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THEORETICAL ASSESSMENT OF THE RELATIVE INCIDENCES OF SENSITIVE AND RESISTANT TUBERCULOSIS EPIDEMIC IN PRESENCE OF DRUG TREATMENT

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Abstract. Despite the availability of effective treatment, tuberculosis (*TB*) remains a major global cause of mortality. Multidrug-resistant tuberculosis (*MDR-TB*) is a form of *TB* that is resistant to at least two drugs used for the treatment of *TB*, and originally is developed when a case of drug-susceptible *TB* is improperly or incompletely treated. This work is concerned with a mathematical model to evaluate the effect of *MDR-TB* on *TB* epidemic and its control. The model assessing the transmission dynamics of both drug-sensitive and drug-resistant *TB* includes slow *TB* (cases that result from endogenous reactivation of susceptible and resistant latent infections). We identify the steady states of the model to analyse their stability. We establish threshold conditions for possible scenarios: elimination of sensitive and resistant strains and coexistence of both. We find that the effective reproductive number is composed of two critical values, relative reproductive number for drug-sensitive and drug-resistant strains. Our results imply that the potential for the spreading of the drug-resistant strain should be evaluated within the context of several others factors. We have also found that even the considerably less fit drug-resistant strains can lead to a high *MDR-TB* incidence, because the treatment is less effective against them.

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1. **Introduction.** Multidrug-resistant tuberculosis (*MDR-TB*) is not a new phenomenon. Resistance to *TB* drug has been reported since the early days of the introduction of chemotherapy and, in spite of its global magnitude and several decades of study, the problem has not yet been adequately addressed. *TB* remains a major global health problem and it is responsible for approximately two million deaths each year.

MDR-TB is a specific and particularly a dangerous form of drug-resistant tuberculosis, which is defined as the form of disease caused by resistance of a strain of *Mycobacterium tuberculosis (MTB)* to two or more of the antituberculosis drugs. Clinically, the most important pattern of multidrug resistance is resistance to both isoniazid and rifampin, the two most powerful antituberculosis drugs used in combination chemotherapy. *MDR-TB* is generally treatable, however, the efficacy of treatment of drug-resistant cases is reduced compared with that of drug-sensitive cases.

Studies have found that drug-resistance transmission increases as the duration of previous treatment increases [17]. In most instances, drug resistance develops because of inadequate or erratic therapy, although it has been shown that persons previously treated for drug-sensitive tuberculosis can be reinfected with drug-resistant strains [12], [20], [30], [41].

In the real world treatment of patients with active-*TB* requires a multiple drug regimen; treatment is highly effective (with a 95% healing rate) if the patient harbors drug-sensitive strains and is compliant with the treatment regimen [7]. However, treating *MDR-TB* is much harder than treating drug-sensitive tuberculosis, and unlike drug-sensitive tuberculosis, the risk of dying from *MDR-TB* is higher. People who have it need to take more antituberculosis drugs for longer time. Treatment for up to two years or in some cases even longer periods may be required.

For many years, drug-resistant tuberculosis was believed to be less fit, i.e. less transmissible, than drug-sensitive tuberculosis. In 1985, Snider and colleagues compared the risk of infection among persons exposed to drug-resistant strains with the risk among persons exposed to drug-susceptible strains [42]. They found no evidence that drug-resistant strains were less fit than drug-sensitive strains. In fact, contacts of previously untreated patients had a similar risk of infection, regardless of whether the strains were drug-resistant or drug-sensitive.

The recent outbreaks of *MDR-TB* support the findings that drug-resistant strains is no less transmissible than drug-sensitive strains and that, in fact, prolonged periods of infectiousness may facilitate transmission. On the other hand, some reports indicate that drug-resistant strains of *MTB* have a lower fitness than drug-sensitive strains, whereas others show no difference in disease transmission [13]. Therefore, a related question is whether drug-resistant strains are as transmissible as their drug-sensitive counterparts.

One theoretical approach widely used to measure the transmissibility of a pathogen is the number of secondary cases generated. In infectious disease epidemiology, this measure reflects the reproductive fitness, and it is also known as the basic reproductive number, R_0. Hence, whether and how fast drug-resistant strains are likely to spread depends on their reproductive fitness [9], [13].

In addition, an often more useful measure is that of *relative reproductive fitness*, where the success of a particular pathogen variant is compared to the success of another. For example, the fitness of a drug-resistant strain can be expressed relative to the fitness of a drug-sensitive strain.

A number of theoretical studies have been performed on the mathematical modelling of coexistence of different pathogens (strains) in the same host [1], [3], [11], [29], [33], [34], [35], [40]. One of the first mathematical model that included the dynamics of both drug-sensitive and drug-resistant tuberculosis was published by Blower et.al. [5]. More recently others have modeled the emergence of drug-resistant tuberculosis and predict the future burden of *MDR-TB* [4], [13], [14], [15], [22], [28], [31], [38].

Here we will model the treatment and the control of both drug-resistant and drug-sensitive tuberculosis to describe the outbreaks of *MDR-TB*. Drug-resistant and drug-sensitive tuberculosis are transmitted in the same way, and the model includes slow *TB*, i.e., the *TB*-cases that result from endogenous reactivation of latent infections. We identify the steady states of the model to analyse their stability in terms of the reproductive number of the disease. Because of the heterogeneity in the fitness of drug-resistant strains, and the unclarity whether *TB* drug-resistant strains are less fit (less transmissible) or more fit (more transmissible) than drug-sensitive strains, we will allow a wide range for the relative fitness of drug-resistant strains in our estimates. In our model we find that the reproductive number is composed of two critical values, relative reproductive number for sensitive (strains sensitive to all drugs) and drug-resistant strains. Paradoxically, we have found that even drug-resistant strains that are considerably less fit (and thus less transmissible) than the drug-sensitive strains can lead to a high *MDR* incidence.

2. **Model formulation.** Our mathematical model monitors the temporal dynamics of susceptible individuals (not infected but susceptible to infection), latent individuals (infected but unable to infect others) and the active-*TB* infections, given by the infectious individuals (i.e., infected individuals that are able to infect others). Since the model assesses the drug-resistant and drug-susceptible tuberculosis transmission, two subclasses of latent and infectious *TB* individuals are required to build it. Hence, the total population ($\widetilde{N}$), is divided into five classes, namely, $\widetilde{S}$, the susceptible individuals; $\widetilde{L}_S$, the drug-sensitive latent individuals; $\widetilde{L}_R$, the drug-resistant latent individuals; $\widetilde{TB}_S$, the drug-sensitive with active-*TB* individuals, and $\widetilde{TB}_R$, the drug-resistant with active-*TB* individuals. Here, to simplify expressions, both active-*TB* and *TB* cases mean active *TB* infectious cases, and the subscripts 'S' and 'R' stand for drug-sensitive and drug-resistant types.

The compartmentalized diagram of the model is shown in Figure 1 and the description of variables and parameters for the model is given Table 1.

We assume that *MTB* infection is transmitted by infectious individuals with active-*TB* ($\widetilde{TB}_S$ and $\widetilde{TB}_R$), and the infection propagates following the pseudo mass-action incidence [27], [33]. The susceptible individuals (S) can be infected with either a drug-sensitive or a drug-resistant strains. The rate of new drug-sensitive and drug-resistant cases are $\widetilde{\beta}_S\widetilde{TB}_S\widetilde{S}$ and $\widetilde{\beta}_R\widetilde{TB}_R\widetilde{S}$, respectively. The transmission coefficients, $\widetilde{\beta}_S$ and $\widetilde{\beta}_R$ specify the transmissibility of drug-sensitive tuberculosis, and the transmissibility of drug-resistant tuberculosis, respectively. The transmission of drug-resistant tuberculosis occurs via two independent but interacting processes: (i) transmission of drug-resistant to susceptible individuals (transmitted resistance) and (ii) conversion of sensitive cases to drug-resistant cases during the treatment (acquired resistance).

