Mathematics of the dynamics of multidrug resistant TB (MDR-TB) in India: Role of timely identification and treatment

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Abstract

Tuberculosis(TB) is one of the leading causes of death worldwide from a single infectious agent with about one quarter of the world's population being infected with *Mycobacterium tuberculosis*, the bacterium that causes the disease in humans. Moreover, with the development of multidrug-resistant TB (MDR-TB), treatment and eventual eradication of the disease have become an even greater challenge. India is the country with the highest burden of TB and MDR-TB. A major factor contributing to this is a lack of drug susceptibility testing (DST). This leads to numerous individuals infected with MDR-TB receiving inappropriate, and ineffective, treatment. We hypothesize that the time delay for these individuals to receive appropriate MDR-TB treatment will impact the number of future MDR-TB cases, as well as deaths. Further, the greater this time delay is, the more cases and more deaths that will result. We propose a mathematical model, which takes the form of a deterministic system of nonlinear differential equations, to analyze the temporal dynamics of drug-sensitive and drug-resistant TB in a population. The model, which is parameterized using relevant data for TB epidemiology and demography from India, is rigorously analyzed and simulated to assess the aforementioned hypothesis. In particular, the impact of the time delay in identifying and treating MDR-TB cases on MDR-TB-induced mortality in India is quantified. Our study shows that the most effective way to reduce future MDR-TB cases and deaths is not to reduce the time delay in MDR-TB infected individuals receiving appropriate treatment, but to reduce the time delay in beginning treatment altogether, regardless of whether or not the MDR-TB infected individual is started on appropriate or inappropriate treatment.

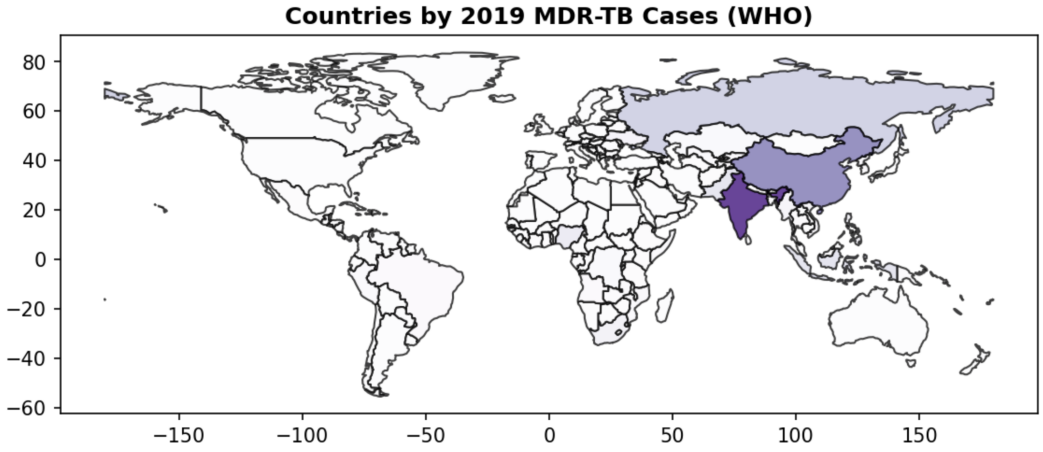

Figure 1: **MDR-TB incidence estimates by the WHO**
Darker colors indicate a greater number of cases. It is estimated that India had the greatest number of MDR-TB cases in the world in 2019.

1 Introduction

TB is one of the leading infectious disease killers in the world [1]. TB is caused by the bacterium *Mycobacterium tuberculosis*, which most often affects the lungs and causes symptoms such as cough with sputum and blood at times, chest pains, weakness, weight loss, fever, and night sweats [2]. TB occurs in every part of the world. In 2019, the largest number of new TB cases occurred in the World Health Organization (WHO) South-East Asian region, with 44% of new cases, followed by the WHO African region, with 25% of new cases and the WHO Western Pacific with 18% [2]. Also in 2019, 87% of new TB cases occurred in the 30 high TB burden countries. Eight countries accounted for two thirds of the new TB cases: India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh and South Africa [2]. Over 95% of TB cases and deaths are in developing countries [2]. With the development of MDR-TB, which is defined as infection caused by TB bacteria with resistance to at least isoniazid (INH) and rifampin (RIF) [1], the challenges of identifying, treating, and eradicating the disease are far from over. MDR-TB can develop when antibiotics typically used to treat TB are misused or mismanaged, such as when individuals do not complete a full course of TB treatment or when healthcare providers prescribe the wrong treatment (incorrect dose or length of time). Antibiotic resistance can also develop if drugs for proper treatment are not available or are of poor quality [3]. Countries such as India, which has the largest number of TB cases in the world and over a quarter of the global TB and MDR-TB burden, continue to struggle to control MDR-TB [4]. In 2016, 2.79 million people in India became ill from TB, and 435,000 died from it. India had 147,000 cases of MDR-TB in 2016 [4], and as shown in Figure 1 [5], had the greatest number of MDR-TB cases in the world in 2019. Because TB and MDR-TB remain a widespread cause of suffering and death in India, it is essential that the dynamics of the disease be further studied in an effort to better learn how to treat and eradicate it.

TB bacteria spread through the air from one person to another when a person with TB disease affecting the upper respiratory tract coughs, sneezes, speaks, sings, or otherwise expels air. Susceptible people nearby may breathe in these bacteria and become infected. When a person breathes in TB bacteria, the bacteria can settle in the lungs and begin to grow. Figure 2 depicts this transmission of TB [6] [7]. Once bacteria settle in the lungs, they can move through the blood to other parts of the body, such as the kidney, spine, and brain. TB disease in the lungs or throat can be

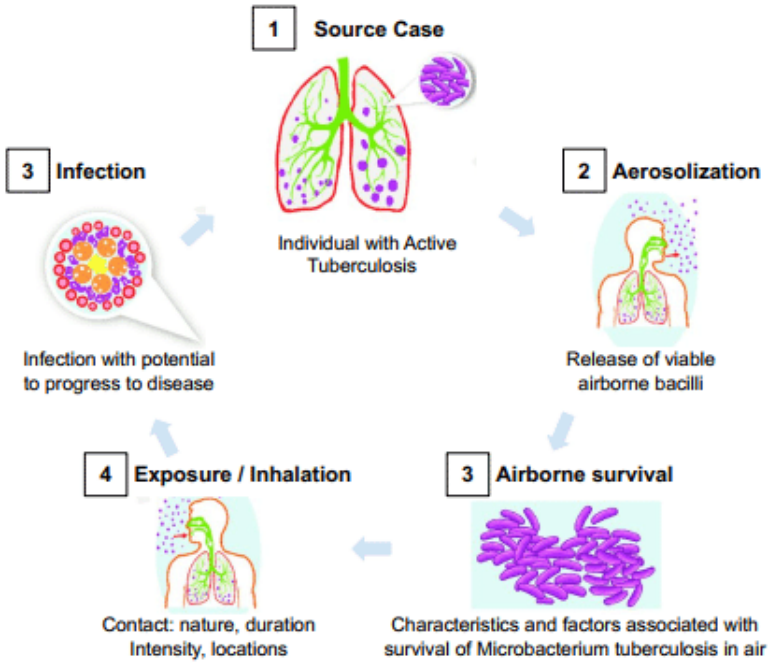

Figure 2: **The transmission of TB from an infectious to a susceptible individual.**

From: State Feedback And Synergetic controllers for Tuberculosis in infected population *via* ResearchGate (2021)

An individual with TB disease can release TB bacteria into the air when they cough, sneeze, or speak. They disperse droplets that contain *M. tuberculosis*. These droplets can dry into particles called droplet nuclei which remain suspended in air for long periods of time. When a susceptible individual is exposed to an infectious individual and inhales these particles, they can develop LTBI and potentially TB disease.

infectious; however, TB in other parts of the body is usually not infectious [8].

There are two kinds of tests that are used to detect TB bacteria in the body: the TB skin test and TB blood tests [9]. A positive TB skin or blood test only tells that a person has been infected with TB bacteria. It does not tell whether the person has latent TB infection (LTBI), which is uninfectious and asymptomatic, or active TB, referred to as TB disease, which is infectious and symptomatic. The incubation period for TB is measured from exposure time to time of development of a positive TB skin test. In most individuals, the incubation period varies from approximately two to 12 weeks. However, the risk for developing active disease is highest in the first two years after infection and development of a positive TB skin test [10]. Other tests, such as a chest x-ray and a sample of sputum, are needed to see if a person has TB disease [9].

Both LTBI and TB disease can be treated. Without treatment, LTBI can progress to TB disease, and if not treated properly, TB disease can be fatal. In the absence of treatment, on average 1 in 10 people with LTBI will get sick with TB disease in the future [11]. The risk is higher for people with HIV, diabetes, or other conditions that affect the immune system [11]. A combination of diagnostic test results, lifestyle, and pre-existing conditions determine whether or not an individual with LTBI should seek treatment [11]. Preferred treatment of LTBI typically involves a short course (3-4 months) of one or a combination of INH, RIF, or rifapentine (RPT) [12], and treatment should be modified if an individual is exposed to MDR-TB [12]. TB disease is commonly treated with a first-line anti-TB agent such as: INH, RIF, ethambutol (EMB), or pyrazinamide (PZA) for six to nine months [13].

