tuberculosis transmission. Smoking has been shown to weaken the immune system, making individuals more susceptible to infection [25]. In addition to including the smoker population, the use of fractional-order models could provide further insights into the memory and hereditary effects often observed in epidemiological processes. Traditional integer-order models assume that disease dynamics depend only on current states, whereas fractional-order models allow for a more comprehensive representation of how past states influence present and future trends. This approach is particularly useful in modeling infectious diseases like TB, where latent infections, delayed immune responses, and prolonged treatment regimens introduce significant temporal dependencies. Fractional calculus could help capture these complexities and refine predictions regarding TB spread under various intervention scenarios.

By integrating both smoking behavior and fractional-order dynamics, future studies could offer a more nuanced understanding of how lifestyle factors and long-term disease memory contribute to tuberculosis transmission. This addition would not only improve model accuracy but also help identify high-risk populations that require targeted interventions, such as smoking cessation programs and specialized TB treatment strategies. Moreover, the global existence of weak solutions for this coupled fractional system can be established [26], allowing researchers to explore a broader range of epidemiological variables and transmission pathways [27]. Particular attention should be given to critical risk factors identified by medical professionals, such as co-infections (e.g., TB-HIV comorbidity), socioeconomic determinants, and healthcare accessibility.

The findings of this study carry significant implications for public health policy and practice, particularly in the context of combating tuberculosis (TB) and its drug-resistant strains. By identifying optimal control strategies, our results underscore the importance of integrating targeted interventions, such as treatment adherence programs and preventive measures, into comprehensive TB control frameworks. These strategies can help reduce the prevalence of drug-resistant TB while mitigating its transmission within communities. Policymakers could leverage these insights to allocate resources more effectively and design evidence-based interventions tailored to specific population dynamics. Furthermore, the study emphasizes the critical need for ongoing research to refine control strategies and address emerging challenges in TB management, ultimately supporting the global effort to achieve TB elimination targets.

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