MODELING MAJOR FACTORS THAT CONTROL TUBERCULOSIS (TB) SPREAD IN CHINA*

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Abstract. This article introduces a novel model that studies the major factors jeopardizing the TB control programme in China. A previously developed two strain TB model is augmented with a class of individuals not registered under the TB control programme. The paper investigates the basic reproduction number and proves the global stability of the disease free equilibrium. The presence of three endemic equilibria is established in the model. With the help of numerical simulations a comparative study has been performed to test the validity of the model presented here to the real data available from the Ministry of Health of the People's Republic of China. Sensitivity and elasticity analysis gives the key parameters that would govern the successful tuberculosis control in China.

Keywords: Tuberculosis model in China, disease-free equilibrium, global stability, basic reproduction number

1. Introduction

Tuberculosis or TB (short for tubercles bacillus) is a common and, if left untreated, often deadly infectious disease in humans. This disease is caused by various strains of mycobacteria. The strain, responsible for most cases of the disease in humans, is Mycobacterium Tuberculosis [1]. TB is mainly a pulmonary disease but can also infect other parts of the human body. It is an aerosol carrier disease which spreads when people cough, sneeze or spit. It is mainly asymptomatic in humans, but a certain percentage of latent TB patients progress towards active TB. Individuals with active TB are infectious.

Nearly a third of the world population is affected by this disease [2]. The 13th annual report published by World Health Organization (WHO) estimated about 9.27 million cases of TB in 2007, 55% [3] of which are in Asia. The top two leading countries in the number of TB cases are India (2.0 million) and China (1.3 million) [3].

In 1990s WHO established a new wing of the Stop TB Strategy, called DOTS (directly observed treatment, short course) to monitor the spread of Tuberculosis in the world.

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The primary components of DOTS include government commitment in TB control, diagnosis based on sputum-smear microscopy tests done on patients who actively report TB symptoms, direct observation short-course chemotherapy treatments, a definite supply of drugs, and standardized reporting and recording of cases and treatment outcomes [4]. Many countries are now ready to accept DOTS to control the spread of TB. Short-course chemotherapy is the most effective treatment strategy available at present. According to a study performed in [5] the potential effects of DOTS in developing countries are much higher, compared to the results attained in the industrialized countries where drugs became available in 1940's. The success of chemotherapy in controlling TB lies in decreasing the number of deaths due to TB [6]. In spite of all the control strategies, appearance of drug resistant strains is of significant concern due to treatment failure or long exposure to the treatment[7]. WHO has undertaken a number of steps to stop the conversion of wild strains into drug-resistant strains. Measures include reforming the strategies undertaken by DOTS in TB control programmes[8]. Geographical distribution of multi-drug resistant (MDR) strains is higher in Russia, Israel, Ecuador and some provinces of China [9].

Tuberculosis has always been a significant problem in China. China ranks second in the number of TB cases in the world. Detection rate increased very slowly in 1990s. At the same time a high conversion rate to MDR was observed. The outbreak of severe acute respiratory syndrome (SARS) in 2003, exposed China's malfunctioning health care system. Several reforms have been applied following the 2003 SARS outbreak. In 2004 and 2005, country's 64% and 80% respectively of the tuberculosis cases have been diagnosed and treated under the Tuberculosis control programmes [21]. A new five-year initiative program was announced on 1 April 2009 which primarily aims to use innovative technologies to improve the detection and treatment of tuberculosis (TB) in China. Apart from all the programmes undertaken by the government there are still inherent problems in the country which are yet to be resolved. This includes the low case detection rate of TB for a group of individuals who are not registered in the TB control programme [10]. Poverty plays a big role in governing this fact. Rural migrants working in urban areas lack proper conditions to have medical insurance and they often fail to visit the health care institutions [11, 12, 13, 14]. They are termed as "floating" population [10]. There is no record or any data in the government register of the TB control programme of these population. They continue to move around with acute TB infections without receiving any proper treatment. It is also hard to distinguish them from the general mass, since they lack any kind of records. They develop an acute MDR due to lack of treatment. In this paper we identify this class as a distinct part of

our model. It is expected that proper control of TB cannot be achieved if this class is neglected, as it serves as a source of TB infection.

We structure our discussion in this paper in the following way. Section 2 discusses the TB model in China. In Section 3 basic reproduction number R_0 has been calculated along with identification of different equilibria and their stability. Section 4 - sensitivity analysis of some parameters have been performed. In section 5 we compare the model presented in this paper with the real data available from Ministry of Heath in China. In section 6 we extend our model to include other factors which affect TB in China. Figure 1 presents an overview of the incidence TB infected cases in China over the years. It is clear from the graph, that TB incidence declines in the period 2003-2007 after the outbreak of SARS. Effectiveness of government in controlling TB resulted in a steady decline of the incidence since then.

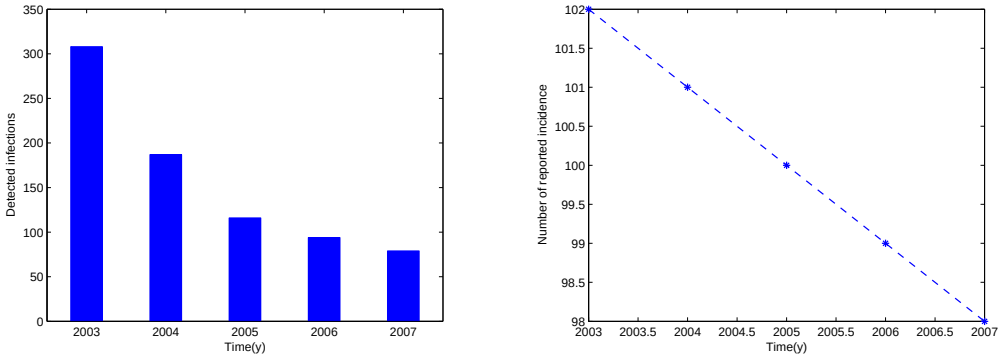

FIGURE 1. (Left)(Fig.a) Data showing the number of infected persons out of every 10^5 persons in the population from 2003-2007; (Right)(Fig.b) Graph of the number of reported incidence per year (out of every 10^5 persons in the population).

2. A Tuberculosis Model With Application To TB Spread In China

This paper discusses a Tuberculosis transmission model based on the conditions prevalent in China. As discussed in the Introduction, a huge percentage of the population in China does not go through the proper TB control programme offered by the Chinese government and other world organizations. This leads to a large pool of undetected infectious TB cases which are recognized as unregistered TB cases. In our paper we consider both registered and unregistered TB cases; prioritizing the unregistered ones, which jeopardize the effectiveness of TB control measures in China and other countries where this problem exists.

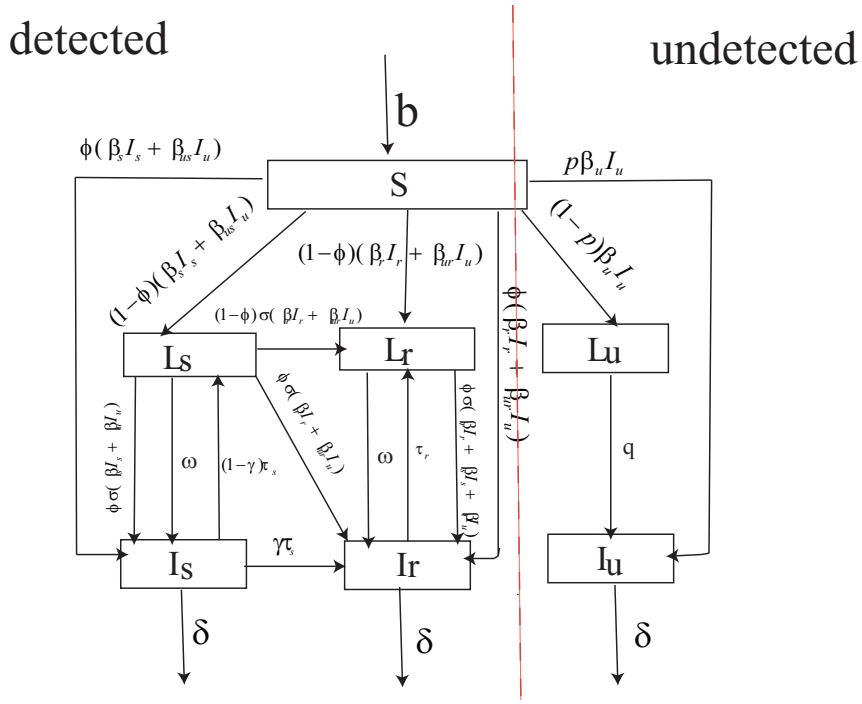

FIGURE 2. TB model in China. The dotted line separates the detected compartment from the undetected compartment.

We divide the TB transmission framework in two compartments named "Detected" and "Undetected". The detected compartment represents the TB cases which are registered under TB Control programmes and receive proper treatment. We take advantage of the model proposed in [9] to model this compartment. We follow their procedure and discuss the effect of both sensitive and resistant strains in the model. Population size in the absence of TB has been assumed to be asymptotically constant. Five major classes comprise the host population in the detected compartment – Susceptible (S), who have never been exposed to any strain of the Mycobacterium tuberculosis and hence they do not have any antibodies against the bacteria. The susceptible are infected at a rate proportional to the existent cases of infectious TB individuals both from the compartment where they are detected under TB control programmes and also from the undetected compartment. It is not possible to distinguish an infectious TB individual in the undetected compartment from the host population. Thus, we include infection by infectious individuals in the undetected compartment; however, the newly infected

individuals may be detected as infected, and enter the infected classes in the detected compartment. A person may be identified to have latent or infectious TB, under suitable tests when the bacteria invades the host cells. A part of the newly infected individuals move to the latent class upon infection and the other part immediately develops active TB. The latent class (L) represents the percentage of hosts who have been infected by the bacteria but have not developed active tuberculosis. Bacteria is present inside the host cell in an inactive state. Latent TB represents the state of TB which is not symptomatic or contagious. But latent individuals have the risk of developing active TB. A percentage of latent individuals develops active TB and moves to the infected (I) class due to endogenous reactivation (ω) or exogenous reinfection. Infected class consists of individuals with active TB who are capable of infecting others. Both the latent and infected class have been subdivided into two subclasses: drug resistant and drug sensitive class. The drug resistant class represents the form of TB which is resistant to most anti-TB drugs available. Some believe that they emerge from the "mismanagement of multidrug-resistant TB (MDR-TB)" [15]. Drug sensitive class consists of the cases which have not developed MDR-TB yet. It is assumed that a portion of latent individuals infected with the drug sensitive strain (L_s) may develop latent drug resistant TB (L_r) or may be superinfected by an infectious individual with a drug-resistant TB (I_r). A fraction (γ) of the class infected by the sensitive strain may develop active TB due to treatment failure of non-resistant strains.

The other compartment in our model named as "Undetected" compartment represents the percentage of individuals who are unregistered in the TB control programmes. As a first step we assume the infection in this class results from the interaction of individuals in this compartment only. All secondary cases caused by an infected individual registered under TB control programme are assumed to be monitored by the authorities and hence they do not fall into the unregistered compartment. In section 6 we propose an extension of baseline model that lifts that restriction and allows individuals infected by an infectious individual in the detected compartment to remain undetected. To build our baseline model we use a simple TB model proposed in [16] to design the TB framework in the undetected compartment. It comprises of three main groups; susceptible (S), latent (L_u) and infected (I_u) classes. A fraction (p) of the susceptible individuals infected by TB develop active TB whereas the rest have latent TB. TB individuals in the latent stage develop active TB by endogenous reactivation at a constant rate (q). There is no treatment since they are not detected. We do not separate them into drug sensitive and drug resistant strain since they are not verified by any TB control agency and data for such a distinction do not exist. One part of them may develop drug sensitive strain

and the other part drug resistant. The infected with sensitive or drug-resistant TB enter the respective classes in the detected compartment.