Table 1: Previous Groups of Drugs to treat MDR-TB

Group	Drugs (abbreviations)
Group 1: First-line oral agents	Pyrazinamide (PZA), ethambutol (EMB), rifabutin (Rfb)
Group 2: Injectable agents	Kanamycin (Km), amikacin (Am), capreomycin (Cm), streptomycin (S)
Group 3: Fluoroquinolones	Levofloxacin (Lfx), moxifloxacin (Mfx), ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line agents	Para-aminosalicylic acid (PAS), cycloserine (Cs), terizidone (Trd), ethionamide (Eto), protionamide (Pto)
Group 5: Agents with unclear role in treatment of drug resistant-TB	Clofazimine (Cfz), linezolid (Lzd), amoxicillin/clavulanate (Amx/Clv), thioacetazone (Thz), imipenem/cilastatin (Ipm/Cln), high-dose isoniazid (high-dose INH), clarithromycin (Clr)

Table 2: Newly Recommended Groups of Drugs to treat MDR-TB

Group	Drugs
Group A:	Three drugs to be prioritised and used, if possible, in all regimens: levofloxacin/moxifloxacin, bedaquiline, and linezolid
Group B:	Two drugs to be possibly added to all regimens: clofazimine and cycloserine/terizidone
Group C:	"Other" agents (including injectables, which, if using, should use amikacin) to be used as a substitute to complete a regimen of at least four drugs when agents from groups A and B cannot be used

MDR-TB treatment can become quite complex. As shown in Table 1 [14], it was previously recommended that MDR-TB regimens be made up of at least four drugs, including at least PZA, a fluoroquinolone, an injectable anti-TB drug, and either cycloserine or PAS (para-aminosalycylic acid) if cycloserine cannot be used [15]. MDR-TB treatment regimens typically last 20-24 months, with an 8-month intensive phase, during which the anti-TB injectable is administered [16]. It is recommended that individuals with MDR-TB be treated using mainly ambulatory care rather than hospitalization; however, this treatment is usually directly observed (DOT) [15]. As shown in Table 2, MDR-TB treatment has begun changing in recent years, largely due to the development of two new drugs, bedaquiline, which blocks the ability of *M. tuberculosis* to make ATP, and delamanid, which destabilizes the bacterial cell wall. These drugs have contributed to the shift to shorter duration treatments, lasting only 9-10 months. This shorter regimen is made up of at least four drugs, typically from groups A and B, but with Group C agents used as a substitute to complete the regimen when agents from groups A and B cannot be used. It is recommended that this shorter regimen be followed whenever possible [16]; however, it has only recently started to be implemented in India. Research continues with the goal of identifying the combination and duration of drugs which treats MDR-TB most effectively, as globally only 57% of MDR-TB cases are successfully treated [17].

The development of MDR-TB has contributed to the challenge of controlling the spread of TB. Because the newly developed shorter treatment regimens are not widely used across the globe, many individuals must receive treatment for long periods of time, approaching two years. Drugs used to treat MDR-TB are also more expensive and toxic than those which treat drug-sensitive

TB [18]. MDR-TB alone is not the only factor leading to the continued spread of TB. Inadequate diagnostics and treatment, the need for expansion of short-course DOT, and HIV coinfection are also contributors [18]. The results of TB smear tests are not always reliable, and many facilities lack DST to identify MDR-TB cases [18]. TB treatment utilizes drugs that have been on the market for many years: INH was first used in 1952, RIF in 1965, and EMB in 1968 [18]. These drugs, like those used to treat MDR-TB, require a somewhat long treatment, six to nine months, and failure to adhere to long treatment courses results in development of resistant strains and relapse [18]. DOT programs have been initiated to encourage individuals to complete treatment and prevent this relapse and development of drug resistance; however, not all individuals receive treatment through these programs, so efforts must continue to make them more inclusive and available. Finally, HIV coinfection enhances TB spread as it compounds the problems of accurate diagnosis as well as adequate treatment. TB causes more rapid deterioration of the immune systems of people with HIV or AIDS, and they are 100 times more likely to have active TB during their lifetime than people who are HIV-negative [18]. To combat these issues, a vaccine, although not widely used, as well as newer treatments, particularly short-course treatments of MDR-TB using bedaquiline and delamanid have been developed. Other drugs, such as the high-dose rifamycins, the 8-methoxyquinolones, and the nitroimidazoles, as well as novel oxazolidinones and ethylenediamines are being studied to discover their effectiveness in treating TB and MDR-TB [19]. Ideally, use of these drugs can help make treatment regimens shorter, simpler, and safer.

Various modeling methods can be used to study diverse biological aspects of the disease in order to gain a greater understanding of the transmission and treatment of MDR-TB. Han et al. [20] used a deterministic, compartmental model, including both wild type and MDR-TB, to predict the impacts of shorter duration treatment regimens on both MDR-TB percentage among new cases and overall MDR-TB cases in southeast Asia. Agusto et al. [21] also present a determinsitic model; however, they focus on the impact of categories of individuals in isolation and lost to follow-up on the transmission dynamics of drug-sensitive TB, MDR-TB, and extensively drug-resistant TB (XDR-TB). Law et al. [22] constructed a dynamic Markov model of TB transmission, including a probabilistic framework reflecting complex treatment-seeking pathways, underlying drug-resistance, and the acquisition of drug-resistance during treatment. They then used this model, along with India-specific epidemiological data, to examine annual risk of infection, incidence of new disease, prevalence of untreated TB, and TB-related mortality.

In order to study the impact of time delay in the identification and treatment of MDR-TB cases leading to high mortality rates, we developed an 8-compartment SEIS-based model. The states in the model account for individuals receiving treatment. Through mathematical analysis and numerical simulation, the dynamics of TB and MDR-TB transmission are rigorously analyzed. In particular, time delay, in infected individuals receiving treatment altogether and in receiving appropriate MDR-TB treatment, is varied with the goal of examining its effects on the number of new MDR-TB cases as well as on the number of deaths.

2 Methods

2.1 Model Formulation

The objectives of this study will be achieved *via* the design, analysis, and simulation of a mathematical model for monitoring the temporal dynamics of both drug-sensitive and MDR-TB with the presence of treatment in the population. Specifically, the model to be designed splits the total population of individuals in the community at time t, denoted by $N(t)$, into the mutually-exclusive compartments of Susceptible ($S(t)$), exposed/latent with wild ($E_{_W}(t)$) or MDR-TB ($E_{_R}(t)$), those

with symptoms of wild ($I_W(t)$) or MDR-TB ($I_R(t)$), those treated against drug-sensitive TB ($T_W(t)$), and those receiving appropriate ($T_R(t)$) or inappropriate ($T_{R_I}(t)$) treatment against MDR-TB, so that: $N(t) = S(t) + E_W(t) + E_R(t) + I_W(t) + I_R(t) + T_W(t) + T_{R_I}(t) + T_R(t)$.

2.1.1 Derivations of equations of the model

1. Susceptible population: $S(t)$

   Individuals enter the susceptible population at birth, at a rate of Π. Individuals can also re-enter the susceptible population upon successful treatment for TB or MDR-TB at rates of γ_{T_W} and γ_{T_R} respectively. Individuals can exit the susceptible population upon acquiring infection with either the drug-sensitive TB, at rate β_W, or MDR-TB, at rate β_R, for I_R and $k\,T_{R_I}$, with $0 < k < 1$, which accounts for the reduced infectiousness of individuals in the T_{R_I} class relative to those in the I_R class. Individuals exit all epidemiological compartments due to natural death, at a rate of μ. This yields the following equation, where a dot represents differentiation with respect to time t:

   $$\dot{S} = \Pi + \gamma_{T_W} T_W + \gamma_{T_R} T_R - \frac{\beta_W I_W}{N} S - \frac{\beta_R (I_R + k T_{R_I})}{N} S - \mu S$$

2. Individuals exposed to and latently infected with TB: $E_W(t)$

   This population is generated by the infection of susceptible individuals with TB, at rate β_W. It is decreased by development of active TB, at a rate σ_W, re-infection with MDR-TB, at a rate of $m\,\beta_R$ where $0 < m < 1$ represents the decreased chance of re-infection with respect to initial infection, and natural death, with rate μ. This yields the equation:

   $$\dot{E_W} = \frac{\beta_W I_W}{N} S - \frac{m\beta_R (I_R + k T_{R_I})}{N} E_W - \sigma_W E_W - \mu E_W$$

3. Individuals with active TB: I_W

   Individuals enter the infectious TB population through progression from latent stage, at a rate of σ_W. Individuals re-enter the population when treatment fails, at a rate of $(1-r)\phi_W$, where $0 < r < 1$ represents the fraction of individuals who develop MDR-TB during treatment. Individuals exit the population through treatment initiation, at a rate of $l\,\tau_W$ where $0 < l < 1$ represents the fraction of infectious TB individuals who seek treatment, death caused by TB, at a rate of δ_{I_W}, and natural death, at rate μ. This leads to the equation:

   $$\dot{I_W} = \sigma_W E_W + (1-r)\phi_W T_W - l\,\tau_W I_W - \delta_{I_W} I_W - \mu I_W$$