As discussed previously, the dynamics of epidemic models can be understood in terms of the basic reproductive number of infection, R_0, which is the average

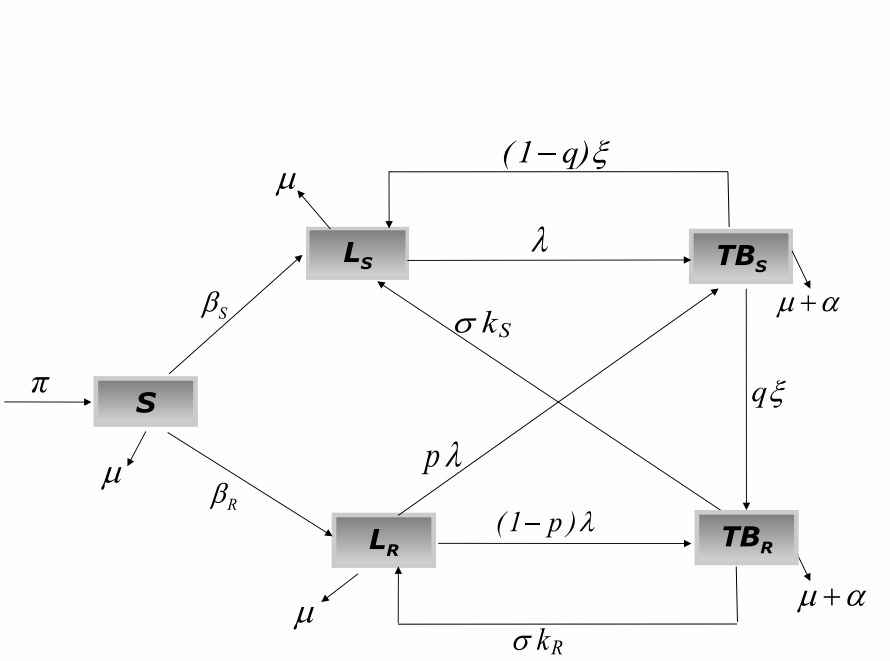

FIGURE 1. Flux diagram of the model.

number of secondary cases caused by one infectious case in a completely susceptible population. It is well-known that the condition $R_0 < 1$ is necessary for disease eradication [26]. Here, the *relative reproductive fitness* function will be approximated by the basic reproductive number of infection (R_0) in the absence of treatment or the effective reproductive number (R) in the presence of treatment [9], [13].

To incorporate competition between drug-resistant and drug-sensitive organisms, we model the drug-resistant strains differ in relative fitness compared to the drug-sensitive strains. The degree to which $\widetilde{\beta}_S$ is greater than $\widetilde{\beta}_R$ determines how much more transmissible the drug-sensitive strain is than the drug-resistant one. It is assumed $\widetilde{\beta}_R = \omega\widetilde{\beta}_S$, $0 < \omega < 1$. However, because of the heterogeneity in the fitness of drug-resistant strain suggested by empirical studies, [23], [44], and the unclarity whether drug-resistant strains are less fit (less transmissible) or more fit (more transmissible) than drug-sensitive strains, the model will also include the possibility that drug-resistant tuberculosis could be more transmissible than drug-sensitive tuberculosis, that is $\omega > 1$.

Some models include a different transfer of some fraction of the susceptibles to the infectious class. See Blower et al. (1995) [6] and Gomes et al. (2004) [24] for examples. Since in our model the question of different rates of progression to the disease is not a central one, we assume that both drug-sensitive and drug-resistant individuals in the latent class will progress at the same rate λ to the infectious class. Hence, the progression rates from latent TB to active-TB are assumed to be proportional to the latent-TB cases, i.e., they are given by $\lambda\widetilde{L}_S$ and $\lambda\widetilde{L}_R$, such that TB cases ($\widetilde{TB}_S$ or $\widetilde{TB}_R$) arising as a result of endogenous reactivation (slow progression) of the primary complex with both the sensitive and the resistant strains.

TABLE 1. Description of variables and parameters for model (1)

Variables	Description
$\widetilde{S}$	susceptible individuals
$\widetilde{L}_S$	drug-sensitive latent individuals who harbour a majority of the sensitive strain with a small minority of resistant strain
$\widetilde{L}_R$	drug-resistant latent individuals who harbour predominantely the resistant strain with a reasonable subpopulation of sensitive strain
$\widetilde{TB}_S$	drug-sensitive with active-TB individuals
$\widetilde{TB}_R$	drug-resistant with active-TB individuals

Parameters	Description
π	susceptibles recruitment rate (births and immigration)
β_S	transmission coefficient of the drug-sensitive strain
β_R	transmission coefficient of the drug-resistant strain
μ	natural mortality rate
α	mortality rate due to TB
ω	the degree of transmissibility of the strain
λ	endogenous reactivation rate (slow progression)
p	proportion of drug-resistant latent TB individuals that develop drug-sensitive infectious TB
q	probability that treatment failure occurs due to the development of antibiotic resistance
k_S	relative treatment efficacy of drug-sensitive patients
k_R	relative treatment efficacy of drug-resistant patients
ξ	treatment rate for the drug-sensitive patients
σ	treatment rate for the drug-resistant patients

Investigations suggest that concurrent infection with multiple strains is possible [10], [16], [18], [37], [39], [43]. In our model we then include a state of mixed latency to reflect the fact that some latent individuals L_R may progress to active-TB with both drug-resistant and drug-sensitive strains. However, the relative risk of drug-sensitive TB individuals emerging during this period of latency is still unclear yet. In some laboratory experiments, resistant strains were less viable than sensitive ones in vitro, and often (though not always) less virulent in guinea pigs [32]. Given that some individuals may harbor infection with both drug-resistant and drug-sensitive strains, the fitness of MTB strains and competition between them during the epidemic are incorporated in the model. Thus, we define p, $0 \leq p < 1$, as the proportion of drug-resistant latent TB individuals who develop drug-sensitive infectious TB and $(1-p)$ as the proportion of drug-resistant latent TB individuals that develop drug-resistant infectious TB. Note that if $p = 0$, then all drug-resistant latent TB individuals progress to active-TB with drug-resistant strains showing that the fitness of drug-resistant strains is a key determinant of the future burden of drug-resistant TB; if $p = 1$, then all drug-resistant latent TB individuals progress to active-TB with drug-sensitive strains, indicating that drug-resistant strains has no fitness. But this is not the current case.

Although we assume that all the drug-sensitive TB individuals ($\widetilde{TB}_S$) are treated with a multiple drug regimen (isoniazid and rifampin), treatment has opposite effects in the population-level: treatment cures drug-sensitive cases, but acquired drug-resistants quickly emerge among patients who receive ineffective or inappropriate treatment regimes and are non compliant with a multiple drug treatment regimens.

In our model the effective treatment of drug-sensitive TB individuals ($\widetilde{TB}_S$) occurs at rate ξ, and acquired drug resistance can arise directly, for whatever reason (with probability q), during the treatment of a drug-sensitive case. Consequently, q, $0 \leq q \leq 1$, is the probability that treatment failure occurs due to the development of antibiotic resistance. Thus, the model includes the possibility that treatment of a drug-sensitive case can result in one of three outcomes; (a) treatment can cure the patients (cases are removed from the $\widetilde{TB}_S$ class at a rate equal to $(1-q)\xi$, and enter into the $\widetilde{L}_S$ class), (b) treatment failure can occur and the patient acquires drug-resistant TB (cases are removed from the $\widetilde{TB}_S$ class at a rate equal to $q\xi$, and enter into the $\widetilde{TB}_R$ class) or (c) treatment failure can occur, yet the patient remains infected with drug-sensitive TB (treated cases remain in the $\widetilde{TB}_S$ class).

It is also assumed that drug-resistant TB cases ($\widetilde{TB}_R$) can be treated at rate σ, but treatment efficacy is reduced; the relative treatment efficacy of drug-resistant cases (in comparison with treatment of drug-sensitive cases) is specified by the parameter k (k_S for drug-sensitive, and k_R for drug-resistant cases). Thus, the model includes the possibility that treatment of drug-resistant TB cases can result in one of three outcomes: (a) treatment can cure the patients, and a few cases can be removed from the $\widetilde{TB}_R$ class at a rate equal to σk_S, and enter into the $\widetilde{L}_S$ class, (b) treatment can cure the patient, and cases are removed from the $\widetilde{TB}_R$ class, at a rate equal to σk_R, and enter into the $\widetilde{L}_R$ class, or (c) treatment failure occurs (treated cases remain in the $\widetilde{TB}_R$ class). Therefore, drug-sensitive and drug-resistant TB cases are untreatable (and/or untreated) if $k_S = k_R = 0$; drug-sensitive and drug-resistant cases are treated, with equal effectiveness if $k_S = k_R = 1$; and drug-sensitive and drug-resistant cases are only partially effectively treated if $0 < k_S < 1$ and $0 < k_R < 1$.

The parameters σ and ξ could be used to calculate both the fraction of infectious cases that are effectively treated and the proportion of cases that receive effective treatment per unit time. They specify the effective treatment rate, and are calculated as the product of the actual treatment rate and the efficacy of treatment. Hence in order to achieve a highly effective treatment rate it is necessary to have both a high treatment rate and a high efficacy of treatment. The model incorporates recruitment (π) and natural death (μ), as well as disease-related death (α), so the total population size may vary in time.