The detected-undetected compartmental model describing TB in China is presented as the system of differential equations as follows.

$$\begin{cases} \frac{dS}{dt} = b - [\beta_s I_s + \beta_r I_r + (\beta_{us} + \beta_{ur} + \beta_u) I_u + \mu] S, \\ \frac{dL_s}{dt} = (1-\phi)(\beta_s I_s + \beta_{us} I_u) S + (1-\gamma)\tau_s I_s \\ \qquad -[\omega + \sigma\phi(\beta_s I_s + \beta_{us} I_u) + \sigma(\beta_r I_r + \beta_{ur} I_u) + \mu] L_s, \\ \frac{dL_r}{dt} = (1-\phi)(\beta_r I_r + \beta_{ur} I_u)(S + \sigma L_s) \\ \qquad -[\omega + \sigma\phi(\beta_s I_s + \beta_{us} I_u + \beta_r I_r + \beta_{ur} I_u) + \mu] L_r + \tau_r I_r, \\ \frac{dI_s}{dt} = \phi(\beta_s I_s + \beta_{us} I_u) S + [\omega + \phi\sigma(\beta_s I_s + \beta_{us} I_u)] L_s - (\tau_s + \mu + \delta) I_s, \\ \frac{dI_r}{dt} = \phi(\beta_r I_r + \beta_{ur} I_u)[S + \sigma(L_s + L_r)] + [\omega + \phi\sigma(\beta_s I_s + \beta_{us} I_u)] L_r \\ \qquad +\gamma\tau_s I_s - (\tau_r + \mu + \delta) I_r, \\ \frac{dL_u}{dt} = (1-p)\beta_u I_u S - (q + \mu) L_u, \\ \frac{dI_u}{dt} = p\beta_u I_u S + q L_u - (\delta + \mu) I_u. \end{cases} \tag{1}$$

The parameters have been defined and their approximate values have been presented in Table 1. Some of the parameter values were estimated using simulation results and the rest were obtained from the reference cited in the table.

Table 1 Two-strain model parameters

Symbol	Definition	Value	Cite
β_s, β_r	Detected transmission coefficient	0.01,0.008	Estimated
b, μ	birth/recruitment rate and natural death rate	0.2, $\frac{1}{65}$	[9]
ϕ	Rate of detected individuals that develop active TB	0.1	[9]
σ	Superinfection rate	0.25	[9]
δ	Death rate due to TB	0.01	[9]
ω	Rate of endogenous reactivation of latent TB	0.0002	[9]
τ_s, τ_r	Rate of treatment of active sensitive and resistant TB	2,1.5	[9]
γ	Sensitive TB treatment failure acquiring resistance	0.0003(or $\gamma = 0$)	[9]
$\beta_u, \beta_{us}, \beta_{ur}$	Undetected transmission coefficient	0.07,0.01,0.01	Estimated
p	Proportion of undetected individuals that develop active TB	0.2	Estimated
q	Rate of endogenous reactivation of undetected latent TB	0.0002	Estimated

3. Equilibria and their stability

In this section we investigate the equilibria and study their stability.

It is easy to observe from the model presented in Section 2 that $N = S+L_s+L_r+I_s+I_r+L_u+I_u \leq \frac{b}{\mu}$. We can normalize this factor and call $\hat{N} = \hat{S}+\hat{L_s}+\hat{L_r}+\hat{I_s}+\hat{I_r}+\hat{L_u}+\hat{I_u} \leq 1$ where $\hat{S} = \frac{\mu S}{b}, \hat{L_s} = \frac{\mu L_s}{b}, \hat{L_r} = \frac{\mu L_r}{b}, \hat{I_s} = \frac{\mu I_s}{b}, \hat{I_r} = \frac{\mu I_r}{b}, \hat{L_u} = \frac{\mu L_u}{b}, \hat{I_u} = \frac{\mu I_u}{b}$. We can replace the terms in the model presented in (1) and have the following set of equations.

$$\begin{cases} \frac{d\hat{S}}{dt} = b' - [\beta'_s\hat{I_s} + \beta'_r\hat{I_r} + (\beta'_{us} + \beta'_{ur} + \beta'_u)\hat{I_u} + \mu]\hat{S}, \\ \frac{d\hat{L_s}}{dt} = (1-\phi)(\beta'_s\hat{I_s} + \beta'_{us}\hat{I_u})\hat{S} + (1-\gamma)\tau_s\hat{I_s} \\ \qquad -[\omega + \sigma\phi(\beta'_s\hat{I_s} + \beta'_{us}\hat{I_u}) + \sigma(\beta'_r\hat{I_r} + \beta'_{ur}\hat{I_u}) + \mu]\hat{L_s}, \\ \frac{d\hat{L_r}}{dt} = (1-\phi)(\beta'_r\hat{I_r} + \beta'_{ur}\hat{I_u})(\hat{S} + \sigma\hat{L_s}) \\ \qquad -[\omega + \sigma\phi(\beta'_s\hat{I_s} + \beta'_{us}\hat{I_u} + \beta'_r\hat{I_r} + \beta'_{ur}\hat{I_u}) + \mu]\hat{L_r} + \tau_r\hat{I_r}, \\ \frac{d\hat{I_s}}{dt} = \phi(\beta'_s\hat{I_s} + \beta'_{us}\hat{I_u})\hat{S} + [\omega + \phi\sigma(\beta'_s\hat{I_s} + \beta'_{us}\hat{I_u})]\hat{L_s} - (\tau_s + \mu + \delta)\hat{I_s}, \\ \frac{d\hat{I_r}}{dt} = \phi(\beta'_r\hat{I_r} + \beta'_{ur}\hat{I_u})[\hat{S} + \sigma(\hat{L_s} + \hat{L_r})] + [\omega + \phi\sigma(\beta'_s\hat{I_s} + \beta'_{us}\hat{I_u})]\hat{L_r} \\ \qquad +\gamma\tau_s\hat{I_s} - (\tau_r + \mu + \delta)\hat{I_r}, \\ \frac{d\hat{L_u}}{dt} = (1-p)\beta'_u\hat{I_u}\hat{S} - (q+\mu)L_u, \\ \frac{d\hat{I_u}}{dt} = p\beta'_u\hat{I_u}\hat{S} + q\hat{L_u} - (\delta+\mu)\hat{I_u}. \end{cases}$$

where $b' = \mu, \beta'_s = \frac{b\beta_s}{\mu}, \beta'_r = \frac{b\beta_r}{\mu}, \beta'_u = \frac{b\beta_u}{\mu}, \beta'_{us} = \frac{b\beta_{us}}{\mu}, \beta'_{ur} = \frac{b\beta_{ur}}{\mu}$. Without loss of generality we can replace the prime terms and the hat functions and use the same set of equations as defined in (1) under section 2. As a result we may assume in our analysis that $b = \mu$ without loss of generality. So we can consider our solution in the set defined by

$$\mathbb{S} := \{(S, L_s, L_r, I_s, I_r, L_u, I_u) \in (\mathbb{R}^+)^7 : S + L_s + L_r + I_s + I_r + L_u + I_u \leq 1\}.$$

This is clearly a positively invariant set and the solutions with initial conditions in this set do not leave the set. We observe that system (1) has four steady states, more precisely, one disease free equilibrium $E_0 = (S^0, 0, 0, 0, 0, 0, 0)$, and three endemic equilibria

$$E_r = (S^r, 0, L^r_r, 0, I^r_r, 0, 0), \quad E_{rs} = (S^+, L^+_s, L^+_r, I^+_s, I^+_r, 0, 0)$$

and

$$E_{rsu} = (S^*, L^*_s, L^*_r, I^*_s, I^*_r, L^*_u, I^*_u).$$

First we calculate the basic reproduction number and analyze the stability of disease free equilibrium.

3.1. **Disease free equilibrium.** The disease free equilibrium is given by

$$E_0 = (S^0, 0, 0, 0, 0, 0, 0).$$

Since we restrict our solution to the set $\mathbb{S}$ without loss of gentility we can assume our $S^0 = 1$. The basic reproduction number R_0, in general, is defined to be the expected number of secondary cases produced, in a completely susceptible population, by a typical infected individual during its entire period of infection. Here,we follow the recipe of [17] to calculate the basic reproduction number which may not give the expected number of secondary cases. O. Diekmann et al in [18] have shown that R_0 is the spectral radius of the next generation matrix. The basic reproduction number for the model presented in system (1) is given by the following expression.

$$R_0 = \max\{R_{0s}, R_{0r}, R_{0u}\},$$

where

$$\begin{aligned} R_{0s} &= \frac{\beta_s(\omega + \phi\mu)}{(\mu+\omega)(\mu+\delta+\tau_s) - (1-\gamma)\tau_s\omega}, \\ R_{0r} &= \frac{\beta_r(\omega + \phi\mu)}{(\mu+\omega)(\mu+\delta+\tau_r) - \tau_r\omega}, \\ R_{0u} &= \frac{\beta_u(q + \mu p)}{(\mu+\delta)(\mu+q)}. \end{aligned} \tag{2}$$

Detail calculations have been provided in the Appendix A1. Following the recipe of [17] we have shown that disease free equilibrium is locally asymptotically stable, i.e. the disease become extinct when $R_0 < 1$. The existence of endemic equilibria is possible only when $R_0 > 1$. This leads us to the following theorem.

Theorem 3.1. *The disease free equilibrium (E_0) is locally stable for $R_0 < 1$ (i.e. all $R_{0s} < 1$, $R_{or} < 1$ and $R_{0u} < 1$) and unstable for $R_0 > 1$ (at least one or more of $R_{0s} > 1$, $R_{0r} > 1$ or $R_{0u} > 1$ is true).*

The proof of this theorem is provided in Appendix A2.

Now we proceed to prove the global stability of the disease free equilibrium.

Theorem 3.2. *If $R_0 < 1$ then the disease free equilibrium is globally asymptotically stable in the set $\mathbb{S}$.*

Proof. First we prove the global stability of the decoupled system represented by the following equations

$$\begin{aligned} \frac{dL_u}{dt} &= (1-p)\beta_u I_u S - (q+\mu)L_u, \\ \frac{dI_u}{dt} &= p\beta_u I_u S + qL_u - (\delta+\mu)I_u. \end{aligned} \tag{3}$$

We consider the following Lyapunov function.

$$\mathcal{L} = qL_u + (q+\mu)I_u.$$

Hence

$$\dot{\mathcal{L}}(t) = \beta_u I_u[(q(1-p) + p(q+\mu))S - (q+\mu)(\delta+\mu)].$$

Note that since $R_0 < 1$ we have $R_{0u} < 1$, and since we restrict our solution to the set $\mathbb{S}$ we have $S \leq 1$. Then

$$\begin{aligned} S \leq 1 \quad &\Rightarrow [q(1-p)\beta_u + p(q+\mu)\beta_u]S - (q+\mu)(\delta+\mu) \\ &\leq [(q+\mu p)\beta_u - (q+\mu)(\delta+\mu)] \\ &= (q+\mu)(\delta+\mu)[R_{0u} - 1], \end{aligned}$$

This proves

$$\dot{\mathcal{L}}(t) \leq I_u(q+\mu)(\delta+\mu)[R_{0u} - 1] \leq 0,$$

in the set $\mathbb{S}$. Also note that $\dot{\mathcal{L}} = 0$ if and only if $I_u = 0$. The largest invariant is $\{\dot{\mathcal{L}} = 0 | L_u = 0, I_u = 0\}$. By Lassale's Invariance principal system (3) is globally asymptotically stable.