4. Individuals receiving treatment for TB: T_W

   This population is generated by the initiation of treatment of infectious TB individuals, at a rate of $l\,\tau_W$ where $0 < l < 1$ represents the fraction of infectious TB individuals who seek treatment. Individuals exit this population through treatment failure, at a rate of ϕ_W and development of MDR-TB during treatment at rate $r\phi_R$. Individuals can also exit by treatment success, at a rate of γ_{T_W}, death due to TB while on treatment, at a rate of δ_{T_W}, and natural death, at a rate of μ. This yields the equation:

   $$\dot{T_W} = l\,\tau_W I_W - (1-r)\phi_W T_W - r\phi_R T_W - \gamma_{T_W} T_W - \delta_{T_W} T_W - \mu T_W$$

5. Individuals exposed to and latently infected with MDR-TB: $E_R(t)$

   This population is generated by the infection of susceptible individuals with MDR-TB, at rate β_R. Individuals also enter the population due to reinfection with MDR-TB at a rate of $m\,\beta_R$ where $0 < m < 1$ represents the decreased chance of re-infection with respect to

initial infection. The population is decreased by development of MDR-TB symptoms causing movement into the infectious stage, at a rate $\sigma_{_R}$, and also by natural death, at rate μ. This yields the equation:

$$\dot{E_{_R}} = \frac{\beta_{_R}(I_{_R}+kT_{_{R_I}})}{N}S + \frac{m\beta_{_R}(I_{_R}+kT_{_{R_I}})}{N}E_{_W} - \sigma_{_R}E_{_R} - \mu E_{_R}$$

6. Individuals infectious with MDR-TB: $I_{_R}$

   Individuals enter this population when they develop MDR-TB symptoms, at rate $\sigma_{_R}$, when they fail MDR-TB treatment at rate $\phi_{_R}$, and when they develop drug-resistance during treatment for wild-type TB at rate $r\phi_R$ where $0 < r < 1$ represents the decreased chance of development of drug resistance. Individuals can exit the population when they begin TB treatment at rate $l\tau_{_R}(1-p)$ where $0 < l < 1$ represents the fraction of individuals who seek treatment, and $0 < p < 1$ represents the decreased chance of immediately beginning MDR-TB treatment. Individuals can also exit when they begin MDR-TB treatment at rate $p\tau_{_R}$, by MDR-TB induced death at rate $\delta_{_{I_R}}$, or by natural death, at rate μ. This yields the equation:

   $$\dot{I_{_R}} = \sigma_{_R}E_{_R} + \phi_{_R}T_{_R} + r\phi_{_R}T_{_W} - l\tau_{_R}(1-p)I_{_R} - lp\tau_{_R}I_{_R} - \delta_{_{I_R}}I_{_R} - \mu I_{_R}$$

7. Individuals receiving inappropriate treatment for MDR-TB: $T_{_{R_I}}$

   This population is generated by infectious MDR-TB individuals beginning incorrect treatment at rate $l\tau_{_R}(1-p)$ where $0 < l < 1$ represents the fraction of individuals who seek treatment and $0 < p < 1$ represents the decreased chance of immediately beginning MDR-TB treatment. The population is decreased by individuals in this compartment switching to the correct treatment at rate α. Natural death, at rate μ, and death caused by MDR-TB at rate $\delta_{_{T_{R_I}}}$ decrease the population as well. This yields the equation:

   $$\dot{T_{_{R_I}}} = (1-p)\,l\,\tau_{_R}I_{_R} - \alpha T_{_{R_I}} - \delta_{_{T_{R_I}}}T_{_{R_I}} - \mu T_{_{R_I}}$$

8. Individuals receiving appropriate treatment for MDR-TB: $T_{_R}$

   Individuals enter this population when they receive MDR-TB treatment initially, at rate $p\tau_{_R}$, where $0 < p < 1$ represents the decreased chance of immediately beginning MDR-TB treatment, and when individuals infectious with MDR-TB due to receiving incorrect treatment switch to correct MDR-TB treatment at rate α. Individuals exit this population when treatment fails, at rate $\phi_{_R}$, or when treatment is successful, at rate $\gamma_{_{T_R}}$. Individuals also exit due to natural death, at a rate of μ, and due to death caused by MDR-TB at rate $\delta_{_{T_R}}$. This yields the equation:

   $$\dot{T_{_R}} = \alpha T_{_{R_I}} + lp\,\tau_{_R}I_{_R} - \phi_{_R}T_{_R} - \gamma_{_{T_R}}T_{_R} - \delta_{_{T_R}}T_{_R} - \mu T_{_R}$$

Model (1) contains the equations which represent our model.

Table 3: Statement of Variables

S	Population of susceptible individuals
E_W	Population of exposed (latently-infected) individuals with drug-sensitive TB
E_R	Population of exposed (latently-infected) individuals with MDR-TB
I_W	Population of individuals with active wild-type TB
I_R	Population of individuals with MDR-TB
T_W	Population of individuals undergoing treatment for TB
T_I	Population of individuals with MDR-TB incorrectly undergoing treatment for TB
T_R	Population of individuals with MDR-TB undergoing treatment for MDR-TB

2.1.2 The system of equations for our model

$$
\begin{cases}
\dot{S} &= \Pi + \gamma_{T_W} T_W + \gamma_{T_R} T_R - \frac{\beta_W I_W}{N} S - \frac{\beta_R (I_R + k T_{R_I})}{N} S - \mu S, \\
\dot{E_W} &= \frac{\beta_W I_W}{N} S - \frac{m \beta_R (I_R + k T_{R_I})}{N} E_W - \sigma_W E_W - \mu E_W, \\
\dot{E_R} &= \frac{\beta_R (I_R + k T_{R_I})}{N} S + \frac{m \beta_R (I_R + k T_{R_I})}{N} E_W - \sigma_R E_R - \mu E_R, \\
\dot{I_W} &= \sigma_W E_W + (1 - r) \phi_W T_W - l \, \tau_W I_W - \delta_{I_W} I_W - \mu I_W, \\
\dot{I_R} &= \sigma_R E_R + \phi_R T_R + r \phi_W T_W - l \tau_R I_R - \delta_{I_R} I_R - \mu I_R, \\
\dot{T_W} &= l \, \tau_W I_W - \phi_W T_W - \gamma_{T_W} T_W - \delta_{T_W} T_W - \mu T_W, \\
\dot{T_{R_I}} &= l (1 - p) \tau_R I_R - \alpha T_{R_I} - \delta_{T_{R_I}} T_{R_I} - \mu T_{R_I}, \\
\dot{T_R} &= \alpha T_{R_I} + l p \, \tau_R I_R - \phi_R T_R - \gamma_{T_R} T_R - \delta_{T_R} T_R - \mu T_R,
\end{cases}
\tag{1}
$$

$$N(t) = S(t) + E_W(t) + E_R(t) + I_W(t) + I_R(t) + T_W(t) + T_{R_I}(t) + T_R(t).$$

Model (1) is based upon the following assumptions:

1. The population has homogeneous mixing, meaning that each individual is equally likely to become infected with TB or MDR-TB.
2. All of the rates are exponentially distributed with regards to time.
3. MDR-TB and XDR-TB are considered under the MDR-TB compartments because cases of XDR-TB are generally very rare both in India and across the globe.
4. Effectively-treated individuals are given the correct dose of medicine, with full-course adherence, do not transmit infection, and they do not develop MDR-TB.
5. For mathematical tractability, we assume that reinfection with the same strain does not occur. However, individuals who are latent with the wild strain can acquire reinfection with the MDR-TB strain.

6. For simplicity, we do not categorise TB cases in terms of slow and fast progressors.

7. Treated individuals who failed to complete their treatment do not become latent (they, instead, revert to the corresponding infectious class).

8. Superinfection is not possible. An individual cannot become infected with TB and MDR-TB at the same time.

9. Individuals who recover from TB do not have natural immunity.

Figure 3 depicts the schematic diagram of our model. The state of variables and parameters of Model (1) are described in Tables 3 and 4 respectively.

