Stability and Sensitivity Analysis of Treatment and Distancing in a Mathematical Model for Co-existing Drug-Sensitive and Drug-Resistant Tuberculosis Strains in Bangladesh

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ABSTRACT

This abstract provides a summary of a study that employs mathematical modeling to analyze a dual-strain tuberculosis (TB) structure in Bangladesh, focusing on the identification of drug-resistant (DR) and drug-susceptible (DS) strains. The model features a distinctive element known as "amplification," which illustrates how insufficient treatment of DR TB can arise from the management of DS TB. Utilizing both analytical and numerical techniques, the research investigates the disease's dynamics and its potential long-term implications. The primary findings indicate that the long-term dynamics of TB within a population are influenced by the basic reproduction numbers for each strain, referred to as R_0 and R_0 r. The disease tends to naturally decline when there are fewer cases compared to a single growth rate. Conversely, if R_0 exceeds both R_0 and one, DR TB will continue to exist while DS TB is eradicated. If R_0 surpasses R_0 and one, both strains will persist together. Additionally, the research conducted an analysis of vulnerability to identify the key factors impacting the disease's transmission rate. It was determined that the transmission rates (β_s and β_r) of both strains significantly influence the progression of the illness. This underscores the necessity for public health initiatives to focus on strategies that minimize interactions between infected and uninfected individuals, such as educating patients on respiratory safety and enhancing ventilation systems. Another critical factor is the treatment rate (τ_s and τ_r). The social implications of this study are considerable, suggesting that an effective approach for nations like Bangladesh is to improve treatment accessibility by lowering costs through universal healthcare. Timely and appropriate treatment of DS TB is the most effective method to mitigate resistance development, while adequate management of DR TB is crucial to prevent its proliferation within the population.

Keywords: Tuberculosis (TB), Mathematical Investigation, Drug Resistance, Amplification, Basic Reproduction Number (R_0), Studying of Vulnerability.

INTRODUCTION

Globally, tuberculosis (TB) causes significant morbidity and mortality, making it a serious public health concern (Syeda Mariam Riaz et. al.) [1]. The World Health Organization (WHO) confirmed that Tuberculosis (TB) is the biggest factor behind passing away from only one spread of illness in 2019, with over 10.0 million additional infections and 1.2 million mortality. Nearly 70% of all cases worldwide occur on the African and Asian continents combined, indicating that the illness burden is disproportionately high in environments with limited resources (Jiseon Lee et. al.) [2]. The disease, which is caused by the Mycobacterium tuberculosis (MTB) bacteria, is mainly communicated through the respiratory system because an infected individual can pass the bacteria to a vulnerable host by aerosolized droplets emitted while coughing or sneezing (Dheda, Keertan et. al.) [3]. A key component of the epidemiology of tuberculosis is the intricate life cycle of the bacillus within a human host (Bianca Sossen et. al.) [4]. Latent tuberculosis infection can result from the germs going into a non-replicating, dormant stage after the initial inhalation. People with LTBI don't have any symptoms and aren't a threat to others (Justin et. al.) [5]. The dormant bacteria may, however, reawaken and

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develop into an infectious disease in 5–15% of patients. In those with weakened immune systems, this rate is noticeably higher. Eradication of tuberculosis is a long-term objective due to the crucial dynamic of latent and active infection (Tunde T. Yusuf et. al.) [6]. A successful public health response must treat both active and latent disease because the sizable pool of latent infections acts as a reservoir for subsequent epidemics (Nathan Kapata et. al.) [7]. The rise of drug-resistant tuberculosis poses an obscure risk for worldwide TB control. These strains, which can spread directly from person to person, are characterized by resistance to the main first-line medications, isoniazid and rifampicin (Mchaki, Betty R et. al.) [8]. But a more common manner for them to appear is when people with drug-susceptible (DS) TB receive insufficient or no treatment (P.G.C. {Nayanathara Thathsarani Pilapitiya}et. al.) [9]. Often referred to as "amplification," this process enables surviving germs to become resistant due to patient non-adherence, inappropriate prescription practices, or irregular access to medication (Geoffrey P. Dobson et. al.) [10]. Compared to treating DS TB, treating DR TB is far more challenging and resource-intensive, requiring longer, more toxic, and substantially more costly regimens (Kai Ling Chin et. al.) [11]. This imposes a significant strain on healthcare systems, especially in developing countries, and highlights the critical necessity to comprehend the fundamental factors contributing to the emergence and spread of DR TB (Xinyue Wang et. al.) [12]. A useful framework for analyzing the intricate interactions between biological and social elements that control infectious disease epidemics, such as tuberculosis, is provided by mathematical modeling (Ram Singh et. al.) [13]. These models have long been used by researchers to predict the possible effects of different intervention measures and to obtain insights into the epidemiology of tuberculosis. Murphy et al. (2002), for example, looked into how biological and socioeconomic variables affect the prevalence of tuberculosis using an SEI (Susceptible-Exposed-Infected) model. Other modeling attempts have looked at certain epidemiological phenomena, like how seasonal changes and exogenous reinfection affect the prevalence of tuberculosis (Eka D.A. Ginting et. al.) [14]. (Khristine Kaith S. Lloren et. al.) [15] Evaluated the combined impacts of vaccination, reinfection, and de novo resistance using a more complex 10-compartment model, emphasizing the critical role that reinfection plays in the development of disease. The body of research demonstrates the effectiveness of mathematical models in representing the complex dynamics of tuberculosis transmission (V.M. Mbalilo et. al.) [16]. The application of mathematical models to inform public health policy is of paramount importance. A theoretical foundation for assessing the efficacy of prophylaxis and treatment was established by early, which showed that reducing treatment failure rates is essential for managing epidemics, particularly in developing nations (Sirwan Khalid Ahmed et. al.) [17]. Multi-strain models have been created more recently to examine the intricacies of medication resistance (Sirwan Khalid Ahmed et. al.) [18]. Using a two-strain model, (Sudipa Chauhan et. al.) [19] determined the best combinations of control measures and came to the conclusion that integrated approaches are more economical and effective. Similar to this, (Md Abdul Kuddus et. al.) [20] examined disease equilibrium states using a two-strain model and found that the disease will endure if the fundamental procreation rates for both strains are greater than the other but will die out if they are less than one.