Based on the above assumptions and definitions, our model is governed by the following system of equations:

$$\begin{cases} \frac{d\widetilde{S}}{dt} &= \pi - \widetilde{\beta}_S \widetilde{TB}_S \widetilde{S} - \widetilde{\beta}_R \widetilde{TB}_R \widetilde{S} - \mu \widetilde{S} \\ \frac{d\widetilde{L}_S}{dt} &= \widetilde{\beta}_S \widetilde{TB}_S \widetilde{S} + (1-q)\xi \widetilde{TB}_S + \sigma k_S \widetilde{TB}_R - (\mu + \lambda)\widetilde{L}_S \\ \frac{d\widetilde{TB}_S}{dt} &= \lambda \widetilde{L}_S + p\lambda \widetilde{L}_R - (\mu + \alpha + \xi)\widetilde{TB}_S \\ \frac{d\widetilde{L}_R}{dt} &= \widetilde{\beta}_R \widetilde{TB}_R \widetilde{S} + \sigma k_R \widetilde{TB}_R - (\mu + \lambda)\widetilde{L}_R \\ \frac{d\widetilde{TB}_R}{dt} &= (1-p)\lambda \widetilde{L}_R + q\xi \widetilde{TB}_S - [\mu + \alpha + \sigma(k_R + k_S)]\widetilde{TB}_R, \end{cases} \tag{1}$$

By summing up the above equations, the variable total population size $\widetilde{N}$ obeys the following differential equation

$$\frac{d\widetilde{N}}{dt} = \pi - \mu\widetilde{N} - \alpha\left(\widetilde{TB}_S + \widetilde{TB}_R\right). \tag{2}$$

When the treatment is effective in reducing disease progression, i.e., $\alpha = 0$, the population size $\widetilde{N}$ evolves as an immigration model with natural mortality, i.e. according to $\frac{d\widetilde{N}}{dt} = \pi - \mu\widetilde{N}$. This equation has a single equilibrium $\widetilde{\widetilde{N}} = N_0 = \frac{\pi}{\mu}$, for any initial value of N_0. Thus, in the long run the population size settles to this constant value. It follows from (2) that $\lim_{t\to\infty} \widetilde{N}(t) \leq \pi/\mu = N_0$.

Equation (2) for $\widetilde{N}$ implies that solutions of (1) starting in the positive orthant $\mathbb{R}^5_+$, either approach, enter, or remain in the subset $\mathbb{R}^5_+$ defined by

$$D = \{\left(\widetilde{S}, \widetilde{L}_S, \widetilde{TB}_S, \widetilde{L}_R, \widetilde{TB}_R\right) \in \mathbb{R}^5_+ : \widetilde{S} + \widetilde{L}_S + \widetilde{TB}_S + \widetilde{L}_R + \widetilde{TB}_R \leq N_0\}.$$

Thus it suffices to consider solutions in the region D. Solutions of the initial value problem starting in D and defined by (1) exist and are unique on a maximal interval [25]. Since solutions remain bounded in the positively invariant region D, the initial value problem is then both mathematically and epidemiologically well-posed, [26]. Consequently, we have the following lemma.

Lemma 2.1. *The biological feasible region D is positively invariant and attracts all solutions in $\mathbb{R}^5_+$.*

Hence, it is sufficient to consider the dynamics of the flow generated by model (1) in D.

Before analysing the model (1) to explore the stability behavior of its equilibria, we rescale the system by defining the new variables: $S = \widetilde{S}/N_0$; $L_S = \widetilde{L}_S/N_0$; $TB_S = \widetilde{TB}_S/N_0$; $L_S = \widetilde{L}_S/N_0$, $TB_R = \widetilde{TB}_R/N_0$, $N = \widetilde{N}/N_0$ and parameters $\beta_S = N_0\widetilde{\beta}_S$ and $\beta_R = N_0\widetilde{\beta}_R$. Using these changes of variables and parameters, system (1) and (2) become:

$$\begin{cases} \frac{dS}{dt} &= \mu - \beta_S TB_S S - \beta_R TB_R S - \mu S \\ \frac{dL_S}{dt} &= \beta_S TB_S S + (1-q)\xi TB_S + \sigma k_S TB_R - (\mu+\lambda)L_S \\ \frac{dTB_S}{dt} &= \lambda L_S + p\lambda L_R - (\mu+\alpha+\xi)TB_S \\ \frac{dL_R}{dt} &= \beta_R TB_R S + \sigma k_R TB_R - (\mu+\lambda)L_R \\ \frac{dTB_R}{dt} &= (1-p)\lambda L_R + q\xi TB_S - [\mu+\alpha+\sigma(k_R+k_S)]TB_R, \end{cases} \tag{3}$$

and

$$\frac{dN}{dt} = \mu(1-N) - \alpha(TB_S + TB_R), \tag{4}$$

so that the rescaled total population size is variable within the unit simplex $0 \leq S + L_S + TB_S + L_R + TB_R = N \leq 1$.

3. Analysis of the model.

In this section, the system (3) is qualitatively analysed to investigate the existence and stability of its equilibria to establish the threshold condition for disease control or eradication.

3.1. **Local stability of the disease-free equilibrium.** In the absence of infection, the system (3) has a unique disease-free equilibrium (DFE), given by $P_0^* = (S^*, 0, 0, 0, 0) = (1, 0, 0, 0, 0)$. Evaluating the system's Jacobian at P_0^* we find

$$A_0 = \begin{bmatrix} a_{11} & 0 & -\beta_S & 0 & -\beta_R \\ 0 & a_{22} & \beta_S + (1-q)\xi & 0 & \sigma k_S \\ 0 & \lambda & a_{33} & p\lambda & 0 \\ 0 & 0 & 0 & a_{44} & \beta_R + \sigma k_R \\ 0 & 0 & q\xi & (1-p)\lambda & a_{55} \end{bmatrix}, \tag{5}$$

where $a_{11} = -\mu$, $a_{22} = a_{44} = -(\mu + \lambda)$, $a_{33} = -(\mu + \alpha + \xi)$ and $a_{55} = -[\mu + \alpha + \sigma(k_S + k_R)]$.

One of the eigenvalues τ_k of the Jacobian matrix (5) is straightforward: $\tau_1 = -\mu$. The other four (after some tedious manipulations) are expressed as the roots of the characteristic polynomial

$$P(\tau) \quad = \quad \tau^4 + a_1^*\tau^3 + a_2^*\tau^2 + a_3^*\tau + a_4^* = 0, \tag{6}$$

where

$$\begin{aligned} a_1^* &= -(a_{22} + a_{33} + a_{44} + a_{55}), \\ a_2^* &= \alpha_1 \left(1 - \tfrac{pq\xi(\mu+\lambda)}{\alpha_1(1-p)} - R^S\right) + \alpha_2(1 - R^R) + (a_{22} + a_{33})(a_{44} + a_{55}), \\ a_3^* &= \alpha_1 \left(1 - \tfrac{pq\xi(\mu+\lambda)}{\alpha_1(1-p)} - R^S\right)[-(a_{44} + a_{55})] + \\ &\quad \alpha_2(1 - R^R)[-(a_{22} + a_{33}) + \tfrac{pq\xi}{(1-p)}] - \alpha_3 \tfrac{q\xi}{(\mu+\lambda)}, \\ a_4^* &= \alpha_1\alpha_2(1 - R^S)(1 - R^R)(1 - R^{Tot}), \end{aligned} \tag{7}$$

It is also straightforward to verify that the parameters α_1, α_2 and α_3 given by

$$\begin{aligned} \alpha_1 &= (\mu + \lambda)(\mu + \alpha + \xi) + \tfrac{p}{(1-p)}(\mu + \lambda)q\xi - \lambda(1 - q)\xi, \\ \alpha_2 &= (\mu + \lambda)[\mu + \alpha + \sigma(k_S + k_R)] - \sigma k_R(1 - p)\lambda, \\ \alpha_3 &= (\mu + \lambda)q\xi \left\{\lambda\sigma k_S + \tfrac{p}{(1-p)}(\mu + \lambda)[\mu + \alpha + \sigma(k_S + k_R)]\right\}, \end{aligned} \tag{8}$$

are all positive. Finally, the parameters β_S^c and β_R^c given by

$$\beta_S^c = \frac{\alpha_1}{\lambda} \quad \text{and} \quad \beta_R^c = \frac{\alpha_2}{(1-p)\lambda}, \tag{9}$$

define, respectively, the sensitive and resistant effective reproductive numbers,

$$R^S = \tfrac{\beta_S}{\beta_S^c} \quad \text{and} \quad R^R = \tfrac{\beta_R}{\beta_R^c}, \tag{10}$$

while

$$R^{Tot} = \tfrac{A}{(1-R^S)(1-R^R)} \tag{11}$$

defines a effective reproductive number modified to allow for chemotherapy, with $A = \frac{\alpha_3}{\alpha_1\alpha_2} < 1$.

Since the characteristic polynomial (6) has a complex coefficients (see the expressions 7), the local stability of the disease-free equilibrium P_0^* cannot be completely resolved by the Routh-Hurwitz stability criterion. Nevertheless, these coefficients give insight by providing conditions which allow us to determine combinations of strain reproductive numbers (R^S and R^R).