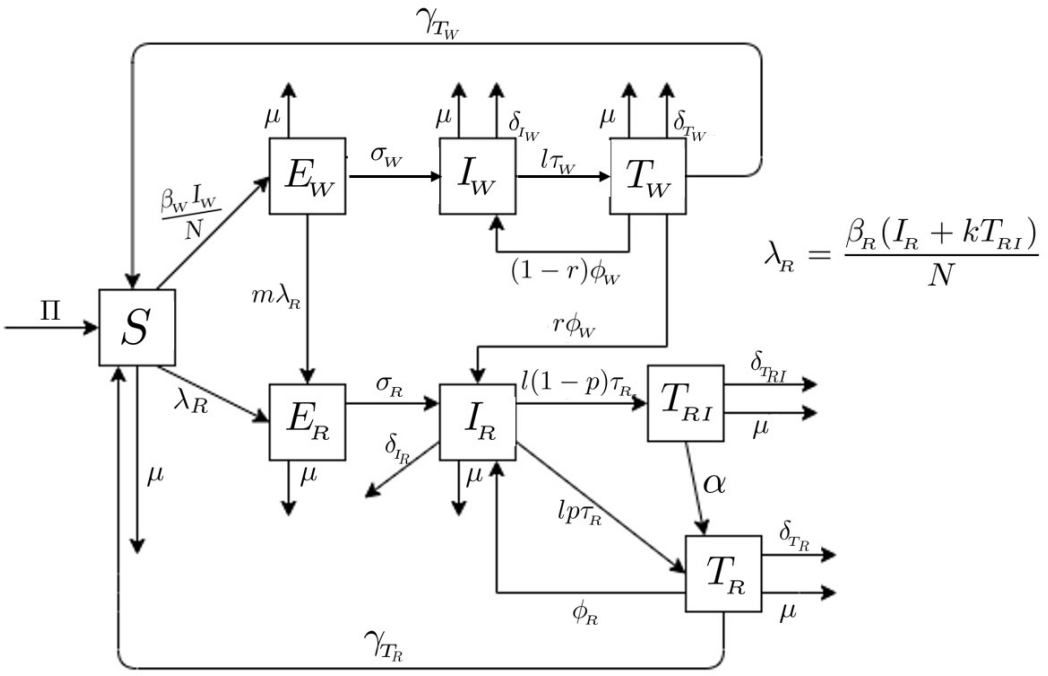

Figure 3: **Flow diagram of Model 1**
Individuals start in the Susceptible class, and some are exposed to infectious TB. After exposure, they move into the Exposed/Latent class, where they remain until death or until the development of active TB. With active TB, individuals are in the Infectious class, where they remain until death or initiation of treatment. Once they start treatment, they are in the Treatment class, where they receive either correct or incorrect treatment. If incorrectly treated they can remain in this class until death or until switching to correct treatment. Once on correct treatment, individuals can remain until death, until treatment fails, or until they are successfully cured and reenter the Susceptible class.

Table 4: Parameters

Symbol	Definition	Value	Units	Source
Π	Recruitment rate into the population	23786577	births per year	[30] [33]
$\frac{1}{\mu}$	Average lifespan for India (2017)	69.2	years	[31]
β_W	Infection Rate for drug-sensitive TB	4.5004	individuals infected per active case per year	estimated & [21]
β_R	Infection Rate for MDR-TB	1.5	individuals infected per active case per year	estimated & [21]
m	Modification parameter for the reduced likelihood of reinfection with MDR-TB in relation to primary infection with MDR-TB	0.06		[21]
k	Modification parameter for the reduced infectivity of incorrectly treated MDR-TB cases in relation to untreated MDR-TB cases	0.5		assumed
σ_W	Progression rate from E_W to I_W	0.0478	per year	estimated
σ_R	Progression rate from E_R to I_R	0.0033	per year	[21]
τ_W	Treatment rate against drug-sensitive TB	2.5064	per year	estimated
τ_R	Treatment rate against MDR-TB	1.2016	per year	estimated
l	Fraction of individuals who seek TB treatment	0.425		[27]
p	Fraction of individuals that seek out MDR-TB treatment	0.58		[23]
α	Rate of switching treatment from TB to MDR-TB	2	per year	assumed
δ_{I_W}	Disease-induced death rate for individuals with drug-sensitive TB	0.11	per year	[34]
δ_{I_R}	Disease-induced death rate for individuals with MDR-TB	0.11	per year	assumed
δ_{T_W}	Death rate for individuals undergoing TB treatment	0.04	per year	[26]
$\delta_{T_{R_I}}$	Death rate for MDR-TB individuals undergoing TB treatment	0.1099	per year	estimated
δ_{T_R}	Death rate for individuals undergoing MDR-TB treatment	0.067	per year	[26]
ϕ_W	Rate at which TB individuals are lost to follow-up or treatment fails	0.1996	per year	[26]
ϕ_R	Rate at which MDR-TB individuals are lost to follow-up or treatment fails	0.2521	per year	[32]
r	Fraction of lost TB cases which develop MDR-TB from non-compliance	0.0162	per year	estimated
γ_{T_W}	Rate at which individuals successfully finish TB treatment	1.58	per year	[26]
γ_{T_R}	Rate at which individuals successfully finish MDR-TB treatment	0.45	per year	[27]

2.2 Data Fitting and Parameter Estimation

Model 1 contains a multitude of parameters and initial conditions, some of which are known from literature and others which are unknown. From the unknown parameters, some could be estimated from literature, some could be calculated from data, and the others were fit to known TB data using the lsqcurvefit function in MATLAB. First, k, p, α and δ_{I_R} will be estimated. The fraction of infectivity of incorrectly treated MDR-TB cases, k, is assumed to be 0.5 as patients having received at least some treatment will likely be less infectious. The fraction of individuals who seek out MDR-TB treatment, p, is estimated to be 0.58, as 58% of infected individuals in India in 2019 had DST results to inform them whether or not their TB had any drug resistances [23]. The rate of incorrectly treated MDR-TB patients initiated on correct treatment, α, is estimated to be 2, as regular TB treatment has an average length of 6 months, so it is initially assumed that it is discovered the wrong treatment was initiated in the time it takes for the TB treatment to fail. The death rate for active MDR-TB, δ_{I_R}, is assumed to be the same as the death rate for those infected with the wild type, and therefore is estimated to be 0.11. The initial conditions for the latent compartments of the fitting simulation (E_W and E_R) could only be estimated. It is estimated that in southeast Asia about 1.8% of all latent TB infections are MDR-TB [24]. It is also estimated that about 40% of all Indians have latent TB [25]. Therefore, the initial conditions for E_W and E_R were estimated to be $480,400,000$ and $6,726,000$.

The parameters which were calculated include $\gamma_W, \gamma_R, \phi_W, \delta_{T_W}$, and l. All of the calculated values were derived from the India's Revised National TB Control Programme 2019 and 2021 reports, where the MDR-TB data was taken from the 2021 report, and the TB data was taken from the 2019 report, so that all of the parameters could be based off of the most recent yearly treatment outcomes data (from 2017) for both strains. [26] [27]. The γs were calculated by finding the percentage of successful outcomes of treatment. For γ_W, that percentage was divided by 0.5 to account for the 6 months of treatment in order to calculate it as 1.48. For γ_R, that percentage was divided by $\frac{5}{3}$ to account for the average 20 months of treatment the individuals diagnosed in 2017 went through, in order to calculate it as 0.4538. ϕ_W was calculated by summing the treatment failure, lost to follow up, and failed to be evaluated categories and finding their percentage of overall cases. Then ϕ_W was divided by 1 in order to produce 0.1996. δ_{T_W} was calculated by finding the percentage of treatment deaths, and then dividing by 1 in order to produce 0.0397.

The parameters which were fit include β_W, β_R, σ_W, σ_R, $\delta_{T_{RI}}$, τ_W, τ_R, and r. These parameters were fit to the correct treatment compartments, T_W and T_R with data found in India's annual TB reports [23] [27]. The infection rate of TB, β_W, was fit to 4.5004, bounded by $(4.5, 15.0)$ [21]. The infection rate of MDR-TB, β_R, was fit to 1.5, bounded by $(1.5, 3.5)$ [21]. The rate of TB progression to symptoms, σ_W, was fit to 0.0478, bounded to $(0, 0.83)$ [28]. The rate of MDR-TB progression to symptoms, σ_R, was fit to 0.0033, bound by $(0, 0.83)$. The death rate for individuals infected with MDR-TB undergoing TB treatment, $\delta_{T_{RI}}$, was fit to 0.1099, bounded by $(\delta_{T_R}, \delta_{I_R})$. The rate of treatment starting from onset of TB symptoms, τ_W, was fit to 2.5064, bounded by $(1.2, 18)$, from the approximate maximums and minimum times until treatment (20 days to 10 months) [29]. The rate of MDR-TB treatment starting from onset of active MDR-TB, τ_R, was fit to 1.2016, bounded by $(1.2, 20)$ [29]. The fraction of lost TB cases which develop drug resistance due to treatment non-compliance, r, was fit to be 0.0184, bounded by $(0.001, 1)$, as based on expert opinion.

3 Mathematical Analysis

3.1 Asymptotic Stability of Disease-Free Equilibrium (DFE)

The model (1) has a unique DFE, given by:

$$(S^*, E_W^*, E_R^*, I_W^*, I_R^*, T_W^*, T_{R_I}^*, T_R^*) = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0, 0, 0\right)$$

3.2 Reproduction Number

In this section, the reproduction number of the model is computed using the next generation method. The control reproduction number, $\mathcal{R}_c$ is the average of secondary number of TB or MDR-TB cases that one infected individual causes in the susceptible population when treatment is available.
The local asymptotic stability of the DFE can be analysed using the next generation operator method [35]. Using the notation in [35], it follows that F and V are given by:

$$F = \begin{pmatrix} 0 & 0 & \beta_W & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_R & 0 & \beta_R k & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \sigma_W + \mu & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma_R + \mu & 0 & 0 & 0 & 0 & 0 \\ -\sigma_W & 0 & \delta_{I_W} + \mu + l\tau_W & 0 & -(1-r)\phi_W & 0 & 0 \\ 0 & -\sigma_R & 0 & \delta_{I_R} + \mu + l\tau_R & -r\phi_W & 0 & -\phi_R \\ 0 & 0 & -l\tau_W & 0 & \gamma_W + \delta_{T_W} + \mu + \phi_W & 0 & 0 \\ 0 & 0 & 0 & -l(1-p)\tau_R & 0 & \alpha + \delta_{T_{R_I}} + \mu & 0 \\ 0 & 0 & 0 & -lp\tau_R & 0 & -\alpha & \gamma_R + \delta_{T_R} + \mu + \phi_R \end{pmatrix}$$

The next generation matrix is FV^{-1}, and

$$\mathcal{R}_c = \rho(FV^{-1}),$$

where ρ denotes the spectral radius. Thus, the control reproduction number for our model is given by $\mathcal{R}_c = \max\{\mathcal{R}_{cW}, \mathcal{R}_{cR}\}$, where $\mathcal{R}_{cW}$ and $\mathcal{R}_{cR}$ are as follows:

$$\mathcal{R}_{cW} = \frac{\beta_W \sigma_W (\gamma_W + \delta_{T_W} + \mu + \phi_W)}{(\mu + \sigma_W)\left\{(\gamma_W + \delta_{T_W} + \mu)(\delta_{I_W} + \mu + l\tau_W) + \phi_W(\delta_{I_W} + \mu + rl\tau_W)\right\}}$$

$$\mathcal{R}_{cR} = \frac{\beta_R \sigma_R (a + \phi_R)(c - kd\tau_R + \mu)}{(\mu + \sigma_R)\left[(c + \mu)\left\{\phi_R(\delta_{I_R} + \mu) + a(\delta_{I_R} + l\tau_R + \mu)\right\} - d\tau_R \phi_R(\delta_{T_{R_I}} + \mu)\right]}$$

where $a = \gamma_{T_R} + \delta_{T_R} + \mu, c = \alpha + \delta_{T_{R_I}}, d = l(p-1)$.