This paper presents a novel two-strain mathematical model, building on previous research and driven by the ongoing danger of tuberculosis and the increasing prevalence of medication resistance in Bangladesh. The public health issue of acquired drug resistance—where a drug-susceptible infection might become a drug-resistant one due to treatment failure—is explicitly incorporated into our Susceptible-Latent-Infectious-Removed-Susceptible (SLIRS) framework. The model can be used to forecast the future course of the epidemic and offers a strong platform for investigating the competitive dynamics between DS and DR TB strains (Mumbu et. al.) [21].

This paper's remaining sections are organized to offer a thorough examination of the suggested model. Using the next-generation matrix approach, we start with a thorough analytical study to obtain estimates for the basic fertilization rates of the DS and DR strains (Maryam Zarean et. al.) [22]. Next, from a mathematical and biological perspective, we determine the criteria required for the maintenance of healthy, single-present, and adjoining pandemic equilibria.

Numerical simulations are used to figure out the mathematical formulas and demonstrate how the system behaves dynamically under various scenarios, so complementing the analytical conclusions (Chinmay Saha et. al.) [23]. To identify the factors that have the biggest effects on we investigate a higher incidence of DS, DR, and total TB infections, as well as vulnerability. The ultimate objective of this study is to produce useful

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insights into the evolution of TB in this country and aid in the creation of efficient, empirically supported control measures (Most Amina et. al.) [24].

Objectives are:

To present a novel two-strain mathematical model for the transmission dynamics of drug-sensitive (DS) and drug-resistant (DR) tuberculosis in Bangladesh.

To explicitly incorporate the public health issue of "amplification," where drug-susceptible infections can become drug-resistant due to treatment failure.

To forecast the future course of the TB epidemic and investigate the competitive dynamics between DS and DR TB strains.

To perform a thorough analytical study to derive the basic reproduction numbers for the DS and DR strains using the next-generation matrix approach.

To determine the conditions for the existence and stability of disease-free, single-present, and co-existent endemic equilibria from both a mathematical and biological perspective.

To identify the key parameters that have the biggest effects on the incidence of DS, DR, and total TB infections through a sensitivity analysis.

To produce useful insights to aid in the creation of efficient, empirically supported control measures for the evolution of TB in Bangladesh.

Techniques and resources

In order to examine his study proposes a deterministic mathematical representation for the epidemiological patterns of drug-sensitive (DS) and drug resistance (DR) tuberculosis organisms. The population is divided into the following mutually exclusive compartments under the model:

At risk: People who have not yet contracted tuberculosis.

Potentially contaminated ($L_i(t)$): Refers to individuals considered sick but are not experiencing a severe illness. Drug-sensitive and drug-resistance to TB both are indicated by the subscripts D and R, respectively. (whereas the initials i = s, r indicates the proportions related to the TB infection that are susceptible to drugs (s) and resistance to drugs (r).)

Infectious ($I_i(t)$): People who have active tuberculosis and are able to spread the infection. (whereas the initials i = s, r indicates the proportions related to the TB infection that are susceptible to drugs (s) and resistance to drugs (r).)

Recovered (R): Individuals who have received effective treatment and are momentarily immune.

One of the model's main assumptions is that drug resistance (DR) might be directly conveyed after insufficient treatment for drug-susceptible (DS) TB. Additionally, the process of transient immunity loss is included in the model, wherein recovered people can revert to the susceptible state at a consistent per-capita rate. The entire population Growth N(t) is determined by

$$N(t) = S(t) + L_s(t) + I_s(t) + L_r(t) + I_r(t) + R(t)\,. \qquad (1)$$

While active TB cases in $I_i(i = s, r)$ incur disease-related death at a rate of $\phi_i(i = s, r)$, individuals in the other compartments die naturally as its similar consistent amount μ. Newborn deaths take place in the vulnerable compartment to maintain a stable population size. At an amount that changes with time $\lambda_i(t) = \beta_i I_i(t)$, where β_i is the rate of propagation among susceptible as well as infected people, a prevalent MTB

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organism can harm people in the S area i ($i = s, r$). People migrate to the latently infected compartment L_i after contracting the strain $I_i (i = s, r)$. Autonomous proliferation of dormant bacteria at an amount α_i causes a percentage of people with latent infections to become active TB. The rate of treatment for individuals with drug-sensitive (DS) active TB, I_i, is τ_s. Some of them, denoted by ρ, will recover well after treatment and join the recovered group. Unfortunately, drug resistance develops in the complementary proportion $(1 - \rho)$, which is the leftover fraction. This may occur as a result of improper medication adherence or insufficient treatment. They are transferred to the drug-resistant (DR) compartment I_r as a result. In the same way, patients with DR-active TB receive treatment at their own pace, τ_r.

Table 1: Measurement evaluation and modeling.

Parameters	Description	Estimated value	
N	Population in 2015	159,000,000	29
μ	Birth/death rate	$1/70$ per year	30
β_s	Transmission rate for DS TB	1.57×10^{-8}	Fitted
β_r	Transmission rate for DR TB	6.25×10^{-9}	Fitted
α_s	Progression rate from L_s to I_s	0.129 per year	16
α_r	Progression rate from L_r to I_r	0.129 per year	16
ω_s	Recovery rate for DS TB	0.287 per year	12
ω_r	Recovery rate for DR TB	0.12 per year	12
ρ	Proportion of treated patients who amplify	0.07 per year	11
ϕ_s	Disease related death rate for DS TB	0.37 over 3 years	16
ϕ_r	Disease related death rate for DR TB	0.37 over 3 years	16
τ_s	Treatment rate for DS TB	0.94 per year	20
τ_r	Treatment rate for DR TB	0.78 per year	20
γ	Rate of losing immunity	0.10 per year	12

The World Health Organization's (WHO) yearly incidence data for drug-sensitive (DS) and drug-resistant (DR) tuberculosis (TB) are compared with the results of our suggested model in Figure 2. The model's best fit to the data is represented by the green solid curve, while the WHO-reported data points are displayed as blue dots. This comparison is displayed for DS TB in the graph on the left and for DR TB in the graph on the right. This graphic illustrates how closely the model's predictions match actual data.