The global stability of the system defined by (S, L_r, L_s, I_r, I_s) has been argued in [9] by the use of numerical results when $R_0 < 1$. We prove here this global stability for a special case.

Proof of global stability in a particular case

We assume here $\phi = 0, \gamma = 0, (1-p)q + \frac{p\beta_u(q+\mu p)}{\delta+\mu} < 1$. In this particular case we can show global stability of the disease free equilibrium without treating the compartments separately. We find a single Lyapunov function to prove this result.

For $\phi = 0, \gamma = 0, \frac{(1-p)q}{(q+\mu p)} + \frac{p\beta_u}{\delta+\mu} < 1$, then the system reduces to the following form.

$$\begin{cases} \dfrac{dS}{dt} = b - [\beta_s I_s + \beta_r I_r + (\beta_{us} + \beta_{ur} + \beta_u)I_u + \mu]S, \\ \dfrac{dL_s}{dt} = (\beta_s I_s + \beta_{us} I_u)S + \tau_s I_s - [\omega + \sigma(\beta_r I_r + \beta_{ur} I_u) + \mu]L_s, \\ \dfrac{dL_r}{dt} = (\beta_r I_r + \beta_{ur} I_u)(S + \sigma L_s) - (\omega + \mu)L_r + \tau_r I_r, \\ \dfrac{dI_s}{dt} = \omega L_s - (\tau_s + \mu + \delta)I_s, \\ \dfrac{dI_r}{dt} = \omega L_r - (\tau_r + \mu + \delta)I_r, \\ \dfrac{dL_u}{dt} = (1-p)\beta_u I_u S - (q+\mu)L_u, \\ \dfrac{dI_u}{dt} = p\beta_u I_u S + qL_u - (\delta+\mu)I_u. \end{cases} \tag{4}$$

We choose k such that $qk < (\delta+\mu)(q+\mu p) - p\beta_u(q+\mu p) - (\delta+\mu)(1-p)q$. Note that our last assumption is the case considered says that k may be chosen positive. We have:

$$\frac{qk + (\delta+\mu)(1-p)q + p\beta_u(q+\mu p)}{(\delta+\mu)(q+\mu p)} < 1.$$

We consider the following Lyapunov function,

$$\mathcal{L} = \frac{k\beta_u}{\omega(\beta_{us}+\beta_{ur})}[\omega(L_s+L_r) + (\mu+\omega)(I_s+I_r)] + (\delta+\mu)L_u + \frac{\beta_u(q+\mu p)}{q}I_u.$$

Clearly $\mathcal{L}$ is positive. Hence

$$\begin{aligned}\dot{\mathcal{L}} = \; & \frac{k\beta_u}{\omega(\beta_{us}+\beta_{ur})}[((\tau_s+\mu+\delta)(\mu+\omega) - \omega\tau_s)I_s(R_{0s}S-1) \\ & +((\tau_r+\mu+\delta)(\mu+\omega) - \omega\tau_r)I_r(R_{0r}S-1)] \\ & +I_u\frac{\beta_u}{q}[(qk + (\delta+\mu)(1-p)q + p\beta_u(q+\mu p))S \\ & -(q+\mu p)(\delta+\mu)] + L_u(q+\mu)(\delta+\mu)(R_{0u}-1)\end{aligned}$$

Using the value for k we can have the following form of $\dot{\mathcal{L}}$,

$$\begin{aligned}\dot{\mathcal{L}} = \; & \frac{k\beta_u}{\omega(\beta_{us}+\beta_{ur})}[((\tau_s+\mu+\delta)(\mu+\omega) - \omega\tau_s)I_s(R_{0s}S-1) \\ & +((\tau_r+\mu+\delta)(\mu+\omega) - \omega\tau_r)I_r(R_{0r}S-1) \\ & -\mu\omega(L_s+L_r)] + L_u(q+\mu)(\delta+\mu)[R_{0u}-1] \\ & +\tfrac{\beta_u}{q}I_u(q+\mu p)(\delta+\mu)[\frac{qk + (\delta+\mu)(1-p)q + p\beta_u(q+\mu p)}{(\delta+\mu)(q+\mu p)}S - 1].\end{aligned}$$

Since

$$S \le 1, R_0 < 1 \Rightarrow R_{0s} < 1, R_{0r} < 1, R_{0u} < 1,$$

and from the way k was chosen, we can see that $\dot{\mathcal{L}} \le 0$. Also $\dot{\mathcal{L}} = 0$ if and only if $L_s, I_s, L_s, I_r, L_u, I_u$ are all zero. Note that the largest invariant set when $(L_s, I_s, L_r, I_r, L_u, I_u) = (0,0,0,0,0,0)$ is $(S^0, 0, 0, 0, 0, 0, 0)$.

Hence the set $\{x \mid \dot{\mathcal{L}} = 0\}$ is the singleton given by E_0. By Lassale's invariance principle global stability can be established in this case. □

Note: In $\mathbb{S}$ solutions cannot be unbounded.

From the above statement it is clear that $R_0 < 1$ implies the existence of disease free equilibrium only, at least in the case when the additional assumptions are statisfied. Now we discuss the situation when $R_0 > 1$. Since we know, $R_0 = \max(R_{0s}, R_{0r}, R_{0u})$, $R_0 > 1$ implies any one or more of R_{0r}, R_{0s}, R_{0u} is greater than one. In this case one can establish the existence of the endemic equilibria which we discuss in the following section.

3.2. **Endemic Equilibria. Case 1.** (Boundary Equilibria)

Investigating the existence of boundary equilibria we observed that this type of equilibria is attained in system (1) only when $I_u = 0, L_u = 0$. This simplifies the model to the structure presented in [9]. We are not going to repeat the work by the authors of [9]. We merely state the following theorems that give conditions for existence of equilibria in the case $I_u = 0$, $L_u = 0$. Detailed proof has been given in [9].

Theorem 3.3. *There exists a unique non-trivial equilibrium of the form* $E_r = (S^r, 0, L_r^r, 0, I_r^r, 0, 0)$ *in system (1), for* $R_{0r} > 1$.

Theorem 3.4. *The equilibrium* E_r *is stable for* $R_{0s}(E_r) < 1$ *and unstable for* $R_{0s}(E_r) > 1$, *where*

$$R_{0s}(E_r) = \frac{S^r\beta_s(\phi(\mu + \sigma\beta_r I_r^r) + \omega)}{(\mu + \sigma\beta_r I_r^r + \omega)(\mu + \delta + \tau_s) - \omega\tau_s(1-\gamma)}.$$

is the invasion reproduction number of the sensitive strain at the equilibrium of the resistant strain.

Theorem 3.5. *The existence of the region of boundary equilibrium where both the resistant and sensitive strains persists, i.e.* $E_{rs} = (S^+, L_s^+, L_r^+, I_s^+, I_r^+, 0, 0)$, *is given by the curve* $R_{0s}(E_r) > 1$.

Case 2. (Co-existence Equilibria)

Now we verify the condition for the existence of co-existence equilibrium represented as

$$E_{rsu} = (S^*, L_s^*, L_r^*, I_s^*, I_r^*, L_u^*, I_u^*).$$

In this paper we present analytical results for the case $\phi = 0$ and $p = 0$. We use numerical simulations to explain the existence in the general case when $\phi \neq 0$. We show in this text the existence of these equilibria in a specific region of the three dimensional (R_{0s}, R_{0r}, R_{0u}) space. We present the following theorem which explains the existence of E_{rsu}.

Theorem 3.6. *Assume* $R_{0u} > 1$. *In the region of the three-dimensional space* $\{R_{0s}, R_{0r}, R_{0u}\}$ *enclosed by the planes which satisfy the following conditions,*

$$(A1) \quad R_{0u} > R_{0r},$$
$$(A2) \quad b > \tfrac{\mu+\beta_s+\beta_r}{R_{0u}},$$
$$(A3) \quad \tfrac{\beta_u}{\beta_t R_{0u}} - \tfrac{1}{R_{0s}} > \tfrac{\beta_{ur} R_{0u}}{\sigma\beta_k}(\tfrac{1}{R_{0r}} - \tfrac{\beta_u}{\beta_t R_{0u}}),$$

where

$$\beta_t = \beta_{ur} + \beta_{us} + \beta_u, \qquad \beta_k = \beta_{us} + \beta_u$$

a co-existence equilibrium exists.

Proof. Detailed proof has been given in the Appendix A3. We provide a few simplifications of some terms here. If we call

$$A = \frac{\frac{\omega}{\tau_s+\mu+\delta}(\frac{S^*\beta_s\beta_u}{\beta_t} + (1-\gamma)\tau_s) + \frac{\omega\gamma\tau_s}{(\tau_s+\mu+\delta)(\tau_r+\mu+\delta)}(\frac{S^*\beta_s\beta_u}{\beta_t} + \tau_r) - (\mu+\omega)}{(\mu+\omega) - \frac{\omega}{\tau_r+\mu+\delta}(\frac{S^*\beta_r\beta_u}{\beta_t} + \tau_r)}.$$

Note that A as defined above can be expressed as

$$A = \frac{\frac{\omega\gamma\tau_s}{(\tau_s+\mu+\delta)(\tau_r+\mu+\delta)}(\frac{S^*\beta_s\beta_u}{\beta_t} + \tau_r) + \frac{\omega\beta_s}{\tau_s+\mu+\delta}(\frac{\beta_u}{\beta_t R_{0u}} - \frac{1}{R_{0s}})}{\frac{\omega\beta_r}{\tau_r+\mu+\delta}(\frac{1}{R_{0r}} - \frac{\beta_u}{\beta_t R_{0u}})}.$$

We prove that both the top and the bottom of this fraction are positive. The four surfaces in assumptions (A1)-(A3) enclose an area in the three dimensional space (R_{0s}, R_{0r}, R_{0u}) where there is possibility of existence of co-existence equilibria. Note that if a_1 denotes the following expression

$$a_1 = \sigma(\beta_r\beta_k\frac{\omega}{\beta_t(\tau_r+\mu+\delta)}[A + \frac{\gamma\tau_s}{\tau_s+\mu+\delta}]) - \frac{\beta_{ur}\beta_s}{\beta_t S^*}\frac{\omega}{\tau_s+\mu+\delta},$$

we show below that $a_1 > 0$. Consider

$$P = \sigma\beta_r\beta_k\frac{\omega}{\beta_t(\tau_r+\mu+\delta)}A - \frac{\beta_{ur}\beta_s}{\beta_t S^*}\frac{\omega}{\tau_s+\mu+\delta}.$$

P can be simplified as follows:

$$\begin{aligned} P &= \sigma\beta_r\beta_k\frac{\omega}{\beta_t(\tau_r+\mu+\delta)}A - \frac{\beta_{ur}\beta_s}{\beta_t S^*}\frac{\omega}{\tau_s+\mu+\delta} \\ &= \sigma\beta_r\beta_k\frac{\omega}{\beta_t}\left[\frac{A}{(\tau_r+\mu+\delta)} - \frac{\beta_{ur}\beta_s}{\sigma S^*}\frac{1}{\beta_r\beta_k(\tau_s+\mu+\delta)}\right]. \end{aligned}$$

We denote by H the term inside the bracket, i.e.

$$H = \frac{A}{(\tau_r+\mu+\delta)} - \frac{\beta_{ur}\beta_s}{\sigma S^*}\frac{1}{\beta_r\beta_k(\tau_s+\mu+\delta)}.$$

H can be rewritten in the following form

$$H = \frac{1}{(\tau_s+\mu+\delta)}\frac{[\frac{\gamma\tau_s}{(\tau_r+\mu+\delta)}(\frac{S^*\beta_s\beta_u}{\beta_t} + \tau_r) + \beta_s(\frac{\beta_u}{\beta_t R_{0u}} - \frac{1}{R_{0s}}) - \frac{\beta_{ur}\beta_s}{\sigma S^*}\frac{1}{\beta_r\beta_k}D]}{D},$$

where

$$D = \beta_r(\frac{1}{R_{0r}} - \frac{\beta_u}{\beta_t R_{0u}}).$$

From assumption (A3),

$$\beta_s(\frac{\beta_u}{\beta_t R_{0u}} - \frac{1}{R_{0s}}) - \frac{\beta_{ur}\beta_s}{\sigma S^*}\frac{1}{\beta_r\beta_k}D$$

is positive. Hence, H is positive. This in turn implies that P is positive and a_1 is positive. We derive a quadratic equation in terms of L_s as $a_1L_s^2 + a_2L_s + a_3 = 0$, where a_1 is the same as above. We already showed that a_1 is positive. We prove in the appendix that a_3 is negative. Therefore, L_s is the unique positive solution of the quadratic equation. □

Hence the co-existence equilibrium region is given by the region enclosed by the three planes mentioned above.