We have computed the $\mathcal{R}_c$ using the parameter values we showed in Table 4 :

$$\mathcal{R}_{c_W} = 3.2117$$
$$\mathcal{R}_{c_R} = 0.6169$$

Hence, the control reproduction number is $\mathcal{R}_c = \max\{\mathcal{R}_{c_W}, \mathcal{R}_{c_R}\} = \max\{3.2117, 0.6169\} = 3.2117$. Following the theorem below, the model 1 is locally asymptotically stable.

Theorem 1 *The DFE of the model 1 is locally-asymptotically stable if $\mathcal{R}_c < 1$, and unstable if $\mathcal{R}_c > 1$ [36].*

The epidemiological implication of the above result is that a small influx of individuals infected with TB or MDR-TB into the community will not generate a large outbreak if $\mathcal{R}_c < 1$.
In order to numerically test Theorem 1, four simulations were run with different combinations of $\mathcal{R}_{c_R}$ and $\mathcal{R}_{c_W}$ being greater than or less than one. These simulations are contained in Figure 4.

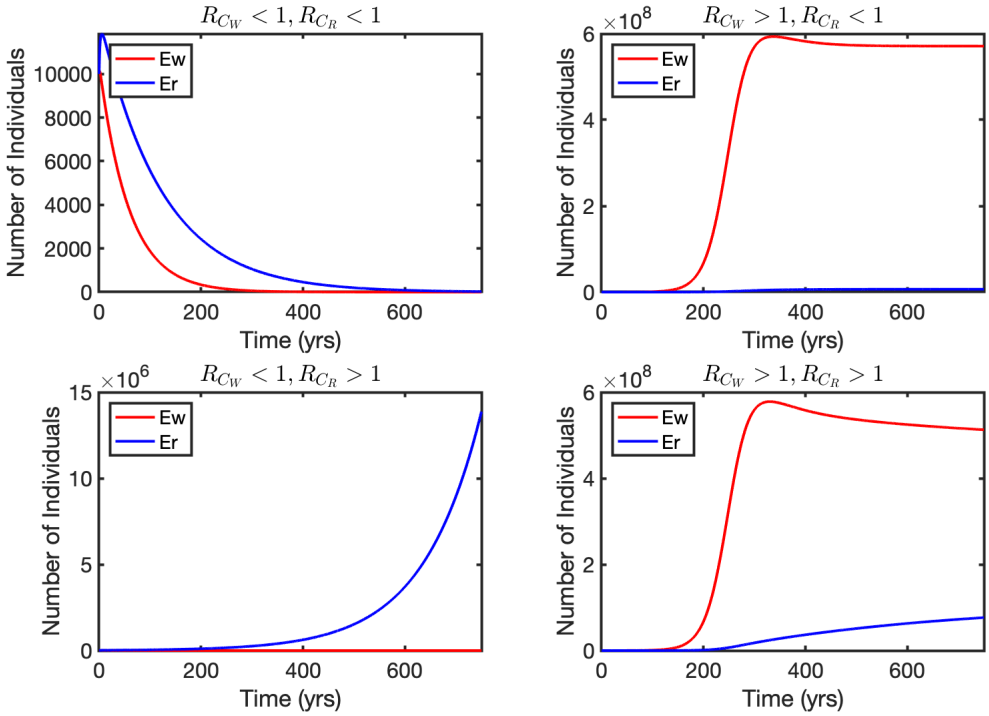

Figure 4: **Simulations displaying the fate of the respective TB and MDR-TB strains depending on the $\mathcal{R}_{C_R}$ and $\mathcal{R}_{C_W}$**

In A (top left), both $\mathcal{R}_{C_R} < 1$ and $\mathcal{R}_{C_W} < 1$, and both E_W and E_R converge to the DFE. In B (top right), $\mathcal{R}_{C_R} < 1$ and $\mathcal{R}_{C_W} > 1$, E_W converges to an endemic equilibrium and E_R is much lower proportionally, but converges to an endemic equilibrium as well. See Figure 5 for more information on B. In C (bottom left), $\mathcal{R}_{C_R} > 1$ and $\mathcal{R}_{C_W} < 1$, and E_W converges to the DFE while E_R converges to an endemic equilibrium. In D (bottom right), both $\mathcal{R}_{C_R} > 1$ and $\mathcal{R}_{C_W} > 1$, and both E_W and E_R converge to an endemic equilibrium.

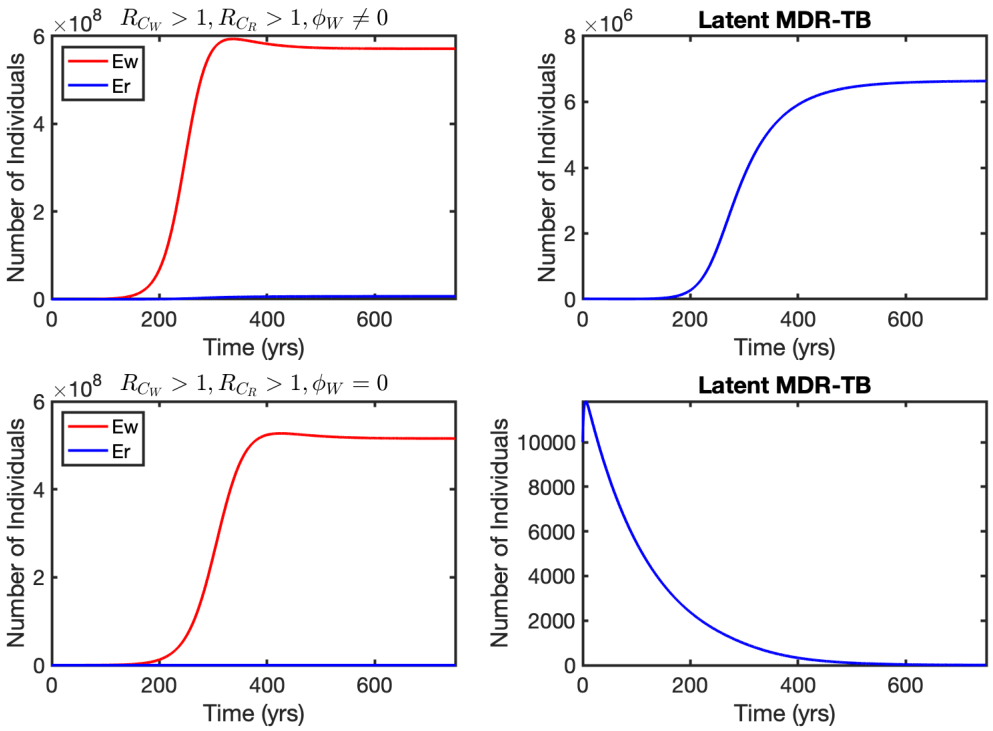

Figure 5: **Simulations displaying the fate of the respective TB and MDR-TB strains when $\mathcal{R}_{C_R} < 1$ and $\mathcal{R}_{C_W} > 1$, while varying ϕ_W.**

In A (top left), $\mathcal{R}_{C_R} < 1$ and $\mathcal{R}_{C_W} > 1$, E_W converges to an endemic equilibrium and E_R is much lower proportionally, but converges to an endemic equilibrium as well. In B (top right), the E_R from A is plotted in isolation to demonstrate the convergence to the endemic equilibrium. In C (bottom left), $\phi_W = 0$, $\mathcal{R}_{C_R} < 1$ and $\mathcal{R}_{C_W} > 1$, and E_W converges to an endemic equilibrium, and E_R converges to the DFE. In D (bottom right), the E_R from B is plotted in isolation to demonstrate the convergence to the DFE.

3.3 Parameter Sensitivity Analysis

Sensitivity analysis shows how important each parameter is to disease transmission by allowing us to discover which parameters have a high impact on the reproduction number. R_c contains numerous parameters and it is important to find out which are the most significant in the model (1). It was found that the parameters with the greatest influence were β_W, β_R, σ_R, τ_W, τ_R and l. The values for these parameters had to be carefully estimated in order to accurately determine the impact of time delay on future MDR-TB cases and deaths. A small variation in the highly sensitive parameters could lead to large quantitative changes [37].