Additionally, people with active tuberculosis can go from the I_i compartment to the R compartment by recovering naturally at a rate of ω_i. The flow diagram in Figure 1 illustrates this process as well as other population movements. Table 1 contains the precise values for every parameter utilized in this model, including the recovery rate ω_i. Deterministic systems of chaotic basic mathematical problems control the overall dynamics of drug-sensitive (DS) and drug-resistant (DR) tuberculosis transmission:

$$\frac{dy}{dx} = \mu N - \beta_s I_s S - \beta_r I_r S - \mu S + \gamma R + \phi_s I_s + \phi_r I_r, \qquad (2)$$

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$$\frac{dL_s}{dt} = \beta_s I_s S - \alpha_s L_s - \mu L_s, \quad (3)$$

$$\frac{dI_s}{dt} = \alpha_s L_s - \omega_s I_s - \mu I_s - \tau_s I_s - \phi_s I_s, \quad (4)$$

$$\frac{dL_r}{dt} = \beta_r I_r S - \alpha_r L_r - \mu L_r, \quad (5)$$

$$\frac{dI_r}{dt} = \alpha_r L_r - \omega_r I_r - \mu I_r + \rho\tau_s I_s - \phi_r I_r - \tau_r I_r, \quad (6)$$

$$\frac{dR}{dt} = \omega_s I_s + \omega_r I_r - \gamma R + \mu R + (1-\rho)\tau_s I_s + \tau_r I_r. \quad (7)$$

It is simple to demonstrate that every state variable in the differential equation system stays non-negative for all times $t > 0$ when the initial conditions are non-negative. We can also calculate the overall population size, $N(t)$, using equations (2) through (7) requires

$N(t)$ = constant

It seems sense that the size of each individual compartment, such as S, L, I, etc. must likewise be restricted since the initial conditions are non-negative while the overall individuals remain steady. These factors lead to the following viable zone for the system of equations (2) through (7):

$$D = \{(S, L_s, I_s, L_r, I_r, R) \in \mathbb{R}_+^6 : S + L_s + I_s + L_r + I_r + R = N\}$$

Simulation of prediction of dimensions

The majority of the modeling variables were determined based on current global literature or local evaluations, according to reports from the National TB Control Program (NTP) and the World Health Organization (Table 1). Bangladesh's total population in 2015 was estimated to be roughly 159,000,000. Biological life expectancy, symbolized by (μ), was determined as the opposite of Bangladesh's lifespan of 70 years. In Bangladesh, treatment success rates for drug-sensitive (DS) and drug-resistant (DR) tuberculosis (TB) were approximately 94% and 78%, correspondingly, according to WHO data from 2020 (Burhan et. al.) [25]. We fitted the method we used was applied to the DS and DR TB mortality statistics for Bangladesh, which were acquired from WHO and NTP reports from 2000, to 2018, respectively, in order to estimate the two remaining important parameters, β_s and β_r. In order to reduce a mean discrepancy among both estimated and actual yearly incidence of either DS or DR TB, the least-square optimization method was used to determine the most appropriate (see Fig. 2) variables, β_s and β_r. Information is provided in the additional materials.

Studying of vulnerability

A global studying of vulnerability was performed to determine their own partial rank correlation coefficients (PRCCs) data variable and different outcome measures using Latin Hypercube Sampling (LHS) (Md Afsar Ali et. al.) [26]. This was accomplished by giving each variable (i.e.$\beta_s, \alpha_s, \omega_s, \phi_s, \tau_s, \beta_r, \alpha_r, \omega_r, \phi_r, \tau_r, \rho$ and γ) a uniform distribution between half and four times its baseline value (Table 1). After that, 10,000,000 simulated draws were made for each variable, giving the study a solid dataset. The modeling procedure was run for each of the 10,000,000 essential variable configurations and the results, including the incidence and prevalence of the disease, were captured. We specifically studied the equilibrium prevalence for three important metrics: overall TB ($I_s + I_r$) rates, which is the sum of drug-sensitive (DS) and drug-resistant DR TB(I_r), denoted by DS and DR, respectively, and drug-sensitive DS TB (I_s), represented by DS. The method outlined Υ_j^i can be used to determine the vulnerability rates for each model variables using the analytical formulas for R_{0s} and R_{0r}. The rate in which a variable varies in response to a change in a specific variable can be identified through these coefficients. Regarding β_s, for instance, we all have:

$$\Upsilon_{\beta_s}^{R_{0s}} = \frac{\partial R_{0s}}{\partial \beta_s} \times \frac{\beta_s}{R_{0s}}$$

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We can change β_s, the vulnerability rates for the fundamental reproduction number R_{0s} are represented by $\Upsilon_{\beta_s}^{R_{0s}}$.

Basis for the authorization, The study was carried by using aggregated surveillance data for drug-sensitive (DS) and drug-resistant (DR) TB from the National TB Control Program (NTP) in Bangladesh and the World Health Organization (WHO) (Sarker et. al.) [27]. Since all analyses were conducted at an aggregate level, no private information was used. The James Cook University human ethics approval board accepted the research protocol, H7300, and all procedures were conducted in accordance with it.

RESULTS

Fundamental evolution of rate, There are two healthy states S and R and four unhealthy states L_s, I_s, L_r, I_r in the configuration. There are no active cases at the healthy constant state, where $L_s^* = I_s^* = L_r^* = I_r^* = R^* = 0$, consequently $S^* = N$. We applied the methods to figure out the fundamental production amounts for the DS and DR TB strains (Karmakar et. al.) [28]. The linearized infection components obtained from equations (2) through (7) are the primary goal of this method.

$$\frac{dL_s}{dt} = \beta_s I_s N - \alpha_s L_s - \mu L_s, \quad (8)$$

$$\frac{dI_s}{dt} = \alpha_s L_s - \chi_s I_s \quad (9)$$

$$\frac{dL_r}{dt} = \beta_r I_r N - \alpha_r L_r - \mu L_r, \quad (10)$$

$$\frac{dI_r}{dt} = \alpha_r L_r - \chi_r I_r - \rho\tau_s I_s, \quad (11)$$

The total rates at which people are taken out of the active DS and DR TB infection states are represented by the values $\chi_s = \omega_s + \phi_s + \tau_s + \mu$ and $\chi_m = \omega_r + \phi_r + \tau_r + \mu$. The fluctuations within these infected states around the non-infectious optimum are described by the ordinary differential equations (ODEs) from (8) to (11). This is predicated on the idea that the infection-induced decline in the vulnerable population is negligible enough to be disregarded.