Note: We observe that the expression for S^* is given by $\frac{1}{R_{0u}}$. Since S^* belongs to $\mathbb{S}$, this is only possible when $R_{0u} > 1$. Otherwise the last two equations of system 1 will only result in a trivial solution for (L_u, I_u) and hence only boundary equilibrium or disease free equilibrium exists.

Figure 3 and Figure 4 show a simulated result for the existence of the coexistence equilibrium using randomly chosen parameters. $b = 0.75, \beta_r = 0.001, \beta_s = 0.10, \beta_{us} = 0.10, \beta_{ur} = 0.05, \beta_u = 0.05, \delta = 0.2, \mu = 0.01, \tau_s = 2.0, q = 0.01, \omega = 0.002, \phi = 0.10, \gamma = 0.003, \sigma = 0.25, \tau_r = 1.5$.

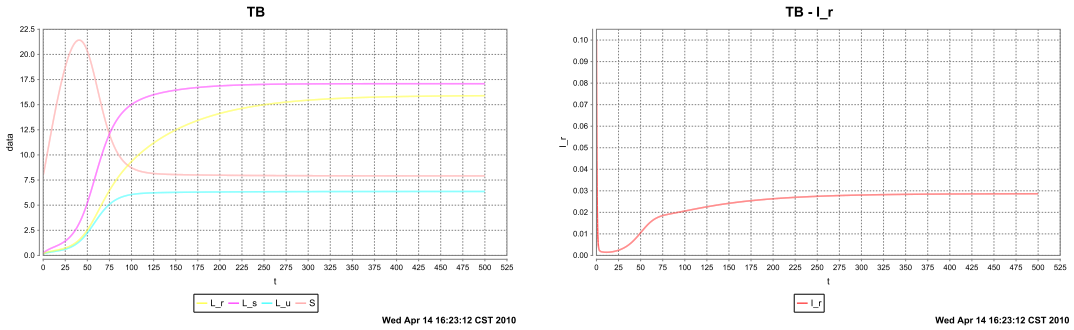

FIGURE 3. (Left) Shows co-existence of S^*, L_s^*, L_r^*, L_u^*; (Right) Existence of I_r.

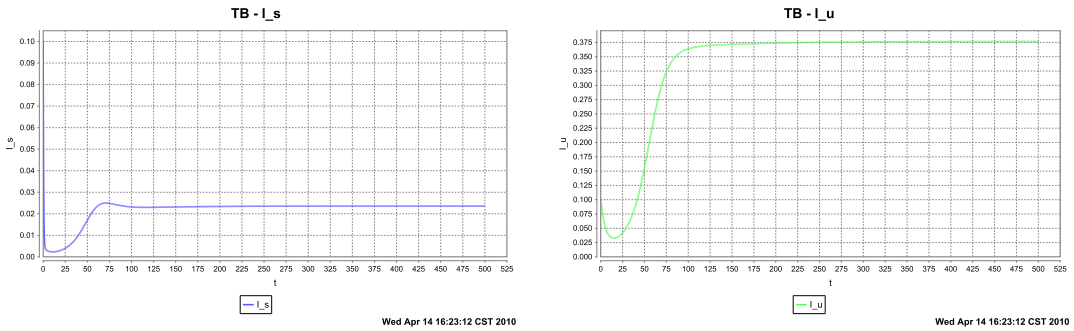

FIGURE 4. (Left) Existence of I_s; (Right) Existence of I_u.

4. SENSITIVITY ANALYSIS

A major role in governing the control of sensitive and resistant strains is played by τ_s, τ_r, which represent the treatment rates of the TB individuals infected with drug sensitive strains or drug resistant strains of the bacteria respectively. Over the years it has been observed that due to the failure in the treatment of TB cases, a large proportion

of TB infected individuals move to the drug-resistant class from the drug-sensitive class. In epidemiological terms it signifies that these individuals develop a MDR strains as a result of failure in TB treatment. This has a huge significance in China (see [10] for discussion). The fraction of latent individuals infected by the drug-sensitive strain that develop active TB, γ, also plays an important role in governing the number of individuals in the two infected classes which are detected by TB control programme. In Figure 5 we present a comparative study of the treatment of both drug resistant and the drug sensitive strains for different treatment rates. Figure 5 shows an increase in the proportion of individuals infected with MDR strains of virus; an increase, caused primarily by treatment failure. On the other hand, the proportion of individuals infected with drug sensitive strains decreases. Furthermore, Figure 5 also suggests that if the rate of treatment for the sensitive strain increases, there is a greater possibility of controlling the conversion rate of sensitive strains to drug resistant strains. This fact is supported by Figure 6, which suggests that a 10 time increase in the value of γ reduces the proportion of individuals with drug sensitive strain more than 20%. Data available from [10] give that the MDR rate among the relapse TB cases in China is 17.1% which is significantly higher compared to the new TB cases (calculated to be 7.6%). More recent surveys in China show that the MDR rate is 5.7% among new TB patients and 25.6% among previously treated cases [19]. The survey suggests that there is an annual emergence of 100,000 cases of MDR-TB in China only [19].

Figure 7 through Figure 9 explain the behavior of the reproduction number of the resistant, sensitive, and the undetected class with respect to different parameters. Our aim is to make the basic reproduction number R_0 less than one, so that the disease becomes extinct. Since the basic reproduction number is the maximum of the reproduction number of the three different classes (sensitive, resistant and undetected), we want all of them below one. We first observe the behavior of these three reproduction numbers separately and with respect to different parameters. The main factors governing TB epidemiology is the treatment rate and the transmission rate. The left graph in Figure 7 and Figure 8 illustrate the behavior of the drug resistant strain reproduction number and drug sensitive strain reproduction number, respectively. For a fixed treatment rate, the reproduction number increases sharply with an increase in the transmission rate. The rate is faster in the case of sensitive strain as compared to the resistant strain. As expected, the reproduction numbers can be controlled with an increase of the successful treatment rate as discussed in the above paragraph. The graphs on the right side of Figure 7 and Figure 8 discuss the behavior of the reproduction numbers in the respective classes with death rate due to TB and transmission rate. It is observed that in both the

classes with an increase in transmission rate the value of reproduction number increases. For a fixed death rate due to TB, the reproduction number increases almost linearly with the transmission coefficient. In Figure 9 we observe that either for a fixed natural death rate or for death rate due to TB, reproduction number increases at an exponential rate with transmission coefficient in this class. The increase is faster for lower values of death rate, which from epidemiological perspective can be explained with much lower social distancing within the population when the death rate is lower. From the above discussion we can conclude that decrease in the transmission rate may result in lowering the reproduction number below one, which may result in the extinction of the disease.

To understand how the reproduction number of the undetected class can be lowered,

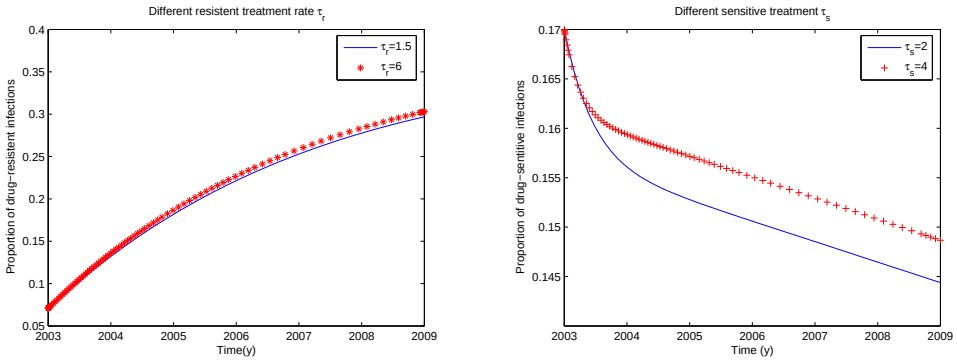

FIGURE 5. (Left) Proportion of drug-resistant infections over the time for different treatment rate τ_r; (Right) Proportion of drug-sensitive infections over the time for different treatment rate τ_s.

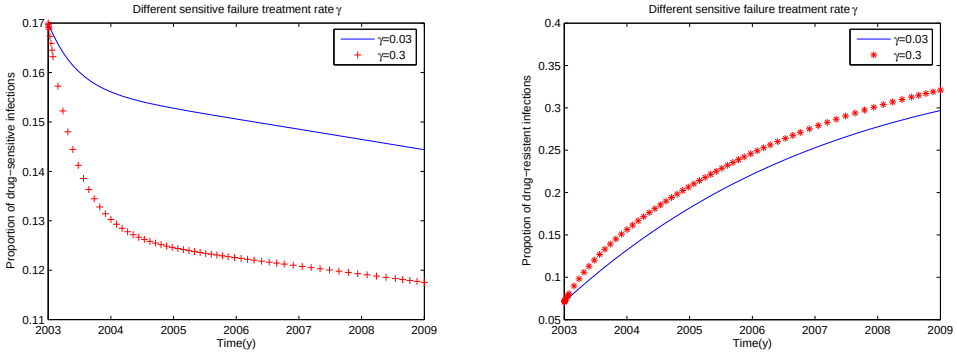

FIGURE 6. (Left) Proportions of drug-sensitive infections for different proportion acquired resistance γ due to failure in treatment of sensitive strains infected TB individuals; (Right) Proportions of drug-resistant infections for different proportion acquired resistance γ from class I_s.

we consider its elasticity with respect to key parameters that can be affected by control

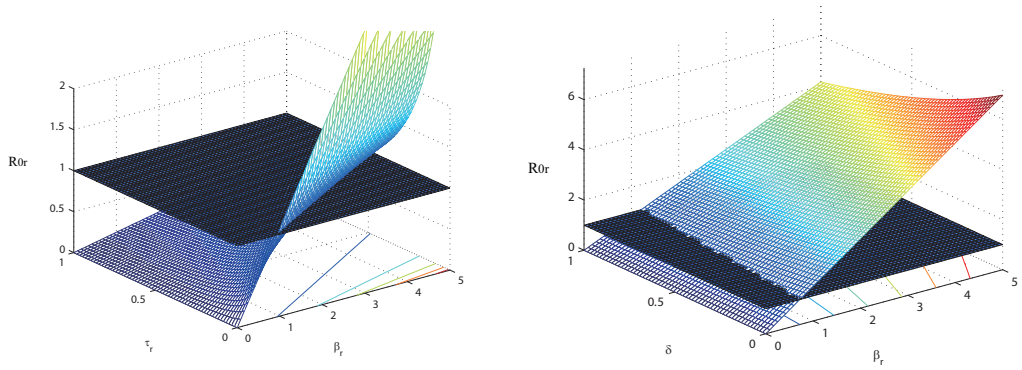

FIGURE 7. (Left) Drug resistant reproduction number (R_{0r}) plotted with respect to different treatment rate (τ_r) and transmission coefficient (β_r); (Right) R_{0r} plotted with death rate due to TB (δ) and transmission coefficient (β_r).