TABLE 2. Local stability of disease-free equilibrium

Fitness conditions	**Eventual epidemiological outcomes**
$\mathcal{R}^S < 1 - A$, $\mathcal{R}^R < 1 - A$, $R^{Tot} < 1$	P_0^* stable (eradication of TB_S and TB_R)
otherwise	P_0^* unstable (coexistence of TB_S and TB_R)

One rule of the Routh-Hurwitz criterion states that all coefficients of the characteristic polynomial (6) must be positive, that is, $a_n^* > 0$, with $n = 1, 2, 3, 4$. From (7) it should be noted that a_1^* is always positive; and whenever $R^R > 1$ and $R^S > 1 - \frac{pq\xi(\mu+\lambda)}{\alpha_1(1-p)}$, then a_3^* is negative. Moreover, $R^R < 1$ and $R^S < 1 - \frac{pq\xi(\mu+\lambda)}{\alpha_1(1-p)}$, indicate the possibility of both $a_2^* > 0$ and $a_3^* > 0$.

The next task is to establish that a_4^* is positive. We check this statement by using the theory of **M**-matrices. For the complete proof, see the Appendix. Note that, in particular, the Appendix can also be used to show that both a_2^* and a_3^* are positive, i.e., whenever a_4^* is positive, then both a_2^* and a_3^* are positive.

In summary, by the theory of **M**-matrices, whenever $a_4^* > 0$ all the eigenvalues of the Jacobian matrix (5) have negative real part. Hence, the disease-free equilibrium P_0^* is locally asymptotically stable if $R^S < 1 - A$, $R^R < 1 - A$ and $R^{Tot} < 1$. If one of these conditions does not hold the disease-free equilibrium P_0^* becomes unstable. Thus, we have established the following result.

Lemma 3.1. *The disease-free equilibrium P_0^* exists and is locally asymptotically stable (LAS) whenever*

$$R^S < 1 - A, \quad R^R < 1 - A \quad \textit{and} \quad R^{Tot} = \frac{A}{(1-R^S)(1-R^R)} < 1,$$

with $A = \frac{\alpha_3}{\alpha_1\alpha_2} < 1$. Otherwise, it is unstable.

From the three conditions of Lemma 3.1, it is clear that if $R^R = 0$, then the disease-free equilibrium P_0^* is locally asymptotically stable if $R^S < 1 - A$ or, equivalently, if $R^{Tot} < 1$. If $R^S = 0$, then the disease-free equilibrium P_0^* is locally asymptotically stable if $R^R < 1 - A$ or, equivalently, if $R^{Tot} < 1$.

We have also noted that in the absence of treatment (i.e., $\xi = \sigma = 0$) the reproduction number modified to allow for chemotherapy, R^{Tot}, goes to zero, while $R^S > 0$, $R^R > 0$ and $R^S \neq R^R$. In this case, the effective reproductive number is modeled by only two case reproductive numbers, the case reproduction number of the drug-sensitive (R^S) and of the drug-resistant (R^R) strains, such that both $R^S < 1$ and $R^R < 1$ must be satisfied to prevent an outbreak of, or to eradicate, the disease.

The most important long-term dynamics of drug-sensitive (TB_S) and drug-resistant (TB_R) tuberculosis can be expressed in terms of the baseline conditions on the basic case reproduction number given in Table-2.

Thus, if the reproduction numbers of both sensitive ($R^S > 0$) and resistant cases ($R^R > 0$) are less than $1 - A$, and $R^{Tot} < 1$, then TB goes to extinction. This, clearly, is the ultimate aim of the control. If one of them does not hold, then the *MDR-TB* can emerge as a result of incomplete adherence to, or ineffective treatment regimens, or inadequate drug supply, or non compliance or a combination

of these factors. This implies that there exists a range of values for R^S and R^R as well as R^{Tot}, for which both drug-sensitive and drug-resistant strains can invade a disease-free population, and the trivial equilibrium point, P_0^*, becomes unstable.

Hence, the baseline conditions given in Table-2 are left as an open question. We will investigate them more later on. Next, we explore the existence and stability of the positive endemic equilibria of the model (3).

3.2. **Endemic equilibria.** First, the model (3) monitors the populations, so that the negative endemic equilibria are biologically meaningless. As a consequence, the endemic equilibria of the model correspond to the case where the disease may persist in the population, with $TB_S > 0$ and $TB_R > 0$.

However, since these equilibria (if they exist) cannot be clearly expressed in closed form, we shall discuss their existence based on some specific conditions on the model parameters. To do so, we note that the right hand side of the last equation of system (3) at equilibrium gives:

$$L_R = \frac{[\mu+\alpha+\sigma(k_S+k_R)]TB_R - q\xi TB_S}{(1-p)\lambda}. \tag{12}$$

To ensure the existence of a feasible endemic equilibrium we need to require positive coordinates, i.e., $TB_S > 0$ and $TB_R > 0$ with $0 \leq p < 1$ and $0 \leq q \leq 1$.

Substituting (12) into the right hand side of the third equation of system (3) at equilibrium we find

$$L_S = \frac{[(\mu+\alpha+\xi)(1-p)+pq\xi]TB_S - p[\mu+\alpha+\sigma(k_S+k_R)]\ TB_R}{(1-p)\lambda}. \tag{13}$$

Therefore, from equations (12) and (13), $L_R > 0$ and $L_S > 0$ if and only if

$$\Phi\ TB_S < TB_R < \left\{\Phi + \frac{(\mu+\alpha+\xi)(1-p)}{p[\mu+\alpha+\sigma(k_S+k_R)]}\right\} TB_S\ , \tag{14}$$

where $\Phi = \frac{q\xi}{\mu+\alpha+\sigma(k_S+k_R)} > 0$.

In addition, the first equation of system (3) yields

$$S = \frac{(1-p)\lambda - [\alpha_4\ TB_R + \alpha_5\ TB_S]}{(1-p)\lambda}, \tag{15}$$

where $\alpha_4 > 0$ and $\alpha_5 > 0$ are, respectively, expressed by

$$\begin{aligned} \alpha_4 &= \left[\frac{(\mu+\lambda)(\mu+\alpha)}{\mu} + \sigma\,(k_S + k_R)\right](1-p), \\ \alpha_5 &= \left[\frac{(\mu+\lambda)(\mu+\alpha)}{\mu} + (1-q)\xi\right](1-p). \end{aligned} \tag{16}$$

Hence, to ensure $S > 0$ we require

$$TB_R < (1-p)\lambda + \alpha_5\ TB_S\ . \tag{17}$$

Furthermore, comparing equation (14) with equation (17) it is possible to show that

$$\Phi + \frac{(\mu+\alpha+\xi)(1-p)}{p\,[\mu+\alpha+\sigma(k_S+k_R)]} < \alpha_5$$

and, as a consequence, to ensure $S > 0$, $L_R > 0$ and $L_S > 0$ we only require that equation (14) holds.

Now, substituting (15), (13) and (12) into the right hand side of the second and fourth equations of system (3) we obtain (at equilibrium),

$$[(1-p)\,(\beta_S\lambda - \alpha_1) - \beta_S\alpha_5\ TB_S]\,TB_S = \left[\beta_S\alpha_4\ TB_S - \frac{(1-p)\alpha_3}{(\mu+\lambda)q\xi}\right] TB_R\ , \tag{18}$$

and

$$[\beta_R\alpha_5\ TB_R-(\mu+\lambda)q\xi]\ TB_S \quad = \quad \{[\beta_R\lambda(1-p)-\alpha_2]-\beta_R\alpha_4\ TB_R\}TB_R\ , \tag{19}$$

where α_1, α_2, α_3, α_4 and α_5 are positive (see the expressions (8) and (16)).

Since $TB_S \neq 0$ and $TB_R \neq 0$, dividing the equation (19) by equation (18) we get the following linear equation

$$TB_R \quad = \quad \tfrac{a}{b}-\tfrac{c}{b}TB_S\ , \tag{20}$$

where

$$\begin{aligned} a &= \alpha_1\alpha_2(1-R^S)(1-R^R)(1-R^{Tot}), \\ b &= -\beta_R\alpha_1\alpha_4\left(1+k_b-R^S\right), \\ c &= -\tfrac{\beta_S\alpha_2\alpha_5}{(1-p)}\left(1+k_c-R^R\right), \end{aligned} \tag{21}$$

with $k_b=\frac{\alpha_3}{\alpha_1}\frac{1}{\Psi}>0$, $k_c=\frac{1}{\alpha_2}\Psi>0$ and $\Psi=\frac{\alpha_4(\mu+\lambda)q\xi}{\alpha_5}>0$.