Assume that X is the vector of infected states, expressed as $\mathbf{X}^T = (L_s, I_s, L_r, I_r)^T$, where T is the transpose. We can now represent the infection component using this notation as follows:

$$\mathbf{X} = (T + \Sigma) \quad (12)$$

In order to analyze the model, the matrices T and Σ are essential. The transition matrix, T, records any other changes in the infected states, whereas the transmission matrix, Σ, depicts the process by which new infections are created. The set of ordinary differential equations (8) – (11) is the source of these matrices. The rate at which people in infected state j cause new illnesses in infected state i is indicated by an entry in these matrices with $i, j \in 1, 2, 3, 4$, such as T_{ij}. This method aids in distinguishing the onset of new infections from other occurrences, such as healing, passing away, or changing into a different disease state. Therefore, for the subsystem (8) − (11), we have,

$$T = \begin{pmatrix} 0 & \beta_s N & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_r N \\ 0 & 0 & 0 & 0 \end{pmatrix} \text{ and } \Sigma = \begin{pmatrix} -(\alpha_s + \mu) & 0 & 0 & 0 \\ \alpha_s & -\chi_s & 0 & 0 \\ 0 & 0 & -(\alpha_r + \mu) & 0 \\ 0 & \rho\tau_s & \alpha_r & -\chi_r \end{pmatrix}$$

The following generation matrix, represented as **K**, as described in (the negative sign is a critical part of the equation and must not be forgotten)

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$$K = -T\Sigma^{-1} = T(-\Sigma^{-1}) = \begin{pmatrix} \frac{N\alpha_s\beta_s}{(\alpha_s+\mu)\chi_s} & \frac{N\beta_s}{\chi_s} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{N\alpha_s\beta_r\rho\tau_s}{(\alpha_s+\mu)\chi_s\chi_r} & \frac{N\beta_r\rho\tau_s}{\chi_s\chi_r} & \frac{N\alpha_r\beta_r}{(\alpha_r+\mu)\chi_r} & \frac{N\beta_r}{\chi_r} \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

The principal coefficients of the subsequent generation matrix, K, are the essential expansion numbers for drug-sensitive (DS) and drug-resistant (DR) tuberculosis. These figures, which are represented by the notation R_{0S}, DS and R_{0r}, DR, indicate the typical number of secondary infections that an infected individual would produce. Thus, the following are the fundamental procreation numbers for DS and DR TB:

$$R_{0S} = \frac{N\alpha_s\beta_s}{(\alpha_s+\mu)\chi_s} \quad \text{(a)}$$

and

$$R_{0r} = \frac{N\alpha_r\beta_r}{(\alpha_r+\mu)\chi_r} \quad \text{(b)}$$

In this context, $\frac{\alpha_s}{(\alpha_s+\mu)}and\frac{\alpha_r}{(\alpha_r+\mu)}$ represent as two key estimations. These represent the likelihood that the drug-sensitive (DS) and drug-resistant (DR) strains will migrate from the latent compartment to the infectious compartment, respectively. The average amount of time infectious people spend in states I_s and I_r is likewise indicated by them. The numbers R_{0s} and R_{0r} stand for the anticipated number of drug-resistant (DR) and secondary drug-sensitive (DS) TB cases, respectively, that a single infectious individual would produce if they were placed in a community that is completely susceptible. As noted, it is an astounding discovery that the fundamental expansion numbers for DS TB (R_{0s}) and DR TB (R_{0r}) are regardless of the expansion portion, ρ. In the supplemental resources, particularly in the sections on the existence of equilibria and stability analysis, we present an exhaustive examination of the suggested TB model, defined by equations (2) – (7). This analysis examines the existence and stability of three important optimum points: healthy (E^*), single-present ($E\hat{}$), and jointly transmitted ($E^\dagger$). To put it simply, the healthy optimum is universally linearly reliable if and only if max [R_{0s}, R_{0r}] < 1. In the stability analysis part of the supplementary materials, we demonstrate that the single-existence equilibrium is generally steady when R_{0r} > max [1, R_{0s}]. We used the Monte Carlo approach to examine the co-existence optimum and determine if the criterion R_{0s}> max [R_{0r}, 1] holds. We estimated the real part of the Jacobian matrix's eigenvalues and assessed them at the co-existing an endemic balance (Ef). The steady state coordinates can be described using twelve model parameters: $(\alpha_s, \alpha_r, \beta_s, \beta_r, \omega_s, \omega_r, \phi_s, \phi_r, \tau_s, \tau_r, \rho, \gamma)$. Table 1 shows the initial values for these variables. To analyze the model's behavior, a sample pool $\mathbb{Q} = \prod_{i=1}^{12} M_i \in \mathbb{R}_+^{12}$ was established. This pool is a Cartesian product of twelve closed intervals, $M_i = [m_i - \theta m_i, m_i + \theta m_i]$, where each $m_i, i = 1, \ldots, 12$ represents the initial value of a parameter from Table 1, and $\theta > 0$ sets the variation range. Our research included 10,000 random situations, $Q = (q_1, \ldots, q_{12}) \in \mathbb{Q}$, with each $q_i \in M_i, i = 1, \ldots, 12$ iselected from a homogeneous distribution where there is no correlation among variables. For this study, we picked a 20% variation from the baseline values ($\theta = 0.2$). Figure 3 demonstrates that the mixed prevalent balance is permanent (yellow dots) when the criterion R_{0s} > max [R_{0r}, 1] is met. Otherwise, it is unstable (shown by the blue spots). Figure 4 depicts three points of balance and their specific equilibrium areas in relation to fundamental reproduction numbers for drug-susceptible (R_{0s}) and drug-resistant (R_{0r}) tuberculosis (TB). The healthy optimum ($E*$) is depicted by the magenta-colored region and is bounded by the criterion max [R_{0s}, R_{0r}] < 1. The green colored area represents the single-present optimum ($E\hat{}$) , which occurs when R_{0r} > max [1, R_{0s}]. Finally, the co-existing optimum ($E^\dagger$) is displayed by the yellow-colored area, which corresponds to the requirement R_{0s}> max [R_{0r}, 1].