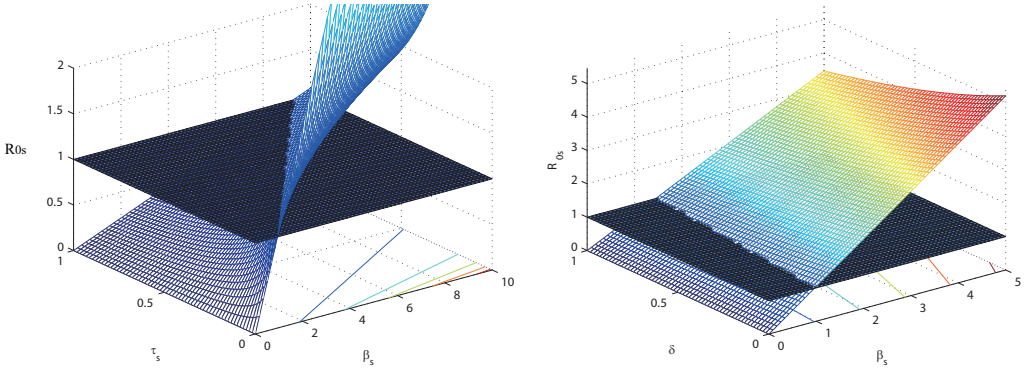

FIGURE 8. (Left) Drug sensitive reproduction number R_{0s} plotted with different treatment rate (τ_s) and transmission coefficient (β_s); (Right) R_{0s} plotted with death rate due to TB (δ) and transmission coefficient (β_s).

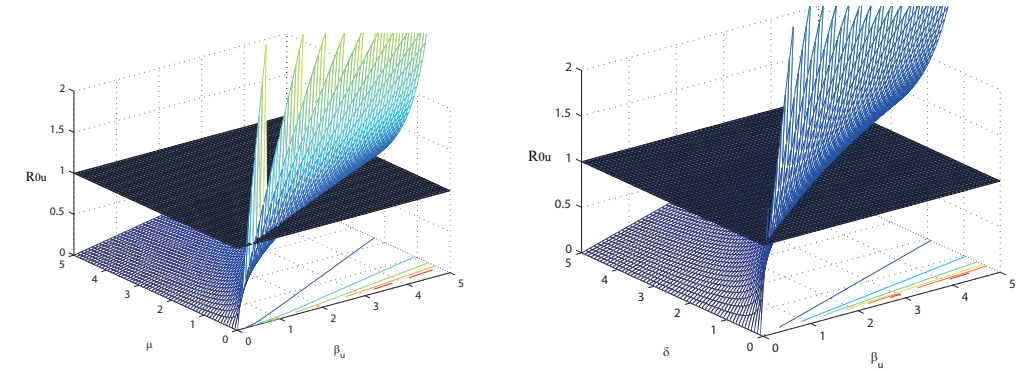

FIGURE 9. (Left) Reproduction number for the undetected compartment R_{0u} plotted with natural death rate (μ) and transmission coefficient (β_u); (Right) R_{0u} plotted with death rate due to TB (δ) and transmission coefficient (β_u).

measures. In particular, we define *elasticity* of quantity Q with respect to parameter ν

as

$$\varepsilon_{\nu}^{Q} = \frac{\partial Q}{\partial \nu}\frac{\nu}{Q}.$$

Improving economic conditions and lifestyle in China lead to lowering the rate of endogenous reactivation q. Various lifestyle changes, such as social distancing, can impact the transmission rate β_u. The elasticities of these two quantities are given as

$$\varepsilon_{\beta_u}^{R_{0u}} = 1 \qquad \varepsilon_{q}^{R_{0u}} = 0.004 \tag{4.1}$$

Elasticity of β_u means that 10% decrease in β_u will result in 10% decrease in R_{0u}. As we see from the elasticities, control measures that impact the transmission coefficient are far more efficient than changes that affect the endogenous reactivation rate q. Improving lifestyle and reducing contact rate in the general population may be such measures.

5. Comparison of our model to TB transmission in China

In this section we compare our results to the real data available from the Ministry of Health Department of China [20]. We use the parameter values as stated in table 1 of this paper. We observe some difference between the data obtained from Ministry of Health in China and the simulated result in the initial phase. This may be caused due to overestimation of some parameter values. But in the later phase nearly from 2004 onwards it almost coincides with the actual data obtained from [20]. The graph shows a decline in the infectious cases from 2003 onwards. The trend in the later years shows that TB is gradually stabilizing. It is attaining its equilibrium value. Due to availability of data on total infected cases only, we cannot analyze in this text the proportion of sensitive and drug resistant strain separately. We merely compare the total infected cases given by $(L_s + I_s + L_r + I_r)$ with the given data. Please consult Figure 10 (a) for the comparisson between the data and the simulation.

As discussed in the sensitivity analysis, for a better control of this disease, which in technical terms means lowering the reproduction number below one, it is essential to prioritize the parameters that primarily determine the transmission of TB. As we discussed in the previous section, these parameters govern the control of the basic reproduction number. The most important parameter seems to be the contact rate which is a part of the three respective transmission rates β_s, β_r and β_u. In epidemiological terms the transmission rate can be controlled by control of the interaction of the infected individuals with the susceptible individuals. We have seen, that even with proper and efficient treatment, if the contact rate increases (increasing the respective transmission rates), the basic reproduction increases sharply, almost exponentially. If it is possible to control the transmission parameter, even with lower treatment rate, TB can be controlled to a

larger extent. It is particularly important to control this parameter in the undetected class. We have seen, from the graphs presented in the previous section, that the basic reproduction number for the undetected class rises at an exponential rate, which is faster as compared to the detected class. This is mainly due to the unavailability of treatment in this class. As discussed in [10], this class tends to jeopardize the effective control strategies in mainland China undertaken by the Chinese government and other health organizations in the world. Hence success of TB control programme lies in lowering the transmission rate of the disease. An increase in successful treatment rate, which means increasing τ_s and τ_r and lowering γ also may result in controlling TB. Treatment without success, results in the increase of γ which at a later stage decreases the number of infected individuals with drug sensitive strain and increases the number of infected individuals with drug resistant strain. Increase in the proportion of individuals affected with the drug resistant strain should be avoided, despite that increase in γ has the positive effect of decreasing the reproduction number of the drug sensitive class. Increase in τ_s and increase in γ both decrease the reproduction number of the sensitive strain, which is evident from Figure 10 (b). It is interesting to note that the increase in τ_s and γ does not directly affect the reproduction number of the resistant strain. However, it may lower the invasion reproduction number of the sensitive strain, thus effectively strengtening the invasion capabilities of the resistant strain essentially leading to the population being infected by resistant TB only. Hence the best method which we can infer from all the discussion made in the text is to control the transmission rate in all the three classes and adopt mixed treatment at the same time.

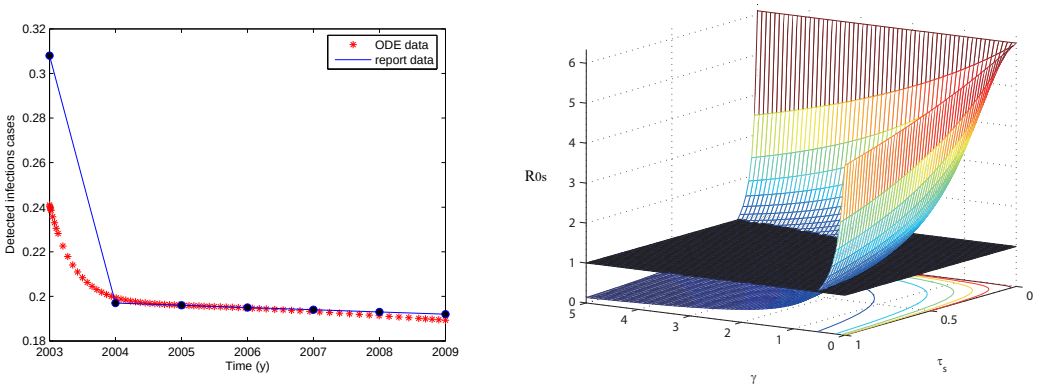

FIGURE 10. (Left) Figure (a) shows the proportion of infected individuals over time. The graphs shows a comparative study of the model data and the real data available from MOHC; (Right) Figure (b) shows the behavior of R_{0s} with γ and τ_s.

6. Extension of the model

The TB model presented in section 2 of this paper assumed that the spread of TB in the undetected class is mainly due to the number of infections caused by the infected under the class classified as undetected. We can relax this assumption and include the infections in this class caused by the infected who are detected under the TB control program. The extension helps us to look at our scenario from a more general perspective. Detection of TB virus in the undetected compartment is not done due to the difficulties discussed in [10] and also in the previous sections. But an individual who does not go for treatment may obtain the infection from an individual who was detected by the TB control agencies. Hence a more general approach would be to include this scenario in our model. We follow the model in [9]. The following shows a general model for TB transmission in China, represented by the system of equations.

$$
\begin{cases}
\dfrac{dS}{dt} = b - [\beta_s I_s + \beta_r I_r + (\beta_{us} + \beta_{ur} + \beta_u) I_u + \beta_s' I_s + \beta_r' I_r + \mu] S, \\
\dfrac{dL_s}{dt} = (1-\phi)(\beta_s I_s + \beta_{us} I_u) S + (1-\gamma)\tau_s I_s \\
\qquad -[\omega + \sigma\phi(\beta_s I_s + \beta_{us} I_u) + \sigma(\beta_r I_r + \beta_{ur} I_u) + \mu] L_s, \\
\dfrac{dL_r}{dt} = (1-\phi)(\beta_r I_r + \beta_{ur} I_u)(S + \sigma L_s) \\
\qquad -[\omega + \sigma\phi(\beta_s I_s + \beta_{us} I_u + \beta_r I_r + \beta_{ur} I_u) + \mu] L_r + \tau_r I_r, \\
\dfrac{dI_s}{dt} = \phi(\beta_s I_s + \beta_{us} I_u) S + [\omega + \phi\sigma(\beta_s I_s + \beta_{us} I_u)] L_s - (\tau_s + \mu + \delta) I_s, \\
\dfrac{dI_r}{dt} = \phi(\beta_r I_r + \beta_{ur} I_u)[S + \sigma(L_s + L_r)] + [\omega + \phi\sigma(\beta_s I_s + \beta_{us} I_u +)] L_r \\
\qquad +\gamma\tau_s I_s - (\tau_r + \mu + \delta) I_r, \\
\dfrac{dL_u}{dt} = (1-p)(\beta_u I_u + \beta_s' I_s + \beta_r' I_r) S - (q + \mu + \sigma p(\beta_s' I_s + \beta_r' I_r + \beta_u I_u)) L_u, \\
\dfrac{dI_u}{dt} = p(\beta_u I_u + \beta_s' I_s + \beta_r' I_r) S + (q + \sigma p(\beta_s' I_s + \beta_r' I_r + \beta_u I_u)) L_u - (\delta + \mu) I_u.
\end{cases}
\tag{5}
$$

New parameters which have been introduced in this section are β_s' and β_r'. Both these parameters determine the transmission in the undetected class of TB due to the individuals infected under drug sensitive and drug resistant strain in the detected compartment. The remaining parameters used in the system of equation (5) have the same meaning as before.