Substituting (20) into equation (18), after some manipulations we obtain the following quadratic polynomial

$$H(TB_S) \quad = \quad a_1TB_S^2+b_1TB_S+c_1=0, \tag{22}$$

where

$$\begin{aligned} a_1 &= \left(\tfrac{c}{a}\alpha_4-\tfrac{b}{a}\alpha_5\right)\beta_S, \\ b_1 &= -\left\{\tfrac{b}{a}\alpha_1(1-p)\left(1-R^S\right)+\tfrac{c}{a}\tfrac{(1-p)\alpha_3}{(\mu+\lambda)q\xi}+\beta_S\alpha_4\right\}, \\ c_1 &= \tfrac{(1-p)\alpha_3}{(\mu+\lambda)q\xi}. \end{aligned} \tag{23}$$

It is important to note that equation (22) can be analyzed for the possibility of multiple endemic equilibria; however this analysis is not an easy task. By solving for TB_S from the quadratic equation (22), and substituting the values of TB_S into the linear equation (20), the solution TB_R can be obtained. Thus, the positive endemic equilibria of the system (3) are obtained by substituting both positive solutions TB_S and TB_R into the expressions in (12), (13) and (15).

More specifically, the previous analysis suggests that the signs of both coefficients (21) and (23) may also give the conditions for the existence of the endemic equilibria. This is explored below.

3.3. **Existence of endemic equilibria.** From now on we must simultaneously investigate equations (20) and (22). Before doing this, since $c_1>0$, from the coefficients (23) we remark that the number of possible positive real roots of the quadratic polynomial (22) only depends on the sign of both a_1 and b_1. Thus, according to Descartes' rule of signs, if $a_1<0$, a quadratic polynomial has two real roots with opposite signs, independently of b_1; if $a_1>0$, the quadratic polynomial has zero or a pair of positive real roots if $b_1<0$ and $b_1^2-4a_1c_1>0$, while no positive root could exist if $b_1>0$.

Furthermore, from coefficients (21) it appears necessary the assessment of the possible scenarios for the change of the signs of a, b and c. They are then illustrated below.

Case 1: a and b could have the same sign and c and b opposite signs.

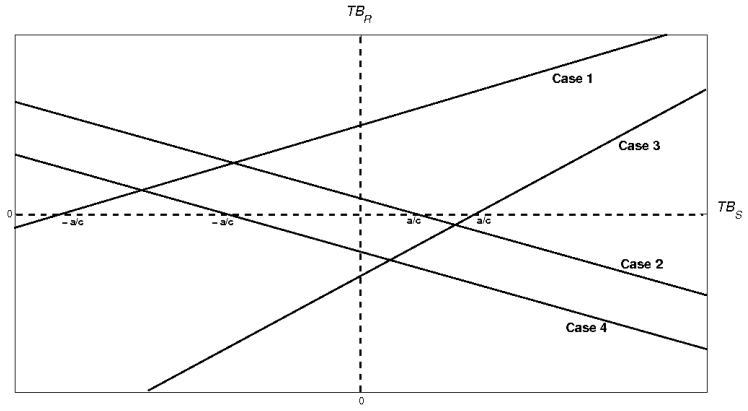

FIGURE 2. Sketch graphs of the linear equation (20) according to the signs of a, b and c.

Case 2: a, b and c could have all the same sign.
Case 3: a and b could have opposite signs as well as c and b.
Case 4: a and b could have opposite signs while both c and b have the same sign.

Figure 2 depicts the sketch graphs of the linear equation (20) for these four possible scenarios.

Note that for Case 1, Case 2 and Case 3 the positive solution TB_R can be obtained whenever $TB_S > 0$, $0 < TB_S < a/c$ and $TB_S > a/c$, respectively (see Figure 2). In contrast, no positive solutions coexist for Case 4, since $TB_S > 0$ implies to $TB_R < 0$. Hence, by analysing the signs of a, b and c corresponding to the three first cases, it is possible to determine the signs of a_1 and b_1.

At this point, it should be pointed out that since the signs of a, b and c also depend on the thresholds $\mathcal{R}^S$, $\mathcal{R}^R$ and R^{Tot}, see (21), the requirements for the coexistence of TB_S and TB_R given in Table 2 are necessary, but do not suffice for the existence of an endemic equilibrium. Hence, from (21), it is possible to state that $\mathcal{R}^S = 1 + k_b$, $\mathcal{R}^R = 1 + k_c$ and $R^{Tot} = 1$ are the additional threshold requirements for the existence of a positive endemic equilibrium.

As a result of such an analysis, considering also the thresholds of Table 2, it is possible to establish when both the quadratic polynomial (22) and the linear equation (20) have positive real root(s) or not and, consequently, whether the system (3) has zero, one or two positive endemic equilibria.

The arrangements for the possible intervals of R^S, R^R and R^{Tot} for which the possibility of positive endemic equilibria exists, are described in Table 3; the range for R^S has been fixed, while varying the ranges of both R^R and R^{Tot}. Note that each arrangement in Table 3 corresponds to one specific case in Figure 2, which in turn corresponds to $a_1 > 0$ and $a_1 < 0$ in the polynomial equation (22).

Apart from this, from both Figure 2 and the coefficients (23), it is possible to check that when Case 1 holds, $a_1 < 0$ follows. Hence, independently of the sign of b_1, the quadratic polynomial (22) and the linear equation (20) have a unique positive real root, i.e., $TB_S > 0$ and $TB_R > 0$, respectively. As a consequence of our previous analysis, the system (3) has then a unique positive endemic equilibrium.

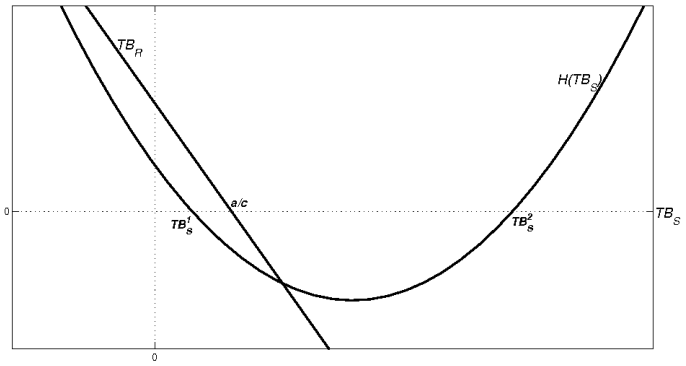

FIGURE 3. Sketch graphs of both linear (20) and quadratic (22) equations for Case-2 and $a_1 > 0$.

In contrast, in Case 2, we have either $a_1 > 0$ or $a_1 < 0$, so that the quadratic polynomial (22) has respectively either two positive real roots or a unique positive real root. As a consequence, the system (3) could have either two positive endemic equilibria or a unique positive endemic equilibrium. In this case, one has $0 < TB_S < a/c$ and $TB_R > 0$, see Figure 2.

Finally, in Case 3, $a_1 > 0$ and the polynomial equation (22) has two positive solutions. As a consequence, the system (3) could have either two positive endemic equilibria or a unique positive endemic equilibrium. In this case, $TB_S > a/c$ and $TB_R > 0$, see Figure 2.

Thus, we must show whether for $a_1 > 0$ in both Case 2 and Case 3, model (3) admits also a unique positive endemic equilibrium. To this end, we still need to analyse the sign of b_1. Instead, we can assess the value that the quadratic polynomial (22) assumes when $TB_S = a/c$ is a root of the linear equation (20). More specifically, by evaluating $H(TB_S = a/c)$ for both $a_1 > 0$ and $a_1 < 0$, it is possible to check whether or not, for $TB_S^1 < a/c < TB_S^2$ we have $H(a/c) < 0$, where TB_S^1 and TB_S^2 denote the positive roots of the quadratic polynomial (22).

From equation (20), it follows then that at $TB_S = a/c$, the quadratic polynomial (22) is given by

$$H(a/c) \quad = \quad -\tfrac{b}{c}\left[\tfrac{a}{c}\alpha_5\beta_S + \alpha_1(1-p)(1-R^S)\right]. \tag{24}$$

Substituting the expressions from (21) into equation (24) leads to

$$H(a/c) \quad = \quad -k_H R^{Tot}(1+k_b-R^S)(1-R^S)\left[1+\tfrac{k_c}{R^{Tot}}-R^R\right], \tag{25}$$

where $k_H = \frac{\alpha_1^2\ \alpha_4\ \beta_R\ (1-p)^2}{\alpha_2\ \alpha_5\ \beta_S\ (1+k_c-R^R)^2} > 0$.

Finally, by using (21) and (16) in (23), one can rewrite a_1, as

$$a_1 \quad = \quad \tfrac{k_{a_1}(1+k_b)}{(R^S-1)(R^R-1)(1-R^{Tot})}\left[R^R - R^S\tfrac{(1+k_c)}{(1+k_b)}\right], \tag{26}$$

with $k_b > 0$ and $k_c > 0$ defined in expressions (21) and $k_{a_1} = \frac{\alpha_4\alpha_5}{\lambda(1-p)} > 0$.

Note that if the expression (23) does not provide the required necessary information about the sign of a_1, we can then use (26) to determine it.