Mathematical models were performed in MATLAB to back up the analytical findings and to see how propagation rates and DS TB therapy effect overall as well as DR-TB rates. We investigated various beginning

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circumstances on each DS and DR TB in every groups. The findings validated a stable state of the model's equilibria. Simulations indicate that tuberculosis will be removed from the population when max [R_{0s}, R_{0r}] < 1. If R_{0r} > max [1, R_{0s}], DS TB will die off but DR TB will survive. Additionally, the requirement R_{0s}> max [R_{0r}, 1] shows that DS and DR, TB will coexist in the population. Additional information and visual representations are included in the additional data, notably Figures S1, S2, and S3. We can mimic the consequences of public health actions by altering a few factors in our model. Reducing contact between individuals can be indicated by reduced transmission rates (β_s or β_r). Similarly, increased treatment rates (τ_s or τ_r) can be used to identify and treat infectious individuals. The effective reproduction number is the new reproduction number that comes from these interventions or the non-susceptibility of a major proportion of the population. As depicted in Figure 5, the growth rate (ρ), has a significant effect on the frequency of both drug-sensitive (DS) and drug-resistant (DR) tuberculosis. In the first region, where $\rho \lesssim= 0.6$, DS TB is the dominating strain. When $\rho \gtrsim= 0.6$, DR TB becomes more common. The expansion route enables DR TB to thrive even when its basic reproduction number is lower than that of the vulnerable variation has a gestation quantity fewer instead of a single as long as the requirement R_{0s}> max [R_{0r}, 1] is met. This study implies that medication treatment may inadvertently cause the onset of DR TB. Our research also demonstrates that the spread of drug-resistant (DR) tuberculosis can be halted if the treatment rate for drug-sensitive (DS) tuberculosis is high enough to eradicate it from the community. In order to attain a viable growth rate below a choice, the DS TB treatment rate needs to be sufficiently high. The effects of DS TB medication ratio (τ_s) and propagation rate (ρ) on overall TB and DR TB rate with fixed pathogenic ratios (β_s, β_r) are depicted in Figures 6 and 7. Propagation raises the rate of both total TB and DR TB. According to Figure 7, as the DS TB medication level rises from zero to roughly 0.8-0.9, a high progression rate initially results in an increase in the prevalence of DR TB. Following this peak, the prevalence of DR TB declines and levels out at a steady level. The percentage of DR TB only increased to a shared average level for low propagation rates. This point depicts the permanent DR TB- just balance which occurs when the basic growth number of DR TB surpasses the actual fertilization rate of DS TB, provided the latter is larger than one. Numerical research has revealed that when growth is particularly high and drug-sensitive (DS) TB is treated, the prevalence of drug-resistant (DR) TB might rise above its natural equilibrium level. This finding emphasizes the vital need of effective therapy for DS TB patients. If not managed properly, insufficient or inadequate therapy can result in the formation of new DR TB cases, allowing the DR strain to become the dominant form of the illness.

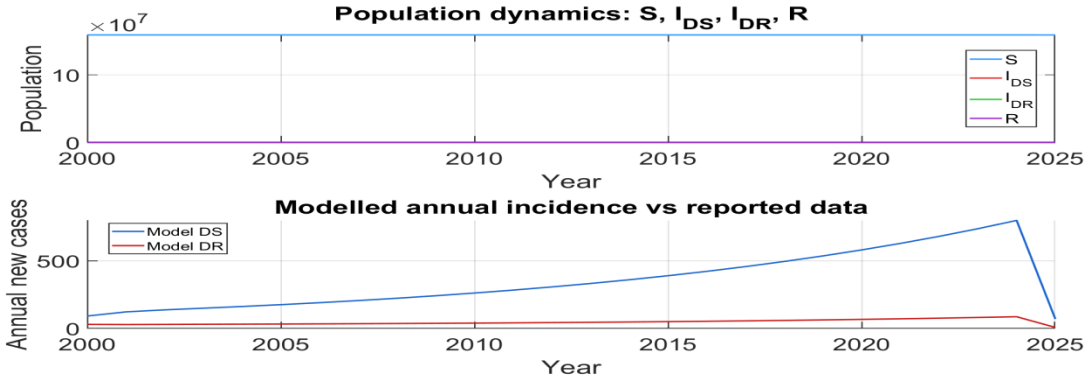

Figure 3. illustrates the stability of the co-existing endemic equilibrium as a function of R_{0s}/R_{0m} (defined by the eigenvalues of the system Jacobian matrix). Random parameter drawings that result in eigenvalues with only negative real parts (stable) are colored yellow, while those that result in eigenvalues with at least one positive real part (unstable) are colored blue. All stable points (yellow) sit above the line $R_{0s} = R_{0r}$, whereas all unstable points (blue) lie below.

The model trajectories and reported WHO incidence data are shown together to validate model behaviour. The simulated annual incidence curves for drug-sensitive and drug-resistant tuberculosis are plotted and were compared with surveillance points. Close agreement between modelled and reported points is indicated in years where treatment and transmission parameters were fitted. The influence of amplification on raising drug-resistant prevalence when treatment of drug-sensitive cases is imperfect is illustrated by the divergent trends. We conducted studying of vulnerability to investigate the quantitative link between the model's parameters and its outputs, such as the prevalence of DS, DR, and total TB. Figure 8 depicts the relationship among the co-

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existing suitable number of DS TB prevalence (I_s) and the model's twelve parameters: $\alpha_s, \alpha_r, \beta_s, \beta_r, \omega_s, \omega_r, \phi_s, \phi_r, \tau_s, \tau_r, \rho$ and γ. These correlations are detected under the condition that $R_{0s} > \max[R_{0r}, 1]$. The figure shows that the rate of DS TB (I_s) is positively correlated with $\beta_s, \alpha_s, \beta_r, \alpha_r$ and γ. This indicates that increasing any of these characteristics will result in an increase in DS TB rates. Our analysis showed that the amount of data transmitted (β_s) reached the highest favorable impact on DS TB rates (I_s) among all variables. Reproduction is directly proportional to β_s, therefore this is expected. The most important public health measure is to reduce exposure between diseased and uninfected persons. This action is more successful than enhancing treatment, lowering recurrence rates, or limiting amplification. As a result, public health resources should be directed toward individuals with high exposure, such as those living in the same household as someone with infectious tuberculosis. The variables $\omega_s, \omega_r, \phi_s, \phi_r, \tau_s, \tau_r$ and ρ have a negative connection with DS TB rates (I_s). Increasing any of these criteria will lower I_s predominance. Our data revealed that medical care velocity τ_s is the subsequent essential factor in determining DS TB rates. This outcome is consistent with WHO recommendations and other studies, all of which emphasize the importance of early treatment and curing infected cases in breaking the chain of tuberculosis transmission within a geographic region. According to our findings, the most effective measures for preventing tuberculosis include swift detection of prospective instances, prompt investigation, and the initiation and profitable conclusion of therapy. Furthermore, we discovered that propagation has a detrimental influence on the spread of DS TB due to individuals with the DS strain become DR TB due to inadequate therapy. Figure 9 illustrates the relationship between DR TB prevalence and the model's twelve parameters ($\alpha_s, \alpha_r, \beta_s, \beta_r, \omega_s, \omega_r, \phi_s, \phi_r, \tau_s, \tau_r, \rho$ and γ) when $R_{0s} > \max[R_{0r}, 1]$. The parameters β_s, α_s, β_r, α_r, and γ have positive Partial Rank Correlation Coefficients (PRCCs), while ω_s, ϕ_s,τ_s, ω_r, ϕ_r and τ_r have negative PRCCs. This is consistent with the observations. At the co-exist equilibrium, amplification (ρ) has a beneficial connection with DR TB rate, as expected given its role in the progression from DS TB to DR TB.