Table 5: Sensitivity Indices of R_c evaluated at the baseline parameter values given in Table 4.

Parameter	**Sensitivity index**
β_W	1
σ_W	0.231396
γ_{T_W}	-0.0913793
δ_{T_W}	-0.0023134
μ	-0.245627
ϕ_W	0.0945284
δ_{I_W}	-0.101968
τ_W	-0.884636
r	-0.00174667
β_R	1
σ_R	0.823371
α	-0.0473528
$\delta_{T_{R_I}}$	-0.0105428
μ	-0.012385
k	0.0592806
τ_R	-0.719232
p	-0.0694611
γ_{T_R}	-0.204486
δ_{T_R}	-0.0304456
ϕ_R	0.241498
δ_{I_R}	-0.195769
l	-0.848252

4 Numerical Simulations

In order to find suitable values for the unknown parameters, the model was fit to India's T_W and T_R data from 2008 to 2019. This fitting was accomplished with the lsqcurvefit function and ODE45 solver in MATLAB.

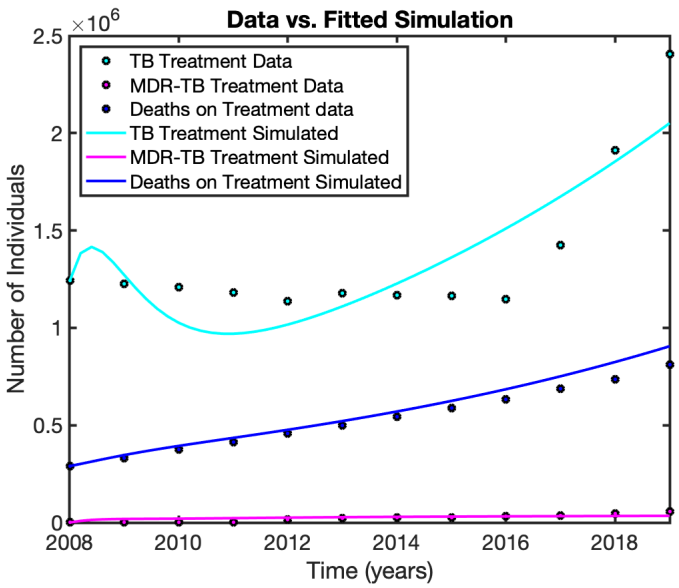

Figure 6: **India's TB data from 2008-2019 Plotted Against the Fitted Simulation Data: a representation of the difference between the data and the fit parameters.**
The data for total deaths while on treatment is included in order to demonstrate that the fitting produces results which are consistent to other streams of data.

After the parameters were collected from the fitting, the simulation of the entire Indian TB epidemic could be run, as seen in Figure 7.

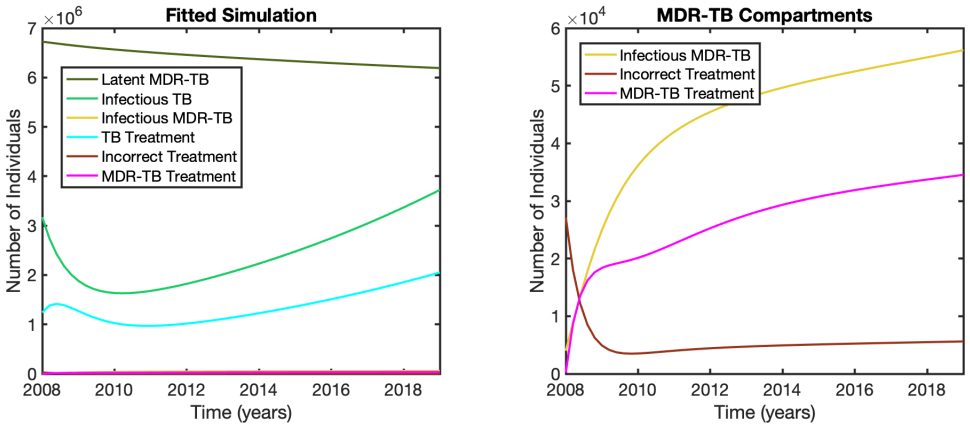

Figure 7: **A Simulation of India's TB Epidemic from 2008-2019: Model 1 with the fit parameters.** 5A (left) contains the Latent MDR-TB, Infectious TB, and TB Treatment compartments of the model. Both the Infectious and Treatment compartments experience a slight decrease around 2010 and increase for the rest of the simulation. 5B (right) contains the plotted MDR-TB compartments of the model. The Infectious MDR-TB and MDR-TB Treatment compartments increase over the simulation, while the Incorrect Treatment compartment immediately decreases and then remains constant.

In order to observe the effects of time delay in treatment on the MDR-TB epidemic, simulations were run in MATLAB using the ODE45 solver. The initial conditions in the predictive simulation were set to the final outputs (2019) of every compartment in the fitting simulation, as seen in Figure 5. The parameters were set as the found, estimated, or fit values in order to display the dynamics of

Table 6: Initial conditions for 2019, from the Fitted Simulation.

S	$777,210,000$
E_W	$92,102,000$
E_R	$6,190,700$
I_W	$3,724,300$
I_R	$56,161$
T_W	$2,051,000$
T_{R_I}	$5,612$
T_R	$34,527$

the model as it continues onto 2068. Initially, α was set to 2.0, or a time delay of 6 months between starting incorrect treatment and transfering to MDR-TB treatment, and τ_R was set to 1.5, or a time delay of 8 months between developing MDR-TB symptoms and being put on any treatment.

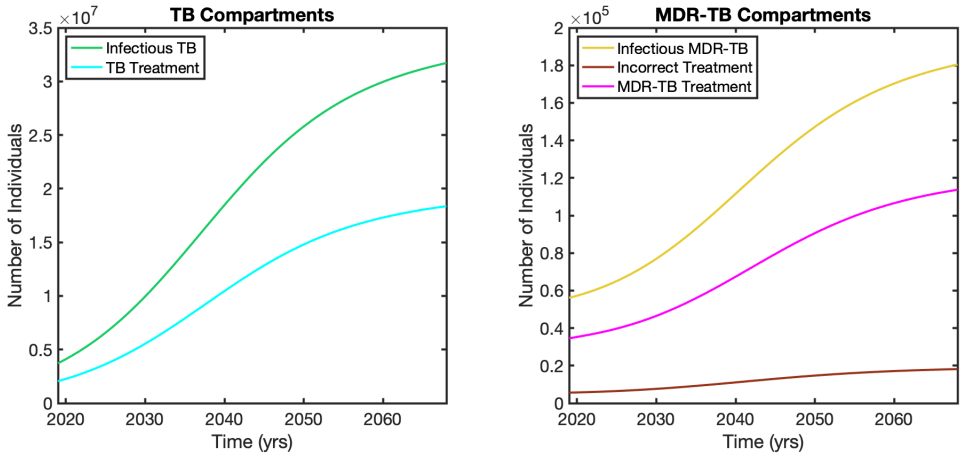

Figure 8: **A Simulation of India's TB Epidemic from 2019-2068: Generated from Fit Parameter Values.**
The dynamics of the predictive simulation are displayed. 6A (left) contains the Infectious TB and TB Treatment compartments. They both increase for the duration of the simulation, with TB Treatment beginning to flatten at the end. However, there is no distinctive leveling-out before 2068. 6B (right) contains the Infectious MDR-TB, Incorrect Treatment, and MDR-TB Treatment compartments. All three compartments increase for the duration of the simulation, with Incorrect Treatment having a lesser rate of increase, respectively.

Then α and τ_R, two rates involved in the initiation of treatment for MDR-TB patients, were varied in order to observe their effects on the total latent and infectious MDR-TB cases and the total number of MDR-TB related deaths. In Figure 7, α, the rate of MDR-TB treatment initiation for individuals incorrectly started on TB treatment, and τ_R, the rate of treatment initiation for infectious MDR-TB individuals, are varied from $24 - 0.5$, where $\frac{1}{\alpha}$ and $\frac{1}{\tau_R}$, the respective times for the initiation of types of MDR-treatment, ranged from 2 weeks to 2 years of delay. When α was varied, τ_R was held to the initial fitting of 1.2016. When τ_R was varied, α was held to the initial estimate of 2.