Figure 3 and Figure 4 can be taken as examples to illustrate Table 3.

TABLE 3. Outcomes for the existence of the endemic equilibria. The effective reproductive number of drug-sensitive and drug-resistant tuberculosis, R^S and R^R, respectively; and $R^{Tot} = \frac{A}{(1-R^S)(1-R^R)}$. Case is defined in page (981) according to the linear equation (20). NRR = Number of possible positive real roots for the equation (22). NEE = number of possible positive endemic equilibrium for the system (3).

R^S	R^R	R^{Tot}	**Case**	**NRR**	**NEE**
$(I)\ 0 < \mathcal{R}^S < 1 - A$	$0 < \mathcal{R}^R < 1 - A$	$\mathcal{R}^{Tot} < 1$	Case 4.	1 $(a_1 < 0)$	P_0^* stable
	$0 < \mathcal{R}^R < 1$	$\mathcal{R}^{Tot} > 1$	Case 2.	1 $(a_1 < 0, H(a/c) < 0)$	1
	$1 < \mathcal{R}^R < 1 + k_c$	$\mathcal{R}^{Tot} < 0$	Case 2.	1 $(a_1 < 0, H(a/c) < 0)$	1
	$\mathcal{R}^R > 1 + k_c$	$\mathcal{R}^{Tot} < 0$	Case 1.	1 $(a_1 < 0)$	1
$(II)\ 1 - A < \mathcal{R}^S < 1$	$0 < \mathcal{R}^R < 1 - A$	$\mathcal{R}^{Tot} > 1$	Case 2.	0, 2 $(a_1 > 0, H(a/c) < 0)$	1
	$1 - A < \mathcal{R}^R < 1$	$\mathcal{R}^{Tot} > 1$	Case 2.	1 $(a_1 < 0, H(a/c) < 0)$	1
	$1 < \mathcal{R}^R < 1 + k_c$	$\mathcal{R}^{Tot} < 0$	Case 2.	1 $(a_1 < 0, H(a/c) < 0)$	1
	$\mathcal{R}^R > 1 + k_c$	$\mathcal{R}^{Tot} < 0$	Case 1.	1 $(a_1 < 0)$	1
$(III)\ 1 < \mathcal{R}^S < 1 + k_b$	$0 < \mathcal{R}^R < 1$	$\mathcal{R}^{Tot} < 0$	Case 2.	0, 2 $(a_1 > 0, H(a/c) < 0)$	1
	$1 < \mathcal{R}^R < 1 + k_c$	$\mathcal{R}^{Tot} > 1$	Case 2.	0, 2 $(a_1 > 0, H(a/c) < 0)$	1
	$1 < \mathcal{R}^R < 1 + k_c$	$\mathcal{R}^{Tot} > 1$	Case 2.	1 $(a_1 < 0, H(a/c) < 0)$	1
	$\mathcal{R}^R > 1 + k_c$	$\mathcal{R}^{Tot} > 1$	Case 1.	1 $(a_1 < 0)$	1
$(IV)\ \mathcal{R}^S > 1 + k_b$	$0 < \mathcal{R}^R < 1$	$\mathcal{R}^{Tot} < 0$	Case 3.	0, 2 $(a_1 > 0, H(a/c) < 0)$	1
	$1 < \mathcal{R}^R < 1 + k_c$	$\mathcal{R}^{Tot} > 1$	Case 3.	0, 2 $(a_1 > 0, H(a/c) < 0)$	1
	$1 < \mathcal{R}^R < 1 + k_c$	$\mathcal{R}^{Tot} < 1$	Case 1.	1 $(a_1 < 0)$	1
	$\mathcal{R}^R > 1 + k_c$	$\mathcal{R}^{Tot} < 1$	Case 2.	1 $(a_1 < 0, H(a/c) < 0)$	1
	$\mathcal{R}^R > 1 + k_c$	$\mathcal{R}^{Tot} < 1$	Case 2.	0, 2 $(a_1 > 0, H(a/c) < 0)$	1

Figure 3 shows the sketch graphs of both linear (20) and quadratic (22) equations for Case 2 and $a_1 > 0$. Both TB_S^1 and TB_S^2 are positive, with $TB_S^1 < a/c < TB_S^2$. However, since $H(a/c) < 0$, one has $TB_R^1 > 0$ and $TB_R^2 < 0$. Hence, for Case 2 and $a_1 > 0$, the system (3) has a unique positive endemic equilibrium.

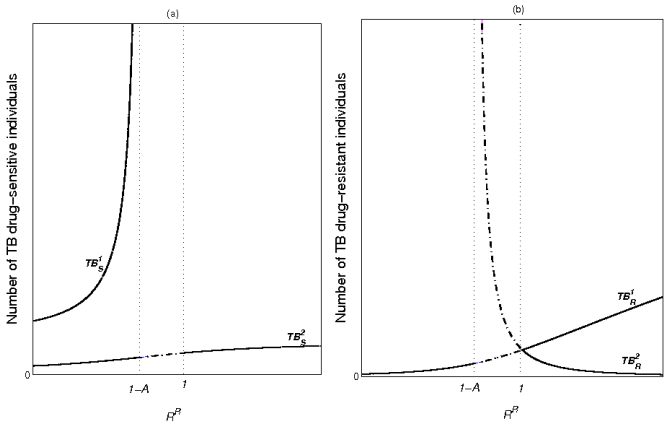

FIGURE 4. Number of populations for proportion of (a) TB drug-sensitive individuals (TB_S) according to the equation (22) and (b) TB drug-resistant individuals (TB_R) according to the equation (20) for the outcome (II) of Table 3. When $1-A < R^S < 1$, $R^R < 1-A$, $R^{Tot} > 1$ and $a_1 > 0$: (a) two positive real roots for TB_S; (b) one positive solution for TB_R (solid line). When $1-A < R^S < 1$, $1-A < R^R < 1$, $R^{Tot} > 1$ and $a_1 < 0$: (a) one positive real root for TB_S; (b) two positive solution for TB_R (dash line). When $1-A < R^S < 1$, $R^R > 1$, $R^{Tot} < 0$ and $a_1 < 0$: (a) one positive real root for TB_S; (b) two positive solution for TB_R (solid line).

Figure 4, corroborates the outcome (II) of Table 3. The value of β_S is fixed, such that $1-A < R^S < 1$, while varying the range for R^R. (a) contains the sketch for the positive real roots (TB_S) of the equation (22); in (b) there is the sketch the positive solution (TB_R) of the equation (20). Independently of sign of a_1, $H(a/c) < 0$; the system (3) always has a unique positive endemic equilibrium in both Case 1 or Case 2.

Thus, by the same logic as outlined in the outcome (II) of Table 3, it follows that when $a_1 > 0$ the quadratic equation in (22) has two positive real roots, $TB_S^1 > 0$ and $TB_S^2 > 0$, which correspond to a unique positive solution, $TB_R^1 > 0$, in the linear equation (20), since $H(TB_S = a/c) < 0$. As a consequence, for $a_1 > 0$, the system (3) has always a unique positive endemic equilibrium.

Finally, the absence of multiple endemic equilibria then suggests that both the disease-free equilibrium and the endemic equilibrium are globally asymptotically stable. Hence, the following conjecture is then suggested.

Conjecture 1. *The system (3) has a disease-free globally asymptotically stable equilibrium when*

$$R^S < 1 - \frac{\alpha_3}{\alpha_1\alpha_2}, \quad R^R < 1 - \frac{\alpha_3}{\alpha_1\alpha_2} \quad \textit{and} \quad R^{Tot} = \frac{\alpha_3}{\alpha_1\alpha_2(1-R^S)(1-R^R)} < 1$$

and has a unique globally asymptotically stable endemic equilibrium otherwise.

4. **Numerical investigations.** In this section we illustrate some of the theoretical results obtained in this paper. We examine the model by integrating the system (3) by the fourth order Runge-Kutta method, and some results of the simulations will be displayed graphically.

TABLE 4. Baseline values for the model 3

Parameter	Value
β_S	variable $(years^{-1})$
β_R	variable $(years^{-1})$
μ	0.0154 $(years^{-1})$
α	0.33 $(years^{-1})$
λ	0.025 $(years^{-1})$
ξ	1 $(years^{-1})$
σ	1/2 $(years^{-1})$
p	0.05
q	0.40
k_S	0.87
k_R	0.53

The baseline parameters values are taken as follows. The inflow of at-risk susceptible adults is chosen to be $0.0143 \leq \mu \leq 0.0154$ per year [46], the TB-induced death $0.22 \leq \alpha \leq 0.39$, [8], [13], and the endogenous reactivation rate (slow progression) $0.0005 \leq \lambda \leq 0.05$, [6], [13]. Drug-resistant strains gain an advantage over drug-sensitive strains because treatments are less effective against drug-resistant strains. The effective treatment rate of drug-sensitive cases is lower than the effective treatment rate of drug-sensitive cases. Thus, we take $\xi = 1.0$, $\sigma = 0.5$; $k_S = 87\%$, $k_R = 53\%$, [45], and $q = 40\%$, [19]. However, due to lack of data, some parameters are assumed within realistic ranges (for illustrative purpose only) based on current understanding of the qualitative and the essential biological and epidemiological features of TB. Unless otherwise stated, the baseline parameters are summarized in Table 4.