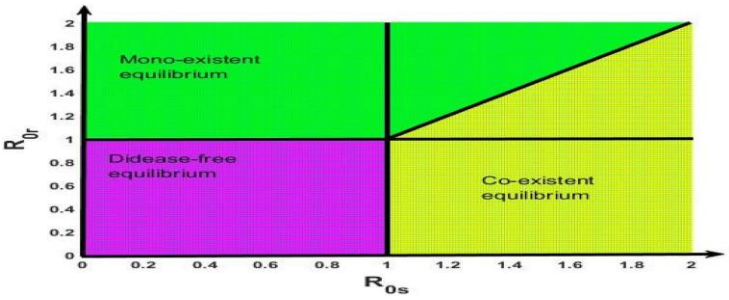

Figure 4 depicts the model's equilibrium points' regions of existence as well as regional stability. The disease-free equilibrium is represented in magenta, while the mono-existent equilibrium is indicated in green. The co-existent equilibrium is in the yellow-shaded area.

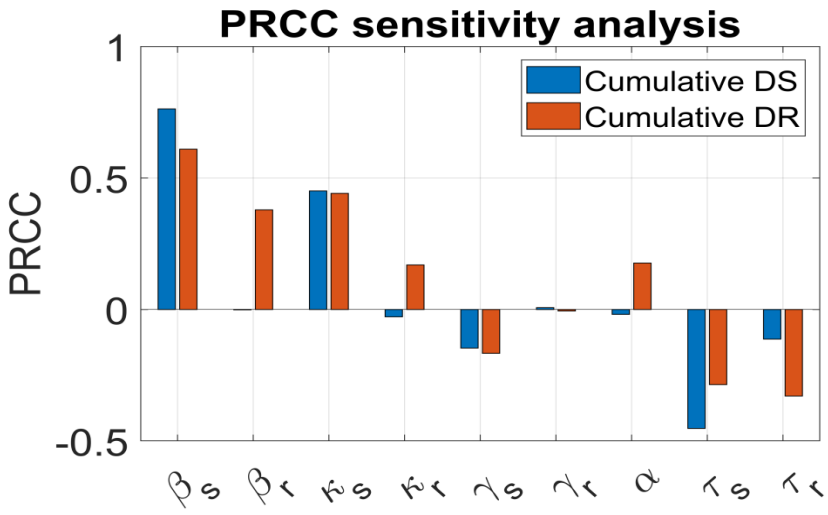

Figure 5 depicts the impact of PRCC amplification (ρ) on DS and DR TB prevalence. All additional values are based on their initial values presented in Table 1.

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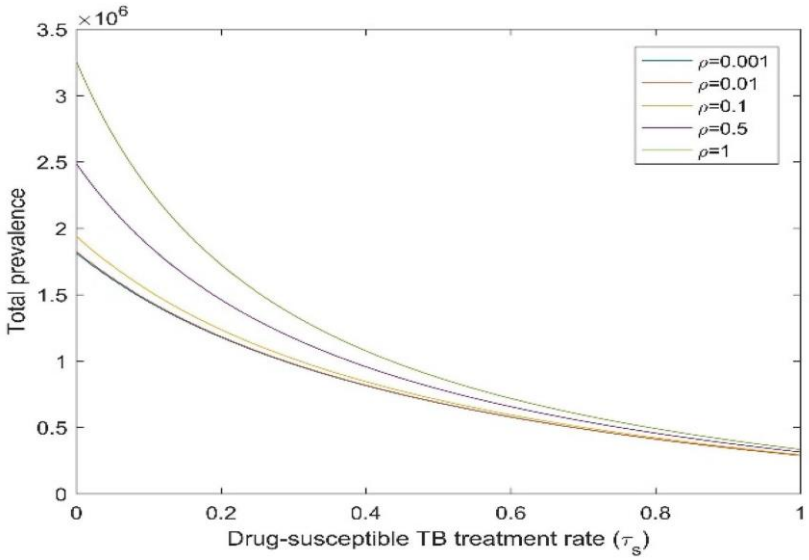

Figure 6 illustrates the impact of DS TB treatment rate (τ_s) on overall TB prevalence when β_s and β_r remain constant. All additional variables are based on the initial values presented in Table 1.

The evaluation of sensitivity was also performed to investigate the overall TB prevalence ($I_s + I_r$) as well as DR TB incidences in connection with any respective variables. This was performed under two conditions: when R_{0s}> max $[R_{0r}, 1]$ and when R_{0r}> max $[R_{0s}, 1]$. The findings of this study are included in the supplemental materials, specifically the studying of vulnerability section and Figures S4 and S5. Table 2 shows the sensitivity indices for R_{0s} and R_{0r} with regard to each parameter. Transmission rates (β_s for DS TB and β_r for DR TB) have a substantial impact on these indicators. The sensitivity indices are $\Upsilon^{R_{0s}} = 1$ and $\Upsilon^{R_{0r}} = 1$, indicating that changing the transmission rates (β_s and β_r) by a specific percentage will result in the same change in reproduction numbers (R_{0s} and R_{0r}).