Figure 11 shows the bifurcation diagram of R_{0r} and R_{0u}. The variation in the treatment rate plays an important role in determining variation in the graph. We obtained the graph by varying the treatment rate in the sensitive strain class only. It has been

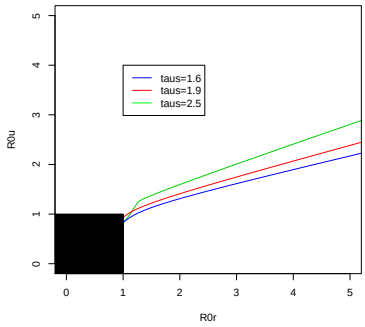

FIGURE 11. Bifurcation diagram showing the change of both R_{0u} which is the reproduction number under undetected compartment and R_{0u} which is the reproduction number of resistant strain under detected compartment.

observed that with an increase in the rate of treatment in the detected class the rate of progression of TB shifts towards the undetected class which lacks treatment. We observe that as the rate of TB increases from 1.6 to 2.5 the slope of the graph increases. γ, which determines the disease progression rate from the drug sensitive strain to drug resistant strain, has been assumed to be very small so that we can actually look at the behavior of TB progression when proper treatment is available in the detected compartment.We used the following numerical value of the parameters to obtain the graph

$$\phi = 0.482, p = 0.64, \beta_u = 0.03174042, \beta_s = 0.085, \beta_{us} = 0.028, \beta_r = 0.19835,$$
$$\beta_{ur} = 0.81, q = 0.02, \beta_s' = 0.015, \beta_r' = 0.026, \mu = 1/65, \omega = 0.2,$$
$$\gamma = 0.001, \tau_r = 2.3, \delta = 0.008$$

The next part of our analysis includes comparing the present model with the one presented before. The present model is more realistic as far as the progression of disease is concerned, but due to the complexities involved in the model we restrict our analysis only to numerical results of this model. It is interesting to observe that with the same choice of parameters, the model presented in Section 2 shows the asymptotic stability of the disease free equilibrium whereas the extended model shows the stability of the coexistent equilibrium. The value of R_0 calculated for both the models have been observed to be less than one (0.0253841 for extended model and 0.000137049 for the model in Section 2). The number of susceptible in the general model decreases whereas that number in the model of section 2 (restricted model) increases thereby proving the global stability of the disease free equilibrium. The number of latent and infected sensitive

individuals behaves almost in a similar fashion. The only difference lies in the fact that in the general model it stabilizes at a higher value proving the stability of coexistence equilibrium. The latent and infected resistent individual behave completely opposite in both models. In the general case these numbers steadily increase whereas in the restricted case they decrease. When we introduce the infection caused in the undetected compartment by the infected individuals in the detected compartment the behavior of the general model becomes significantly different. The latent class behaves in the similar fashion in the early stages but it changes its behavior as time increases. The infected number of individuals in the undetected compartment increases and then stabilizes at a higher value which is absolutely different from the behavior in the restricted model where this number goes to zero eventually. These changes are mainly due to the introduction of the new factor β_r' and β_s' introduced in this new model. Hence we can infer that the present model which talks about the general progression of TB can have potentially very different behavior which needs further investigation to characterize its structure. The numerical value of the parameter which shows this behavior is given as follows.

$b = 67.1782; \beta_s = 0.00248; \beta_{us} = 0.003; \beta_r = 0.00816; \beta_{ur} = 0.005; \mu = 1/80; \delta = 0.0149; \phi = 0.0949; \sigma = 0.0149; \omega = 0.000023; \tau_s = 8.87; \tau_r = 5.891; \gamma = 0.00003; \beta_r' = 0.3; \beta u = 0.00000690489; p = 0.0000901; q = 0.0149; \beta_s' = 0.234;$

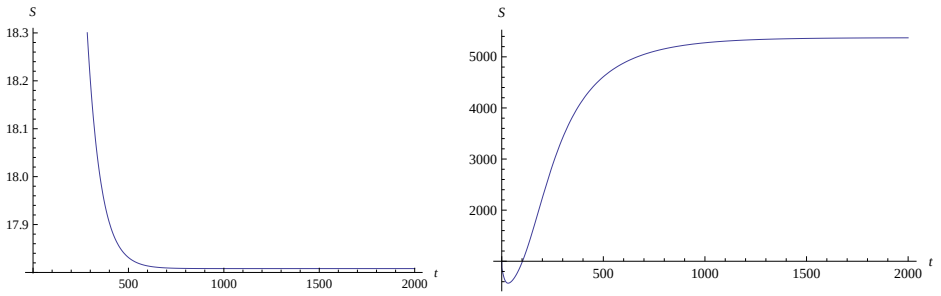

FIGURE 12. (left) Behavior for susceptible individual in the extended model (right) Behavior for susceptible individual in the restricted model

7. Discussion

Chinese government has taken the TB control programme seriously after the outbreak of SARS in 2003. But yet the unregistered class of people continues to serve as a TB-reservoir in the population, possibly destabilizing the disease-free equilibrium and hampering an effective control of TB in this country. In this paper we provided a detailed study of this class and also compared projections obtained from the model with real data.

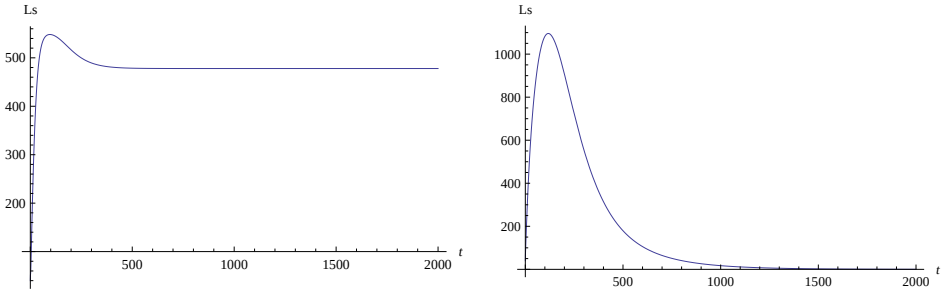

FIGURE 13. (left) Behavior for latent sensitive individual in the extended model (right) Behavior for latent sensitive individual in the restricted model

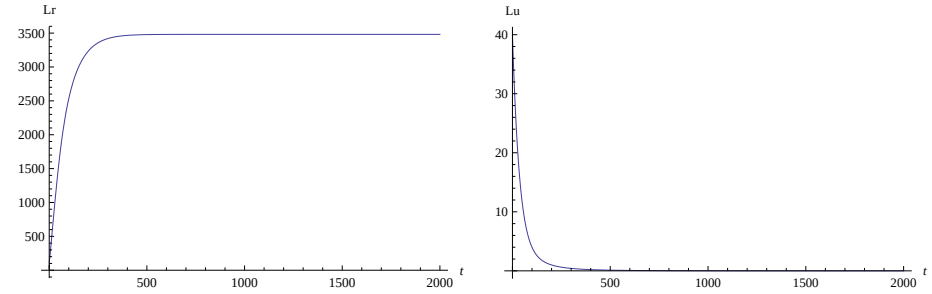

FIGURE 14. (left) Behavior for latent resistant individual in the extended model(right) Behavior for latent resistant individual in the restricted model

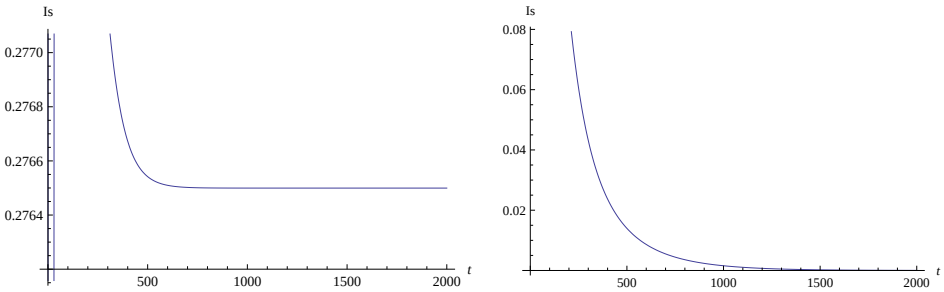

FIGURE 15. (left) Behavior for infected sensitive individual in the extended model (right) Behavior for infected sensitive individual in the restricted model

Using the method explained in [17], we calculated the basic reproduction number R_0. The disease free equilibrium is locally stable if $R_0 < 1$ and unstable when $R_0 > 1$. We find the existence of four equilibria for the model discussed in this paper. For different situations different types of endemic equilibria are present and locally stable. We also prove the global stability of the disease-free equilibrium in a particular case which suggests that subthreshold equilibria arising from the interaction of the two subpopulation

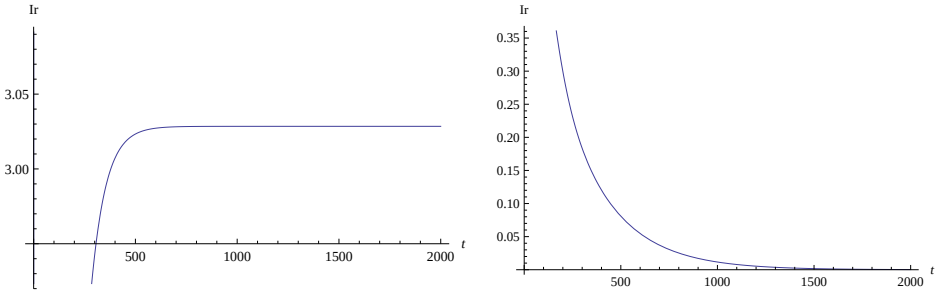

FIGURE 16. (left) Behavior for infected resistant individual in the extended model(right) Shows the behavior of Infected resistant population for the restricted case

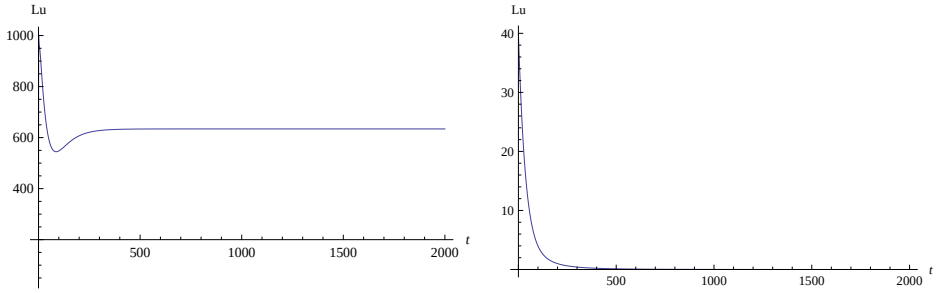

FIGURE 17. (left)Behavior for latent undetected individual in the extended model (right) Shows the behavior of latent undetected population for the restricted case