At this point, it is imperative to mention that there are several parameters that could be considered while studying the existence of the positive endemic equilibria. However, we are only interested in the combined effects of some arrangements involving the effective reproductive numbers (R^S, R^R and R^{Tot}), which represent the key factors for our analysis. This is the reason for which we explore only the variation of both transmission coefficients as stated in the model formulation, $\beta_R = \omega\beta_S$, $\omega > 0$. We assume that both transmission coefficients, β_S and β_R, vary because they strongly influence the reproductive number. As the parameter ω increases, three possibilities arise: (1) transmissibility is smaller for the resistant strain, i.e., $R^S > R^R$; (2) for both sensitive and resistant strains transmissibilities are the same, i.e., $R^S = R^R$; (3) the resistant strain has a larger transmissibility, i.e., $R^S < R^R$.

Thus, the following outcomes are possible. Sensitive strains can persist in the long run if $R^S > 1 - A$ and $R^S > R^R$. As long as TB persists, there will be some drug resistance, because resistance arises by mutation at some constant frequency and will be transmitted at least occasionally. However, if $R^R << 1 - A$, resistant cases will always be relatively few. The greater danger arises when $R^R > 1-A$ when the resistant cases persists. In the worst scenario, $R^R >> 1-A$ and $R^R >> R^S$, and resistant cases through cross immunity outcompete sensitive cases and completely replace them. These are, however, the eventual outcomes, which will take decades to reach. Furthermore, to make a more careful assessment of the control impact, we recall that these baseline conditions and our criteria for containment may be insufficient to prevent outbreaks. If the incidence of *MDR-TB* is likely to decline, we need to know how long it will take to achieve a significant reduction, by analysing the endemic equilibria of system (3).

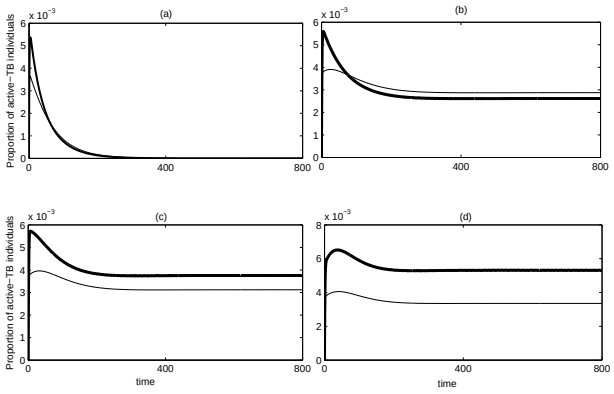

FIGURE 5. Profile of populations for proportion of drug-sensitive (TB_S, thin line) and drug-resistant (TB_R, thick line) of infectious individuals according to outcome (III) of the Table 3. (a) The disease-free equilibrium is stable when $R^S < 1$, $R^R < 1$ and $R^{Tot} < 1$ ($R^S > R^R$). The endemic equilibrium is stable for (b) $1 < R^S < 1+k_b$, $R^R < 1$ and $R^{Tot} < 0$ ($R^S > R^R$); (c) $1 < R^S < 1+k_b$, $1 < R^R < 1+k_c$ and $R^{Tot} < 1$ ($R^S < R^R$); (d) $1 < R^S < 1+k_b$, $R^R > 1+k_c$ and $R^{Tot} < 1$ ($R^S < R^R$). All other parameter values are listed in Table 4.

Figure 5 shows the the populations profiles for the proportion of active-TB individuals according to case (III) of the Table-3. The model undergoes competitive pressure, and has a co-existence equilibrium whenever the eradications conditions given by Lemma 3.1 do not hold. In (a) it should be noted that for some values of β_S and β_R, the treatment rate and the relative treatment efficacy are high enough to ensure the eradication of the disease, i.e., $R^S < 1-A$, $R^R < 1-A$ and $R^{Tot} < 1$. However, increasing the value of both parameters β_S and ω, the treatment rate and relative treatment efficacy will not prevent eradication; both drug-sensitive and drug-resistant strains of tuberculosis emerge; there is a reduction in the proportion of drug-sensitive individuals while the proportion of drug-resistant individuals rises. Furthermore, although the strain with the higher reproduction number dominates the other, the two strains always co-exist (i.e., the strain with the highest reproduction number does not drive out the other strain to extinction) as depicted in Figure 5 (b), (c) and (d). In (b) the drug-resistant tuberculosis is less fit than the drug-sensitive tuberculosis, i.e., $R^S > R^R$; in the presence of treatment, an eventual equilibrium outcome is the control of the drug-resistant tuberculosis. However, certain combinations of the treatment rate and the treatment efficacy by differently affecting the drug-sensitive and drug-resistant strains will ensure that drug resistance gains the competitive advantage (more fit), i.e., that $R^S < R^R$ (see (c) and (d)). Outcome (III) in Table 3 occurs as the parameter β_R increases, switching from Case 2 to Case 1. In other words, as the parameter β_R increases, the dynamics of trajectories of system (3) changes from low $TB_R > 0$ when $0 < TB_S < a/c$ to high $TB_R > 0$ when $TB_S > 0$.

The dynamics of system (3) for the outcomes (I), (II) and (III) of Table 3 undergoes the same pressure of the outcome, switching from Case 2 to Case 1. It follows that when $R^R < 1 + k_c$, $0 < TB_S < a/c$, while $TB_S > a/c$ whenever $R^R > 1 + k_c$.

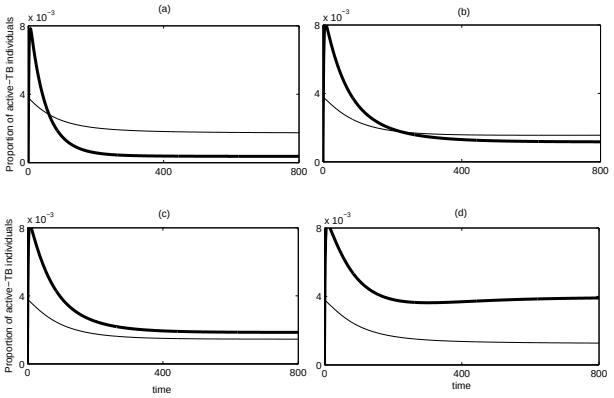

FIGURE 6. Profile of populations for proportion of drug-sensitive (TB_S, thin line) and drug-resistant (TB_R, thick line) of infectious individuals according to outcome (IV) of the Table-3. The endemic equilibrium is stable for (a) $R^S > 1 + K_b$, $0 < R^R < 1$ and $R^{Tot} < 0$ ($R^S > R^R$). (b) $R^S > 1 + K_b$, $1 < R^R < 1 + k_c$ and $R^{Tot} > 1$ ($R^S > R^R$). (c) $R^S > 1 + K_b$, $1 < R^R < 1 + k_c$ and $R^{Tot} < 1$ ($R^S < R^R$). (d) $R^S > 1 + K_b$, $R^R > 1 + k_c$ and $R^{Tot} < 1$ ($R^S < R^R$). All other parameter values are listed in Table 4.

In contrast, outcome (IV) undergoes a different pressure, switching from Case 3 to Case 2, but going through Case 1. Thus, $TB_S > a/c$ when $R^R < 1 + k_c$, and $0 < TB_S < a/c$ whenever $R^R > 1 + k_c$.

Figure 6 depicts an example of the populations profiles for the proportion of active-TB individuals according to outcome (IV) of the Table 3. Similarly as for Figure 5 when the parameter β_R increases, the persistence of both drug-sensitive and drug-resistant tuberculosis (i.e., coexistence) occurs, the dynamics of trajectories of system (3) changes from low $TB_R > 0$ when $TB_S > a/c$ (Case 1 and Case 3) to higher $TB_R > 0$ when $0 < TB_S < a/c$ (Case 2). The drug resistance emerging during treatment significantly decreases the incidence of drug sensitive cases for large value of both β_S and β_R, i.e, $R^S > 1 + k_b$ and $R^R > 1 + k_c$.

For the model with treatment, the above figures also show that TB can be eliminated from the community if the associated thresholds R^S, R^R and R^{tot} can be brought to a values less than $R_0 = 1$, i.e. the classical epidemiological requirement of $R_0 < 1$ is no longer sufficient, although necessary, to effectively control the spread of TB in a community.