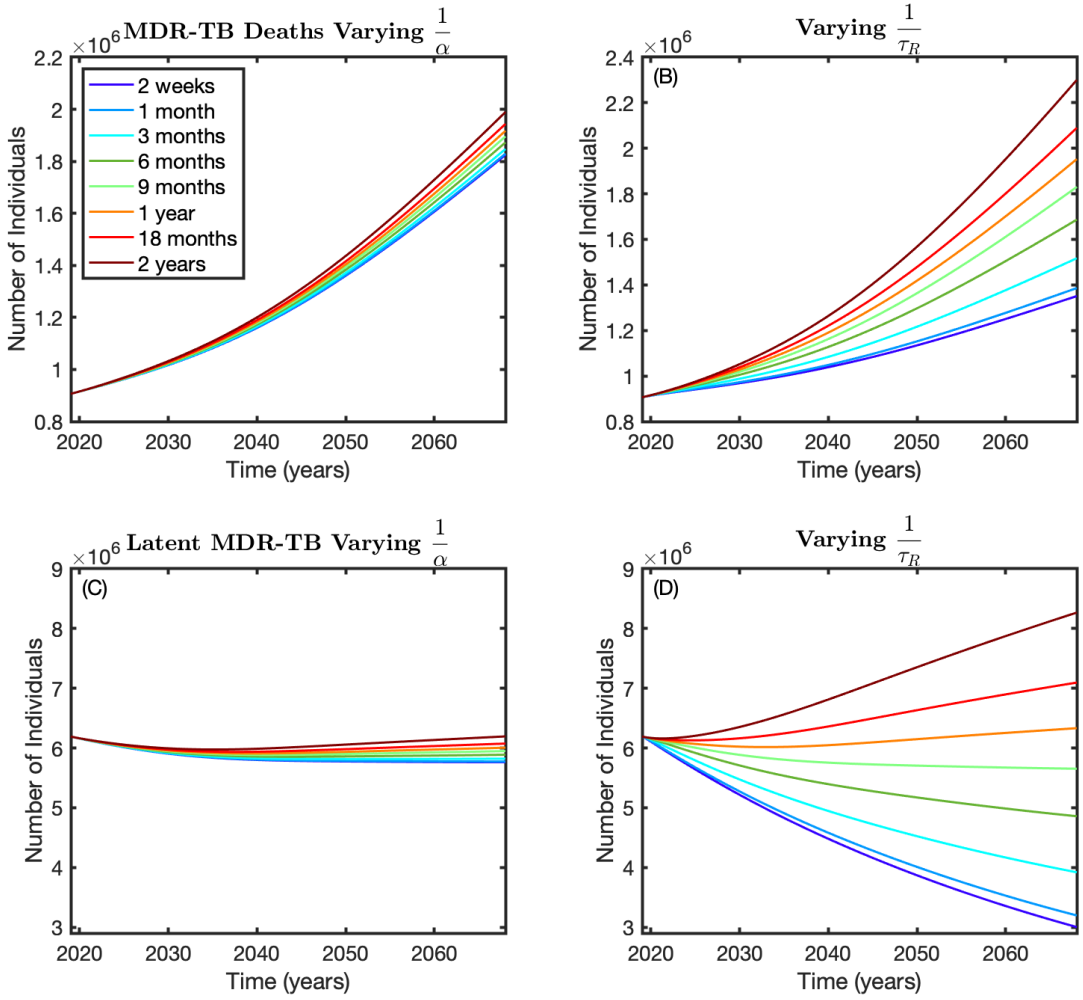

Figure 9: **How Variance in α and τ_R Affect Latent MDR-TB Infections and MDR-TB Related Deaths**
In A and B (top), the effects on MDR-TB related deaths over the simulation based on varying α and τ_R are displayed. The 2068 simulation outcomes of MDR-TB related deaths caused by MDR-TB vary extensively between the different α and τ_R values.
In C and D (bottom), the effects on Latent MDR-TB Infections over the simulation based on varying α and τ_R are displayed. The 2068 simulation outcomes of E_R vary extensively between the different α and τ_R values.

After plotting the effects of variance of α and τ_R in Figure 9 and observing the range of MDR-TB outcomes, a contour plot of $\mathcal{R}_{C_R}$ was created in order to examine the effect of both $\frac{1}{\tau_R}$ and $\frac{1}{\alpha}$ varying over 0 to 2 years on the value of $\mathcal{R}_{C_R}$.

After observing the importance of τ_R on $\mathcal{R}_{C_R}$, a contour plot with $\mathcal{R}_{C_W}$ based on $\frac{1}{\tau_W}$ and $\frac{1}{\gamma_{T_W}}$ was created in order to observe the effect of τ_W on $\mathcal{R}_{C_W}$.

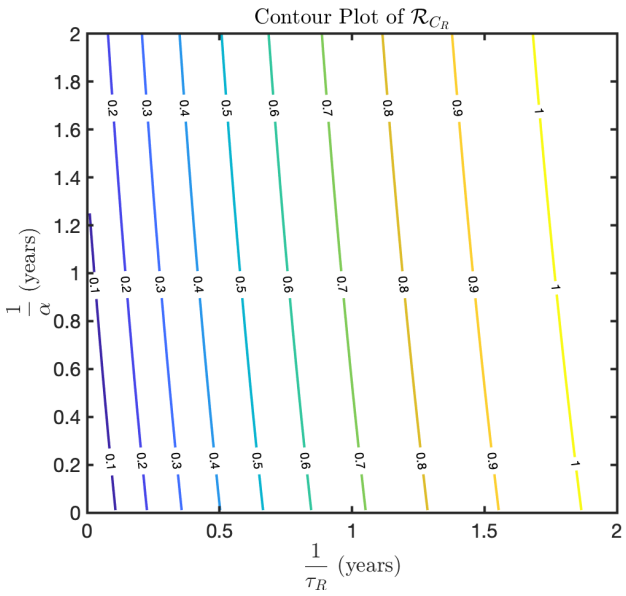

Figure 10: **Contour Plot of $\mathcal{R}_{C_R}$ based on $\frac{1}{\tau_R}$ and $\frac{1}{\alpha}$**

The lines on this plot represent the $\mathcal{R}_{C_R}$ at different values for $\frac{1}{\tau_R}$ and $\frac{1}{\alpha}$. This graph shows that when $\frac{1}{\tau_R}$ goes to 1.5 years, the $\mathcal{R}_{C_R} < 1$.

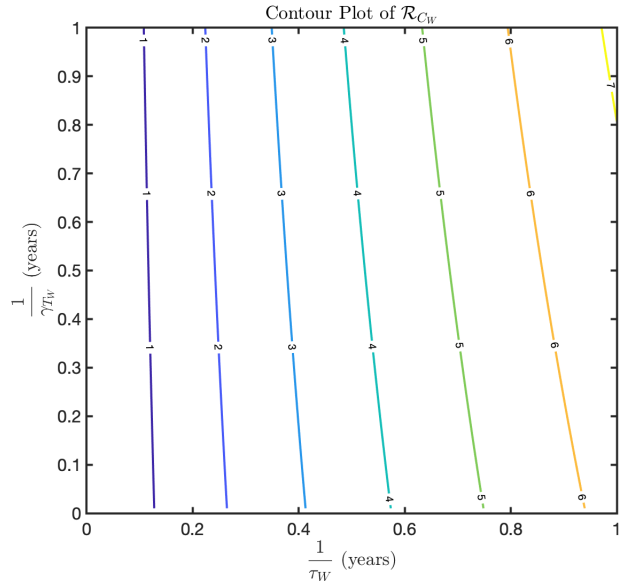

Figure 11: **Contour Plot of $\mathcal{R}_{C_W}$ based on $\frac{1}{\tau_W}$ and $\frac{1}{\gamma_{T_W}}$**

The lines on this plot represent the $\mathcal{R}_{C_W}$ at different values for $\frac{1}{\tau_W}$ and $\frac{1}{\gamma_{T_W}}$. This graph shows that when $\frac{1}{\tau_R}$ goes to 0.1 years, or approximately 1.2 months, the $\mathcal{R}_{C_R} < 1$.

5 Discussion and Conclusions

TB is the leading infectious disease killer in the world [1], and even with the design and implementation of new and advanced treatment regimens, the development of MDR-TB has contributed to India's continued struggle to effectively treat and prevent further transmission of the disease. India has the largest number of TB cases in the world — over a quarter of the global TB and MDR-TB burden [4]. In 2016, 2.79 million people became ill from TB, and 435,000 died from it. India has the greatest number of new cases of MDR-TB, with an estimated 147,000 cases in 2016 [4]. Time delays both in infectious individuals beginning treatment, as well as in individuals infected with MDR-TB receiving appropriate treatment, contribute to the continued suffering due to TB and MDR-TB in India.

Numerous studies have investigated the transmission dynamics of TB and MDR-TB, across the globe and in India, through mathematical modeling. These studies use a variety of modeling methods, from deterministic to Markov, and focus on many different aspects of the disease. The impact of shorter duration treatment regimens [20], individuals in isolation and those lost to follow-up [21], and the acquisition of drug resistance during TB treatment on disease transmission dynamics have been modeled and analyzed [22]. Our study presents a deterministic system of non-linear differential equations representing an 8-compartment SEIS-based model with states accounting for individuals receiving treatment to assess the effects of varied time delays in individuals receiving treatment on future MDR-TB cases and deaths. Parameter values were obtained from relevant literature from India or fitted using a least squares method when necessary due to a lack of available data. The model is shown to have an asymptotically stable DFE when the control reproduction number, $\mathcal{R}_c$, is less than unity. However, this theorem has a notable exception when $\mathcal{R}_{C_R} < 1$, $\mathcal{R}_{C_W} > 1$, and $\phi_{_W} \neq 0$, as displayed in Figures 5A and 5B. Despite not being included in the formula for $\mathcal{R}_{C_R}$, $\phi_{_W}$ has a large role in causing MDR-TB convergence to endemic equilibrium where the DFE would be expected, as shown in Figure 5, and in the fitted and simulated results, as the $\mathcal{R}_{C_R} = .6169$, but the MDR-TB compartments converge to an epidemic equilibrium as seen in Figure 8. In A, (top left), of Figure 5, $\mathcal{R}_{C_R} < 1$ and $\mathcal{R}_{C_W} > 1$, and $E_{_W}$ converges to an endemic equilibrium, and $E_{_R}$ is much lower proportionally, but converges to an endemic equilibrium. In B (top right), the $E_{_R}$ from A is plotted in isolation to demonstrate the convergence to the endemic equilibrium. In C (bottom left), $\phi_{_W} = 0$, $\mathcal{R}_{C_R} < 1$ and $\mathcal{R}_{C_W} > 1$, and $E_{_W}$ converges to an endemic equilibrium, and $E_{_R}$ converges to the DFE. In D (bottom right), the $E_{_R}$ from B is plotted in isolation to demonstrate the convergence to the DFE.