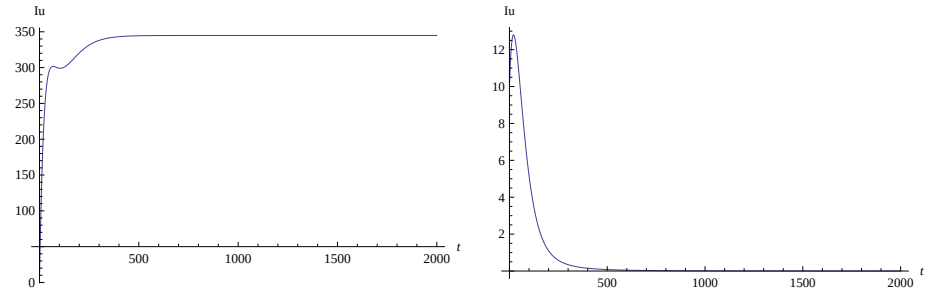

FIGURE 18. (left) Behavior for infected undetected individual in the extended model(right) Shows the behavior of Infected undetected population for the restricted case

and the multiple strains do not occur in this particular case. As per the complexity involved in the model, it is hard to explicitly calculate the co-existence equilibrium. Hence we have analytically proved the existence of this equilibrium in a particular situation and provided simulation results to show stable co-existence, when parameters do not satisfy the assumptions in the special case. We use MATLAB to calculate the values and DEdiscover to draw the simulated graphs.We also used Mathematica for drawing the graphs in the extended model. A detailed report on the sensitivity analysis has been

provided in the text which discusses, the behavior of the solutions and R_0 with changes in the parameter values. We also prepare a comparative study of the real data available from MOHC and the predictions obtained from our model. The model seems to provide a satisfactory result when compared with the real data. Hence we surmise that this model is suitable for making predictions on tuberculosis growth in the future. We have shown, in this text (by simulation results), that TB in China can be controlled to a greater extent if the health professionals focus more on controlling the transmission rate of TB and adopt efficient mixed treatments. Although effective treatment undertaken by the government of China and other world health care organizations would result in lowering the incidence rate, the presence of the undetected compartment, a class which is deprived of any treatment, serves as a TB-reservoir and will not allow for easy elimination of the disease in China. Improving economic conditions and lifestyle in China seem to contribute positively to lowering the prevalence in the undetected class, however, better methods for identification of TB cases and lowering the transmission rate need to be implemented in order to achieve the goal. One way of doing that may consist of screening for TB individuals who move from rural to urban areas.

Our original model has some restrictions. According to the assumptions made in the first half of this paper, the effect of infected individuals, under the detected class, on the undetected class of TB infected patients has been neglected. There is high chance of infection spreading to a person in the unrecognized class from the group of registered individuals under TB programme unless infectious registered individuals are isolated from the general population. In an extension of the model we incorporate transmission from the detected to the undetected compartment. Furthermore, we take into account the recovery of TB patients in this class and reactivation, i.e. we consider the undetected compartment with reinfection similar to the detected compartment, and explore its behavior. Comparing the two models we conclude that for very similar parameters, quite different outcomes are possible. Further studies may be necessary to elucidate the sensitivity of our results to the model.

8. Appendix

8.1. **A1. Reproduction number.** We follow the method explained in [17] to derive the reproduction numbers. First we need to separate the new infections from other factors. We define $\mathcal{F}(X)$ to be the vector which represents the rate of new infections that appear in the population where X is a vector given by $X = (L_s, L_r, I_s, I_r, L_u, I_u, S)$.

In this model

$$\begin{aligned}\mathcal{F}(X) = \quad & \{(1-\phi)(\beta_s I_s + \beta_{us} I_u)S,\ (1-\phi)(\beta_r I_r + \beta_{ur} I_u)S,\ \phi(\beta_s I_s + \beta_{us} I_u)S,\\ & \phi(\beta_r I_r + \beta_{ur} I_u)S, (1-p)\beta_u I_u, p\beta_u I_u, 0\}\end{aligned}$$

and the equilibrium point is represented as $E_0 = (0, 0, 0, 0, 0, 0, S^0)$. Without loss of generality we assume $S^0 = 1$. Hence, $E_0 = (0, 0, 0, 0, 0, 0, 1)$.

We express our system as $\dot{X} = \mathcal{F}(X) - \mathcal{V}(X)$, where $\mathcal{V}(X) = \mathcal{V}^-(X) - \mathcal{V}^+(\mathcal{X})$. According to the definition used in [17], $\mathcal{V}^+(X)$ denotes the vector representing rate of transfer of individuals into each class and $\mathcal{V}^-(X)$ represents the rate of transfer out of each class. Note that each of the elements in $\mathcal{F}, \mathcal{V}^+, \mathcal{V}^-$ is positive. Following the recipe presented in [17] we define the derivatives $D\mathcal{F}(E_0)$ and $D\mathcal{V}(E_0)$ in the following way.

$$D\mathcal{F}(E_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \qquad D\mathcal{V}(E_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}$$

where F and V are 6×6 matrices defined by $F = [\frac{\partial \mathcal{F}_i}{\partial x_j}(E_0)]$ and $V = [\frac{\partial \mathcal{V}_i}{\partial x_j}(E_0)]$ with $1 \le i, j \le 6$. We have

$$F = \begin{pmatrix} 0 & 0 & (1-\phi)\beta_s & 0 & 0 & (1-\phi)\beta_u \\ 0 & 0 & 0 & (1-\phi)\beta_r & 0 & (1-\phi)\beta_u \\ 0 & 0 & \phi\beta_s & 0 & 0 & \phi\beta_u \\ 0 & 0 & 0 & \phi\beta_r & 0 & \phi\beta_u \\ 0 & 0 & 0 & 0 & 0 & (1-p)\beta_u \\ 0 & 0 & 0 & 0 & 0 & p\beta_u \end{pmatrix},$$

and

$$V = \begin{pmatrix} \mu+\omega & 0 & -(1-\gamma)\tau_s & 0 & 0 & 0 \\ 0 & \mu+\omega & 0 & -\tau_r & 0 & 0 \\ -\omega & 0 & \mu+\delta+\tau_s & 0 & 0 & 0 \\ 0 & -\omega & -\gamma\tau_s & \mu+\delta+\tau_r & 0 & 0 \\ 0 & 0 & 0 & 0 & q+\mu & 0 \\ 0 & 0 & 0 & 0 & -q & (\delta+\mu) \end{pmatrix}.$$

The basic reproduction number is obtained by calculating the spectral radius of FV^{-1}. The above form of the matrices F and V clearly shows that FV^{-1} splits into two distinct compartments. The first two eigenvalues R_{0s} and R_{0r} are obtained from the first compartment. As expected it has been verified that they are the same as the ones obtained by [9] in the case of the two strain model. The third eigenvalue of FV^{-1} represents the reproduction number for the undetected compartment. Hence we have

the following values.

$$R_{0s} = \frac{\beta_s(\omega + \phi\mu)}{(\mu+\omega)(\mu+\delta+\tau_s) - (1-\gamma)\tau_s\omega},$$
$$R_{0r} = \frac{\beta_r(\omega + \phi\mu)}{(\mu+\omega)(\mu+\delta+\tau_r) - \tau_r\omega},$$
$$R_{0u} = \frac{\beta_u(q + \mu p)}{(\mu+\delta)(\mu+q)},$$

$R_0 = \max(R_{0s}, R_{0r}, R_{0u})$ gives the basic reproduction number of TB for our model. This completes the calculation of basic reproduction number.

8.2. **A2. Proof of Theorem 3.2.**

Proof. $\mathcal{F}$, X and $\mathcal{V}$ are as defined in A1. We consider the system represented as $\dot{X} = \mathcal{F}(X) - \mathcal{V}(X)$.

Define a set $\mathbb{X}_s = \{x \geq 0 | x_i = 0, i = 1, 2, ..., 6.\}$. Following the method explained in [17] we need to establish the following conditions.

(A1) If $x \geq 0$, then $\mathcal{F}, \mathcal{V}^+, \mathcal{V}^- \geq 0$.

(A2) Let i represent the ith component of the vector then, if $x_i = 0$ then $\mathcal{V}_i^- = 0$. In particular if the first 6 components of the vector X are zero then the first 6 components of the vector $\mathcal{V}^-$ are also zero.

(A3) If $i > 6$ (where 6 is as defined in $\mathbb{X}_s$), $\mathcal{F}_i = 0$, (this corresponds to the uninfected classes [9]).

(A4) If $x \in \mathbb{X}_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+ = 0$ for $i = 1, 2, ..., 6$. This condition proves the invariance of the disease-free subspace.

(A5) If $\mathcal{F}$ is set to zero then all eigenvalues of $Df(x_0)$ have negative real parts, where $Df(x_0)$ represents the jacobian matrix about the DFE x_0.

It is easy to verify the conditions (A1)-(A4). We prove the validity of (A5) in our model here.

Note $X_0 = E_0 = (0, 0, 0, 0, 0, 0, 1)$ and the jacobian matrix $Df(x_0)$ is given by

$$\begin{pmatrix}
-(\mu+\omega) & 0 & (1-\gamma)\tau_s & 0 & 0 & 0 & 0 \\
0 & -(\mu+\omega) & 0 & \tau_r & 0 & 0 & 0 \\
\omega & 0 & -(\mu+\delta+\tau_s) & 0 & 0 & 0 & 0 \\
0 & \omega & \gamma\tau_s & -(\mu+\delta+\tau_r) & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -(q+\mu) & 0 & 0 \\
0 & 0 & 0 & 0 & q & -(\delta+\mu) & 0 \\
0 & 0 & -\beta_s & -\beta_r & 0 & -\beta_{us} - \beta_{ur} - \beta_u & -\mu
\end{pmatrix}$$

Eigenvalues of the jacobian are $-\mu, -(\delta+\mu), -(q+\mu)$ and the eigenvalues of the matrix given by

$$\begin{pmatrix} -(\mu+\omega) & 0 & (1-\gamma)\tau_s & 0 \\ 0 & -(\mu+\omega) & 0 & \tau_r \\ \omega & 0 & -(\mu+\delta+\tau_s) & 0 \\ 0 & \omega & \gamma\tau_s & -(\mu+\delta+\tau_r) \end{pmatrix}$$

[9] has proved that the eigenvalues of this matrix have negative real part. Hence (A5) is proved. By Theorem 2 in [17] it follows that E_0 which represents the disease free equilibrium in our model is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. □

8.3. **A3. Proof of the existence of Co-existence equilibria.**

Proof. We find the co-existence equilibria for the system (1) by solving the following sets of equations.

$$\begin{cases} 0 = b - [\beta_s I_s + \beta_r I_r + (\beta_{us} + \beta_{ur} + \beta_u) I_u + \mu] S, \\ 0 = (\beta_s I_s + \beta_{us} I_u) S + (1-\gamma)\tau_s I_s - [\omega + \sigma(\beta_r I_r + \beta_{ur} I_u) + \mu] L_s, \\ 0 = (\beta_r I_r + \beta_{ur} I_u)(S + \sigma L_s) - (\omega + \mu) L_r + \tau_r I_r, \\ 0 = \omega L_s - (\tau_s + \mu + \delta) I_s, \\ 0 = \omega L_r + \gamma\tau_s I_s - (\tau_r + \mu + \delta) I_r, \\ 0 = (1-p)\beta_u I_u S - (q+\mu) L_u, \\ 0 = p\beta_u I_u S + q L_u - (\delta + \mu) I_u. \end{cases} \tag{5}$$