5. **Conclusion.** Our analysis provides new insights for the interpretation of epidemiological estimates of fitness of *MDR-TB* strains. Our results imply that the potential for the spreading of the drug-resistant strain cannot be evaluated simply by measuring its relative fitness value, but should be evaluated within the context of several others factors, including the treatment, healing rates, treatment efficacy and relative fitness. Further, in order to predict the emergence of drug-resistant strains and hence to establish control strategies, it is necessary to understand the complex nonlinear transmission dynamics of both the drug-sensitive and the drug-resistant strains. Our main qualitative results allow to establish threshold conditions for

possible scenarios: elimination of sensitive and resistant strains and coexistence of both.

Evolution to the coexistence state is the result of inadequate treatment. When treatment is not able to eliminate the drug-sensitive strains, it is even possible that drug-resistant strains displace the drug-sensitive, as a result of the competitive advantage, with larger fitness. The drug-sensitive strains are reduced below a threshold where they are unable to compete. Paradoxically, as in [4], we have also found that even the drug-resistant strains that are considerably less fit than the drug-sensitive strains can lead to a high *MDR* incidence. Drug-resistant pathogens gain an advantage over drug-sensitive pathogens because treatment is less effective against drug-resistant strains, and this selective advantage is modeled by assuming that the effective treatment rate of drug-resistant cases is lower than the effective treatment rate of drug-sensitive cases (the degree of difference in the efficacy of treatment is specified by the parameter k, the relative treatment efficacy, where k_S stands for drug-sensitive, and k_R for drug-resistant cases. The disease eradication requirements (see Table 2) depend on the value of the probability of drug resistance emerging during treatment (q). This result implies that if the effective treatment rate (ξ) and the relative treatment efficacy (K_S and K_R) are high enough to ensure the eradication requirements, extremely high rates of emergence of acquired drug resistance will not prevent eradication. However, if treatment rates are below the critical eradications, a high rate of emergence of drug-sensitive results in a higher prevalence of drug resistance.

Finally, we remark that our model has several simplifying assumptions. The principal one is that it does not consider certain features of the TB infection, in particular the complexities of the immune system response against TB. In this sense, the model is not so specific for TB, and could be applied to any pathogen that presents resistance to drugs. In spite of that, the results are congruent with the ones obtained from the epidemiological point of view. The more remarkable result is that less-fit drug-resistant can emerge even under treatments that successfully reduce sensitive strains.

Appendix. In this Appendix we shall prove, by the use of M-matrices, that the disease-free equilibrium solution for system (3) is locally asymptotically stable for $R^S < 1 - \frac{\alpha_3}{\alpha_1\alpha_2}$, $R^R < 1 - \frac{\alpha_3}{\alpha_1\alpha_2}$ and $R^{Tot} = \frac{\alpha_3}{\alpha_1\alpha_2(1-R^S)(1-R^R)} < 1$, where $\frac{\alpha_3}{\alpha_1\alpha_2} < 1$.

The stability properties of our matrix $A_{\mathbf{0}}$ (5) are determined by using the well-known results on M-matrices. Our references on this topic are given by [2], [21], [36].

Definition. We say that the $n \times n$ matrix $A = [a_{ij}]$ is a non-singular M-matrix if $a_{ij} \leq 0$, $i \neq j$, and there exists a matrix $B \geq 0$ and a real number $s > 0$ such that $A = s\, I - B$ and $s > \rho(B)$, the latter being the spectral radius of B.

The following equivalences are well-known.

Proposition A.1: *A is a non-singular M-matrix if and only if the real part of each of its eigenvalues is greater than zero.*

Proposition A.2: *A is a non-singular M-matrix if and only if all its diagonal entries are positive, and there exists a positive diagonal matrix D, such that AD is strictly diagonal dominant, that is,*

$$a_{ij}\, d_i > \Sigma\, |a_{ij}|\, d_j\,, \qquad\qquad i = 1, ..., n.$$

Looking at our matrix $A_{\mathbf{0}}$ (5) we observe that its diagonal entries are negative. We consider the matrix $-A_{\mathbf{0}}$, so its diagonal elements are positive. According to Proposition A.2, $-A_{\mathbf{0}}$ is a non-singular M-matrix if and only if there exist numbers d_1, d_2, d_3 and d_4 larger than zero such that the following inequalities are satisfied

$$\begin{array}{rcl} (\mu+\lambda)\ d_1 & > & [\beta_S+(1-q)\xi]\ d_2+\sigma k_S\, d_4 \\ (\mu+\alpha+\xi)\ d_2 & > & \lambda\, d_1+p\lambda d_3 \\ (\mu+\lambda)\ d_3 & > & [\beta_R+\sigma k_R]\ d_4 \\ (\mu+\alpha+\sigma\,(k_S+k_R))\ d_4 & > & q\xi d_2+(1-p)\lambda\ d_3. \end{array} \tag{27}$$

Let

$$\left\{\begin{array}{rcl} d_4 & = & 1, \\ d_1 & = & \frac{[\beta_S+(1-q)\xi]d_2\ +\sigma k_S+\varepsilon}{(\mu+\lambda)}, \\ d_3 & = & \frac{\frac{\Pi}{\mu}\beta_R+\sigma k_R+\varepsilon}{(\mu+\lambda)}, \\ d_2 & = & \frac{p\lambda\beta_R+p\lambda\sigma k_R+\lambda\sigma k_S+[\lambda+p\lambda+(\mu+\lambda)]\varepsilon}{(\mu+\alpha+\xi)(\mu+\lambda)-[\lambda\beta_S+\lambda(1-q)\xi]}, \end{array}\right. \tag{28}$$

where $\varepsilon>0$.

Obviously, the first three inequalities given by (27) hold and, to ensure $d_2>0$, we require

$$R^S \ < \ 1-\tfrac{(\mu+\lambda)pq\xi}{(1-p)\alpha_1}\ . \tag{29}$$

Substituting the equations (28) into the last equation of system (27) we have

$$q\xi d_2+(1-p)\lambda\ d_3 \ = \ \tfrac{(\mu+\lambda)q\xi[\,p\lambda\beta_R+p\lambda\sigma k_R+\lambda\sigma k_S]+(1-p)[\lambda\beta_R+\sigma k_R]k_2+\varepsilon\, k_1}{k_2(\mu+\lambda)}\ ,$$

where

$$\begin{array}{rcl} k_1 & = & (1-p)\lambda\alpha_1\left(1-R^S\right)+q\xi\,(\mu+\lambda)\,(2\lambda+\mu)\,, \\ k_2 & = & (\mu+\alpha+\xi)\,(\mu+\lambda)-[\lambda\beta_S+\lambda(1-q)\xi]\,. \end{array} \tag{30}$$

When the equation (29) holds, that is, if $R^S<1$, then we have $k_1>0$. Therefore, the last inequality of the system (27) yields

$$\varepsilon<\frac{1}{k_1}a_4, \tag{31}$$

and, to ensure $\varepsilon>0$, we require $a_4>0$.

Note that a_4, defined by (7), is positive for (a) $R^R<1$, $R^S<1$ and $R^{Tot}<1$ or (b) $R^R>1$, $R^S>1$ and $R^{Tot}<1$. Since the latter condition does not satisfy (29), $a_4>0$ if only if $R^R<1$, $R^S<1-\frac{(\mu+\lambda)pq\xi}{(1-p)\alpha_1}$ and $R^{Tot}<1$.

Furthermore, letting $R^S=0$, then $R^{Tot}<1$ for $0<R^R<1-\frac{\alpha_3}{\alpha_1\alpha_2}$. Similarly, taking $R^R=0$, then $R^{Tot}<1$ for

$$R^S \ < \ 1-\tfrac{\alpha_3}{\alpha_1\alpha_2}\ , \tag{32}$$

where $\frac{\alpha_3}{\alpha_1\alpha_2}<1$.

From equations (29) and (32), it is straightforward to verify that

$$\tfrac{(\mu+\lambda)pq\xi}{(1-p)\alpha_1} \ < \ \tfrac{\alpha_3}{\alpha_1\alpha_2}\ .$$

Therefore, we can take $0<\varepsilon<\frac{1}{k_1}a_4$ so that the last inequality of the system (27) is satisfied, and the system (28) has positive solution when $R^S<1-\frac{\alpha_3}{\alpha_1\alpha_2}$, $R^R<1-\frac{\alpha_3}{\alpha_1\alpha_2}$, and $R^{Tot}<1$.

This implies that $-A_{\mathbf{0}}$ is a non-singular M-matrix for $R^S < 1 - \frac{\alpha_3}{\alpha_1\alpha_2}$, $R^R < 1 - \frac{\alpha_3}{\alpha_1\alpha_2}$ and $R^{Tot} = \frac{\alpha_3}{\alpha_1\alpha_2(1-R^S)(1-R^R)} < 1$. From Proposition A.1 it follows that the eigenvalues of the Jacobian matrix (5) of system (3) evaluated at the DFE have negative real part.

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