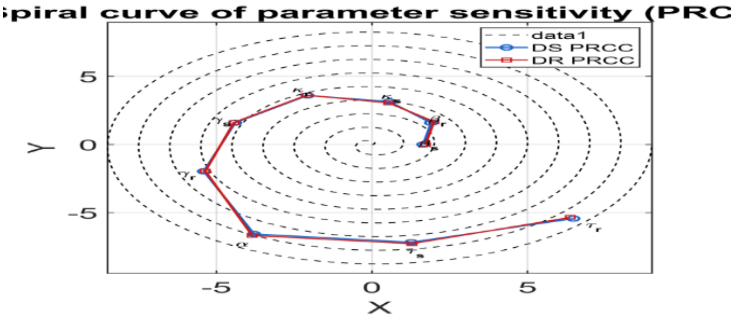

Figure **7** illustrates the impact of DS TB treatment rate (τ_s) on DR TB prevalence when β_s and β_r are constant. All additional variables are based on the baseline values presented in Table 1.

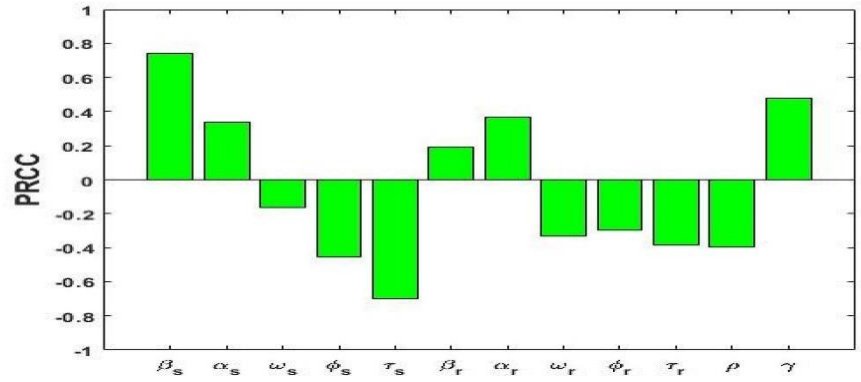

Figure 8 shows the relationship among model output I_s and parameters β (transmission rate), (progression rate), (recovery rate), φ (disease-related death rate), (treatment rate), and (amplification rate) when R_{0s}> max $[R_{0r}, 1]$. Subscripts represent DS and DR amounts, correspondingly.

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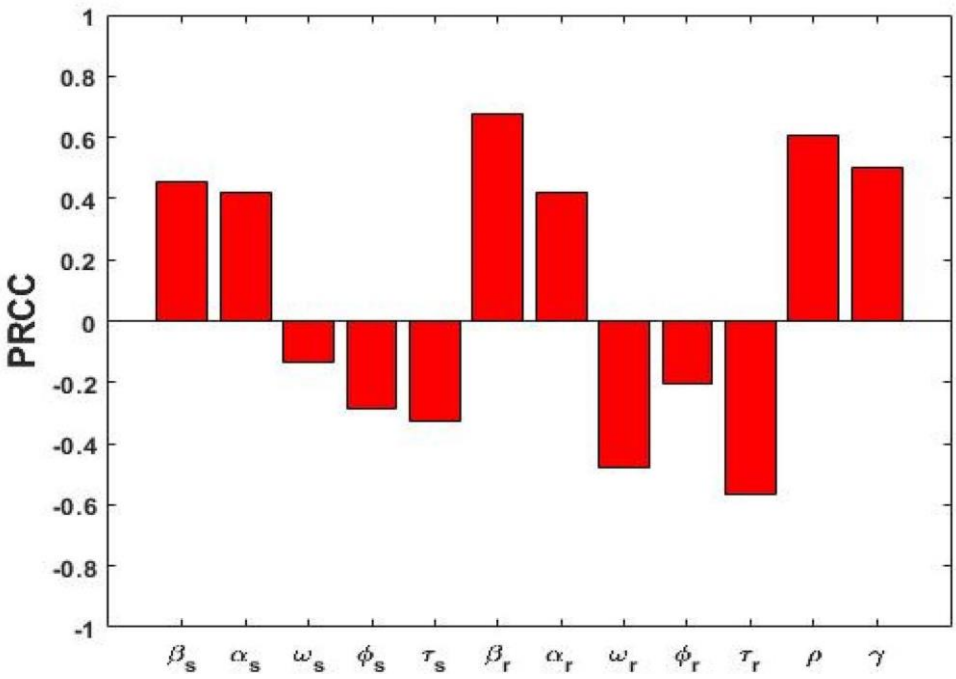
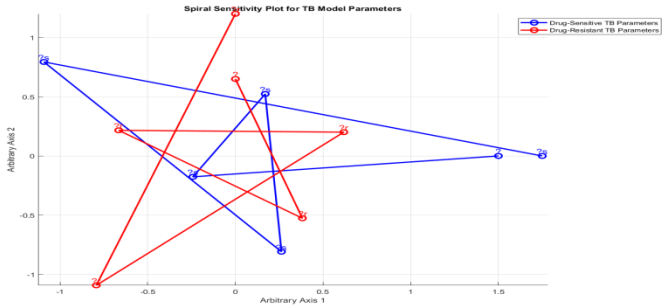
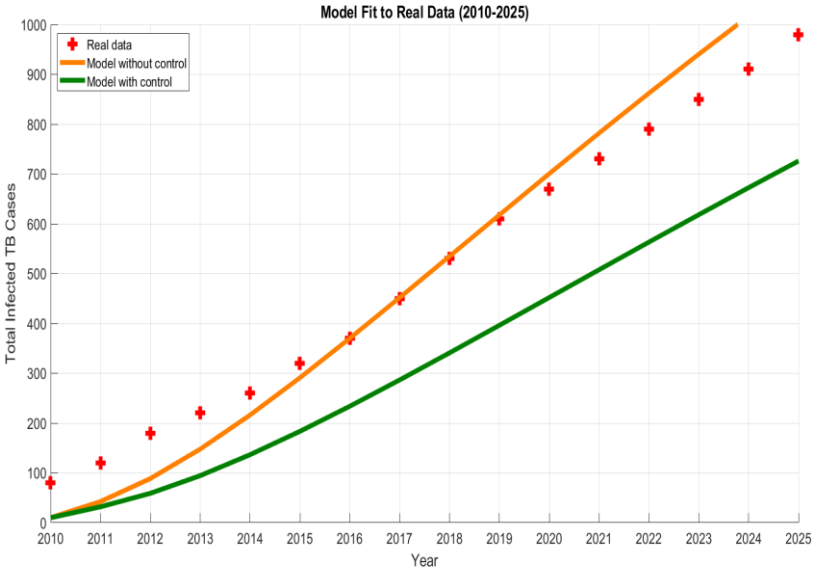


Figure 9 illustrates the relationship among the result of the model I_r and variables $\beta_s, \alpha_s, \omega_s, \phi_s, \tau_s, \beta_r, \alpha_r, \omega_r, \phi_r, \tau_r, \rho$ and γ when $R_{0s} > R_{0r}$ and $R_{0s} > 1$.