Since there exist positive values of L_u and I_u, we get the value of S^* by solving the last two equations of system (5). Note the last two equation are a set of linear homogeneous equations in terms of (L_u, I_u) given as,

$$0 = \beta_u I_u S - (q+\mu) L_u,$$
$$0 = q L_u - (\delta + \mu) I_u$$

From the algebra of equations we know that there exists a non-zero solution if and only if the determinant of the matrix J (given below) is zero.

$$J = \begin{pmatrix} -(q+\mu) & \beta_u S \\ q & -(\delta+\mu) \end{pmatrix}.$$

This gives the solution for S^* as

$$S^* = \frac{(\mu+\delta)(\mu+q)}{q\beta_u}.$$

Note that we can also represent S^* as $\frac{1}{R_{0u}}$. (Note that we have already assumed $p = 0$ in this case). Now we are left to solve the five dimensional system in $(L_s, L_r, I_s, I_r, I_u)$

to find the co-existence solution from following equations

$$\begin{cases} 0 = b - [\beta_s I_s + \beta_r I_r + (\beta_{us} + \beta_{ur} + \beta_u) I_u + \mu] S, \\ 0 = (\beta_s I_s + \beta_{us} I_u) S + (1-\gamma)\tau_s I_s - [\omega + \sigma(\beta_r I_r + \beta_{ur} I_u) + \mu] L_s, \\ 0 = (\beta_r I_r + \beta_{ur} I_u)(S + \sigma L_s) - (\omega + \mu) L_r + \tau_r I_r, \\ 0 = \omega L_s - (\tau_s + \mu + \delta) I_s, \\ 0 = \omega L_r + \gamma \tau_s I_s - (\tau_r + \mu + \delta) I_r. \end{cases} \tag{6}$$

Solving the last two equations in (6) we have the following solutions.

$$I_s = \frac{\omega}{\tau_s + \mu + \delta} L_s,$$
$$I_r = \frac{\omega}{\tau_r + \mu + \delta}(L_r + \frac{\gamma \tau_s}{\tau_s + \mu + \delta} L_s).$$

We can express I_u in terms of I_s and I_r as

$$I_u = \frac{b - (\beta_s I_s + \beta_r I_r + \mu) S^*}{\beta_t S^*}.$$

where we recall that $\beta_t = \beta_{ur} + \beta_{us} + \beta_u$. Adding the second and third equations of system (6) we have the following equation

$$0 = [\beta_s I_s + \beta_{us} I_u + \beta_r I_r + \beta_{ur} I_u] S + (1-\gamma)\tau_s I_s + \tau_r I_r - (\mu + \omega)(L_s + L_r)$$

Substituting the expression for I_u and rearrangin terms, we obtain

$$0 = I_s(\tfrac{S^* \beta_s \beta_u}{\beta_t} + (1-\gamma)\tau_s) + I_r(\tfrac{S^* \beta_r \beta_u}{\beta_t} + \tau_r) - (\mu + \omega)(L_s + L_r) + \tfrac{\beta_{us} + \beta_{ur}}{\beta_t}(b - \mu S^*).$$

Expressing I_s, I_r in terms of L_s, L_r we have

$$-L_r \left[\tfrac{\omega}{\tau_r + \mu + \delta}(\tfrac{S^* \beta_r \beta_u}{\beta_t} + \tau_r) - (\mu + \omega) \right] = L_s(\tfrac{\omega}{\tau_s + \mu + \delta}(\tfrac{S^* \beta_s \beta_u}{\beta_t} + (1-\gamma)\tau_s) +$$
$$\tfrac{\omega \gamma \tau_s}{(\tau_s + \mu + \delta)(\tau_r + \mu + \delta)}(\tfrac{S^* \beta_s \beta_u}{\beta_t} + \tau_r) - (\mu + \omega)) + \tfrac{\beta_{us} + \beta_{ur}}{\beta_t}(b - \mu S^*).$$

We are now in a position to express L_r in terms of L_s as $L_r = AL_s + B$ where

$$A = \frac{\tfrac{\omega}{\tau_s + \mu + \delta}(\tfrac{S^* \beta_s \beta_u}{\beta_t} + (1-\gamma)\tau_s) + \tfrac{\omega \gamma \tau_s}{(\tau_s + \mu + \delta)(\tau_r + \mu + \delta)}(\tfrac{S^* \beta_s \beta_u}{\beta_t} + \tau_r) - (\mu + \omega)}{\tfrac{-\omega}{\tau_r + \mu + \delta}(\tfrac{S^* \beta_r \beta_u}{\beta_t} + \tau_r) + (\mu + \omega)},$$
$$B = \frac{\tfrac{\beta_{us} + \beta_{ur}}{\beta_t}(b - \mu S^*)}{\tfrac{-\omega}{\tau_r + \mu + \delta}(\tfrac{S^* \beta_r \beta_u}{\beta_t} + \tau_r) + (\mu + \omega)}.$$

Since we assume that $b = \mu$, and $R_{0u} > 1$, we have

$$b - \mu S^* = b - \frac{\mu}{R_{0u}} > \mu \left(1 - \frac{1}{R_{0u}}\right) > 0.$$

We can rearrange the denominator of B in the following manner.

$$-\frac{\omega}{\tau_r + \mu + \delta}(\frac{S^* \beta_r \beta_u}{\beta_t} + \tau_r) + (\mu + \omega) = \frac{\omega \beta_r}{\tau_r + \mu + \delta}(\frac{1}{R_{0r}} - \frac{\beta_u}{\beta_t R_{0u}}).$$

Hence it is also a positive number from condition (A1). Therefore, B is a positive number. Let's consider A now. The argument above gives that the denominator of A is positive. The numerator of A can be rearranged as

$$\frac{\omega}{\tau_s+\mu+\delta}(\frac{S^*\beta_s\beta_u}{\beta_t}+(1-\gamma)\tau_s)+\frac{\omega\gamma\tau_s}{(\tau_s+\mu+\delta)(\tau_r+\mu+\delta)}(\frac{S^*\beta_s\beta_u}{\beta_t}+\tau_r)-(\mu+\omega)$$
$$=\frac{\omega\gamma\tau_s}{(\tau_s+\mu+\delta)(\tau_r+\mu+\delta)}(\frac{S^*\beta_s\beta_u}{\beta_t}+\tau_r)+\frac{\omega\beta_s}{\tau_s+\mu+\delta}(\frac{\beta_u}{\beta_t R_{0u}}-\frac{1}{R_{0s}}),$$

which is positive from condition (A3). Thus we have shown that A and B are both positive numbers. Now we proceed to find a positive solution of L_s. We express L_r, I_s, I_r in terms of L_s as explained above and substitute all of them in the third equation of the system (6). We have the following form

$$\begin{aligned}
0 &= (S^*+\sigma L_s)(\beta_r I_r(1-\tfrac{\beta_{ur}}{\beta_t})+\tfrac{\beta_{ur}(b-\mu S^*)}{\beta_t S^*}-\tfrac{\beta_{ur}\beta_s}{\beta_t}I_s)-(\omega+\mu)L_r+\tau_r I_r,\\
0 &= (S^*+\sigma L_s)(\beta_r\tfrac{\omega}{\tau_r+\mu+\delta}[(AL_s+B)+\tfrac{\gamma\tau_s}{\tau_s+\mu+\delta}L_s])(1-\tfrac{\beta_{ur}}{\beta_t})+\tfrac{\beta_{ur}(b-\mu S^*)}{\beta_t S^*}\\
&\quad -\tfrac{\beta_{ur}\beta_s}{\beta_t}\tfrac{\omega}{\tau_s+\mu+\delta}L_s)-(\omega+\mu)(AL_s+B)+\tau_r\tfrac{\omega}{\tau_r+\mu+\delta}(AL_s+B+\tfrac{\gamma\tau_s}{\tau_s+\mu+\delta}L_s).
\end{aligned}$$

Thus we obtain a quadratic equation in terms of L_s^*. We can rewrite as a quadratic in L_s as

$$a_1L_s^2+a_2L_s+a_3=0,$$

where

$$a_1=\sigma(\beta_r\beta_k\frac{\omega}{\beta_t(\tau_r+\mu+\delta)}[A+\frac{\gamma\tau_s}{\tau_s+\mu+\delta}])-\frac{\beta_{ur}\beta_s}{\beta_t}\frac{\omega}{\tau_s+\mu+\delta},$$

and

$$a_3=B[\frac{S^*\omega\beta_r\beta_k}{\beta_t(\tau_r+\mu+\delta)}+\frac{\beta_{ur}(b-\mu S^*)}{\beta_t B}+\frac{\tau_r\omega}{\tau_r+\mu+\delta}-(\mu+\omega)]$$

We can easily show that $a_3 < 0$.

$$\begin{aligned}
a_3 &= B[\frac{S^*\omega\beta_r\beta_k}{\beta_t(\tau_r+\mu+\delta)} + \frac{\beta_{ur}(b-\mu S^*)}{\beta_t B} + \frac{\tau_r\omega}{\tau_r+\mu+\delta} - (\mu+\omega)] \\
&= \frac{\beta_{ur}(b-\mu S^*)}{\beta_t} + \frac{\omega\beta_r B}{\tau_r+\mu+\delta}[\frac{\beta_k}{\beta_t R_{0u}} - \frac{1}{R_{0r}}] \\
&= \frac{\beta_{ur}(b-\mu S^*)}{\beta_t} + \frac{\frac{(\beta_{ur}+\beta_{us})(b-\mu S^*)}{\beta_t}}{\frac{-\beta_u}{\beta_t R_{0u}} + \frac{1}{R_{0r}}}(\frac{\beta_k}{\beta_t R_{0u}} - \frac{1}{R_{0r}}) \\
&= (b-\mu S^*)(\frac{\beta_{ur}}{\beta_t} - \frac{\beta_{ur}+\beta_{us}}{\beta_t}\frac{\frac{-\beta_k}{\beta_t R_{0u}} + \frac{1}{R_{0r}}}{\frac{-\beta_u}{\beta_t R_{0u}} + \frac{1}{R_{0r}}}) \\
&= (b-\mu S^*)(\frac{\beta_{ur}+\beta_{us}}{\beta_t}\frac{\frac{\beta_{us}}{\beta_t R_{0u}}}{\frac{-\beta_u}{\beta_t R_{0u}} + \frac{1}{R_{0r}}} - \frac{\beta_{us}}{\beta_t}) \\
&= (b-\mu S^*)\frac{\beta_{us}}{\beta_t}(\frac{\beta_{ur}+\beta_{us}}{\beta_t R_{0u}(\frac{-\beta_u}{\beta_t R_{0u}} + \frac{1}{R_{0r}})} - 1) \\
&= (b-\mu S^*)\frac{\beta_{us}}{\beta_t\left(-\frac{\beta_u}{\beta_t R_{0u}} + \frac{1}{R_{0r}}\right)}\left[\frac{1}{R_{0u}} - \frac{1}{R_{0r}}\right],
\end{aligned}$$

which is clearly a negative number from condition (A1). Note that $\beta_k = \beta_{us} + \beta_u$. Positivity of a_1 has been shown above. Thus there exists a positive real root for L_s. Since $L_r = AL_s + B$, where we have shown both A and B are positive, L_r is also positive. From the structure of I_s, I_r we can claim that they are also positive.

$$I_u = \frac{b-(\beta_s I_s + \beta_r I_r + \mu)S^*}{\beta_t S^*} > \frac{b-(\beta_s+\beta_r+\mu)S^*}{\beta_t S^*},$$

since I_s, I_r are bounded by 1 in $\mathbb{S}$. Using condition (A2) we can say that I_u is also positive.

With a positive I_u and S^*, we can find a positive value of L_u from the last equation of system (6). This proves the existence of E_{rsu} for a special case. □

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