The spiral sensitivity plot was produced to illustrate parameter influence on tuberculosis dynamics. Drug-sensitive and drug-resistant PRCC values were displayed as distinct spiral curves, enabling direct comparison. Transmission coefficients, treatment rates, and amplification probability were identified as dominant drivers of outcomes. The results highlighted that imperfect treatment played a critical role in sustaining drug-resistant prevalence.



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According to earlier research, if the fundamental growth number of antibiotic-resistant microorganisms is over a certain threshold, even if it is less than one, and the fundamental growth number of sensitive microorganisms is larger than one, both types of bacteria can persist (Tanvir Mahtab Uddin et. al.) [29]. This is not what we found. Our findings demonstrate that the fundamental the increased rate of antibiotic-resistant microorganisms does not need to rise above a certain threshold in order for both strains to coexist. This is a direct result of the amplification pathway, which gives the resistant strain another way to survive and proliferate. The most efficient method of lowering the total burden of the disease is to combine diverse therapeutic techniques, according to several TB modeling studies. We have created a six-compartmental, two-strain SLIRS model specifically for Bangladesh in this study, which incorporates a feature known as amplification. The coupling between the two strains, which illustrates how infected people may become resistant to drugs while undergoing treatment, is a crucial component of our model. We made a number of important assumptions in our investigation that were absent from previous analyses. We believed that naturally occurring genetic alterations in TB bacteria, when exposed to insufficient therapy, are the primary cause of amplification, or the development of drug resistance. In addition, our model incorporates treatment and natural recovery factors that were not taken into account in those earlier investigations. Furthermore, we have included a factor that was not included in previous studies: people who have recovered from tuberculosis may lose their immunity and re-enter the vulnerable group. According to our concept, the fundamental reproduction numbers, R_{0s} and R_{0r} are specifically impacted by the transmission rates $\beta_s(\beta_r)$ rates of advancement $\alpha_s(\alpha_r)$ rates of recovery $\omega_s(\omega_r)$, disease-related mortality rates $\phi_s(\phi_r)$, as well as treatment rates $\tau_s(\tau_r)$. Additionally, sensitivity analysis shows that the transmission rates $\beta_s(\beta_r)$ are the most important factors, and the treatment rates $\tau_s(\tau_r)$. Therefore, the main goal of effective management and eventual eradication of DS TB and DR TB infections should be to lower the contact rates $\beta_s(\beta_r)$ with contagious people. We can reduce contact rates in a number of ways. One method is personal respiratory protection, which involves masks for patients to wear while they cough, sneeze, yawn, or talk to stop the spread of TB bacteria. Patients should also be instructed in basic infection control practices, such as covering their mouth and nose while coughing or sneezing and appropriately discarding used tissues in covered bins. Environmental measures, which include optimizing air exchange and dilution and decontaminating the air in high-risk regions where adequate ventilation is not feasible, are also essential. Regular maintenance and monitoring of any ventilation system is also essential (Iasmin Lourenço Niza et. al.) [30]. Lastly, disease diagnosis-focused public health programs are also required to reduce transmission.

Increasing the treatment rates $\tau_s(\tau_r)$ is the second most important tactic among contagious people. Furthermore, large amplification levels (ρ), especially when combined with high τ_s depict situations of insufficient or poorly managed therapy that encourage the formation of new DR TB cases, and so contribute to a higher prevalence of DR TB. Therefore, in order to effectively address the challenges presented by DR TB, we advise that evaluations of the amplification risk (ρ) be carried out in conjunction with assessments of the reproduction numbers for both DS and DR TB. This will ensure that treatment levels are optimized to minimize the development and spread of DR TB. The most efficient method of preventing medication resistance in underdeveloped countries like Bangladesh is to provide first-line treatment for DS TB that is properly delivered. Preventing an increase in the prevalence of DR TB requires early detection of the disease and the provision of appropriate second-line medication regimens. However, because long-term therapy is expensive, it is difficult to segregate infectious persons. Therefore, increasing treatment rates by lowering treatment costs and implementing universal healthcare is the most sensible and effective way to eradicate both DS TB and DR TB in Bangladesh.

DISCUSSION AND CONCLUSION

This research introduces and evaluates a new TB simulation using two forms of bacteria as well as propagation. This model distinguishes between drug-sensitive (DS) and drug-resistant tuberculosis. In this approach, amplification is defined as the procedure whereby a person with DS TB acquires a type of resistance following a rejection of their first-line medication treatment.

Our model identifies three equilibrium points: healthy, single-present, or mixed. We used the forthcoming matrix approach to obtain the basic number of replications for each strain (R_{0s} for DS TB and R_{0r} for DR TB). Table 1 shows the estimated values for these reproduction numbers, as well as the model's other biological

parameters, based on available data. We also used dynamical systems analysis to study Particular constancy of healthy and single-present equilibria. This research confirms that stability depends on two important threshold values: fundamental reproduction numbers for DS TB (R_{0s}) and DR TB (R_{0r}). If max [R_{0s}, R_{0r}] < 1, the disease-free equilibrium is globally asymptotically stable, implying the disease will eventually die out. The model indicates that if $R_{0r} > \max[R_{0s}, 1]$, DS TB will die out, but DR TB will endure. If $R_{0s} > \max[R_{0r}, 1]$, both DS and DR TB will survive in the community. This approach aids in identifying certain portions of the variable area in which the different exponential levels are either steady or unreliable. This feature enables us to forecast the long-term behavior of DS and DR-TB dynamics. The data can help the Bangladesh National TB Control Program lower infectiousness until the condition max [R_{0s}, R_{0r}] < 1 is reached, when the disease will be eradicated. In previous modeling studies on the transmission patterns of sensitive and resistant tuberculosis bacteria, the existence and stability of both within-host and between-host models were investigated. Studies indicate that when the fundamental reproduction numbers for both sensitive antimicrobial-resistant microorganisms are fewer instead of a single, both strains are eliminated. Assuming the fundamental growth rate of antimicrobial-resistant microorganisms (R_{0r}) exceeds one and those of vulnerable microorganisms (R_{0s}) is fewer instead of a single and solely antibiotic-resistant microorganism will survive.

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