The control reproduction number measures the average amount of new infections that result from a single infection in a population which has treatment available. Additionally, the parameters most sensitive to the control reproduction number were found to be the infection rate of TB, $\beta_{_W}$, the infection rate of MDR-TB, $\beta_{_R}$, the rate at which an individual with MDR-TB develops symptoms, $\sigma_{_R}$, the treatment rate against drug-sensitive TB, $\tau_{_W}$, the treatment rate against MDR-TB, $\tau_{_R}$, and the fraction of individuals who seek TB treatment, l. Finally, the model was numerically simulated. Values for α, the rate of switching from TB to MDR-TB treatment, and $\tau_{_R}$, the treatment rate against MDR-TB, were varied in order to assess their impact on future MDR-TB cases and deaths. From Figure 9A and 9B, when $\frac{1}{\alpha}$ varied 2 weeks to 2 years, the final number of MDR-TB related deaths had a range of 164,700. When $\frac{1}{\tau_{_R}}$ varied 2 weeks to 2 years, the final number of deaths had a range of 949,400. The number of deaths when $\frac{1}{\tau_{_R}}$ was 2 years was 310,800 higher than $\frac{1}{\alpha}$'s value, and when $\frac{1}{\tau_{_R}}$ was 2 weeks, the number of deaths was 473,900 lower than $\frac{1}{\alpha}$'s value at 2 weeks. In Figure 9C and 9D, when $\frac{1}{\alpha}$ varied 2 weeks to 2 years, the final number of latent MDR-TB infections had a range of 432,200. When $\frac{1}{\tau_{_R}}$ varied 2 weeks to 2 years, the final number of latent infections

had a range of 5,266,600. The number of latent infections when $\frac{1}{\tau_R}$ was 2 years was 2,070,000 higher than $\frac{1}{\alpha}$'s value, and when $\frac{1}{\tau_R}$ was 2 weeks, the number of latent infections was 2,760,000 lower than $\frac{1}{\alpha}$'s value at 2 weeks.
The most notable conclusion drawn from these simulations is that τ_R has a greater effect on future MDR-TB incidence and mortality than α. Therefore, rather than focusing on identifying whether an individual has TB or MDR-TB and reducing the time it takes to switch to appropriate treatment when individuals are unknowingly infected with MDR-TB, it is more beneficial for an individual infected with MDR-TB to begin treatment in a timely manner, regardless of whether or not this treatment is appropriate. As India continues its work to stop the spread of TB and MDR-TB, focus should be on administering TB tests and providing test results quickly in order to allow treatment to begin as soon as possible, ideally within 41 days, as that is the value of τ_W which brings $\mathcal{R}_{C_W} < 1$. While our results indicate that it would not have as great of an impact as early treatment initiation, it would also be beneficial to offer more widespread DST, allowing individuals to immediately begin effective treatment.

Several limitations should be considered in interpreting our findings. Our model and results could be improved by the use of parameter values which more accurately reflect the situation of the TB and MDR-TB epidemic in India. Our simulations were based upon publicly available data, which did not include information regarding every value needed. Therefore, while many of the parameter values are assumed based upon expert opinion, others were fit. Despite this, we believe that our estimations and assumptions still adequately capture the dynamics of the TB and MDR-TB epidemic in India. Another aspect of TB and MDR-TB in India which our model does not account for is the recent development and initiation of shorter MDR-TB treatment regimens. Prior to 2018, no one in India is reported to have received short-course MDR-TB treatment. Beginning in 2018, this treatment was offered, and since then, the number of individuals with MDR-TB who receive it has been growing. In 2020, 72% of treated MDR-TB cases in India utilized short-course treatment regimens [27]. Because the majority of the data which we used in this report came from years in which longer treatment regimens were primarily used, we believe that our results still capture the TB and MDR-TB situation in India overall; however, in future studies, taking into account various treatment lengths would allow for more accurate results and predictions.

Our model could be adapted to other countries in order to analyze TB and MDR-TB dynamics across the globe, specifically in developing countries with an increased burden of cases. Further study of TB and MDR-TB dynamics is necessary to better inform public health officials of the most effective ways in which to combat the spread and suffering of TB, leading to the changes needed to truly reduce cases and deaths.

6 Acknowledgements

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Appendices

A Reproduction Number

In order to compute the Basic Reproduction Number we use the next generation matrix method. Then, from the model we obtain the $\mathcal{F}$ and $\mathcal{V}$ matrices.

$$\mathcal{F} = \begin{pmatrix} \frac{\beta_W I_W S}{N} \\ \frac{\beta_R S(I_R + kT_{R_I})}{N} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$\mathcal{V} = \begin{pmatrix} m\beta_R(I_R + kT_{R_I})E_W + \mu E_W + \sigma_W E_W \\ m\beta_R(E_R + kT_{R_I})E_W + \mu E_R + \sigma_R E_R \\ -\sigma_W E_W + \delta_{I_W} I_W + \mu I_W + l\tau_W I_W - (1-r)\phi_W T_W \\ -\sigma_R E_R + \delta_{I_R} I_R + \mu I_R + l\tau_R I_R - r\phi_W T_W - \phi_R T_R \\ -l\tau_W I_W + \gamma_{T_W} T_W + \delta_{T_W} T_W + \mu T_W + \phi_W T_W \\ -l(1-p)\tau_R I_R + \alpha T_{R_I} + \delta_{R_I} T_{R_I} + \mu T_{R_I} \\ -lp\tau_R I_R + \gamma_{T_R} T_R + \delta_{T_R} T_R + \mu T_R + \phi_R T_R - \alpha T_{R_I} \end{pmatrix}$$

Then we obtain the Jacobian of these matrices. We evaluate at the DFE to obtain the F and V matrices shown in mathematical analysis section 6. We then obtain V^{-1} and the next generation matrix, FV^{-1}, which are also shown in the mathematical analysis section.

$$FV^{-1} = \begin{pmatrix} \frac{h\sigma_W}{ad_1cf_1} & 0 & \frac{h}{cd_3+f_1} & 0 & -\frac{\beta_W(r-1)\phi_W}{d_1c+f_1} & 0 & 0 \\ \frac{\sigma_W l\tau_W f_1 g_2 g_3}{ad_1cf_1(d_3d_2d_4+f_2+f_3g_4)} & \frac{\beta_R\sigma_R g_2 g_3}{(\mu+\sigma_R)(d_3d_2d_4+f_2+f_3g_4)} & \frac{l\tau_W f_1 g_2 g_3}{(d_1c+f_1)(d_3d_2d_4+f_2+f_3g_4)} & \frac{\beta_R g_2 g_3}{d_3d_2d_4+f_2+f_3g_4} & \frac{f_1cg_2g_3}{(cg_1+(r-1)l\tau_W\phi_W)(d_3d_4g_2-l\tau_R\phi_R(\alpha+p(\delta_{T_{R_I}}+\mu)))} & \frac{\beta_R kd_2d_4+\beta_R\phi_R(\alpha+kg_4)}{d_3d_2d_4+f_2+f_3g_4} & \frac{\beta_R\phi_R g_3}{d_3d_2d_4+f_2+f_3g_4} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

where,

$$a = \mu+\sigma_W, c = \delta_{I_W}+\mu+\tau_W, d_1 = \gamma_W+\delta_{T_W}+\mu, d_2 = \gamma_R+\delta_{T_R}+\mu, d_3 = \alpha+\delta_{T_{R_I}}+\mu, d_4 = \delta_{I_R}+\mu+\tau_R,$$

$$f_1 = \phi_W(\delta_{I_W}+\mu+r\tau_W), f_2 = \alpha\phi_R(\delta_{I_R}+\mu), f_3 = \phi_R(\delta_{T_{R_I}}+\mu), f_4 = \beta_R\phi_W r, g_1 = d_1+\phi_W g_2 = d_2+\phi_R,$$

$$g_3 = d_3+k\tau_R-kp\tau_R, g_4 = d_4-p\tau_R, h = \beta_W g_1$$

From the next generation matrix, we obtain the following eigenvalues.

$$\lambda_1 = 0$$
$$\lambda_2 = 0$$
$$\lambda_3 = 0$$
$$\lambda_4 = 0$$
$$\lambda_5 = 0$$
$$\lambda_6 = \lambda_W = \frac{\beta_W \sigma_W (\gamma_W + \delta_{T_W} + \mu + \phi_W)}{(\mu + \sigma_W)((\gamma_W + \delta_{T_W} + \mu)(\delta_{I_W} + \mu + l\tau_W) + (\delta_{I_W} + \mu + rl\tau_W)\phi_W)}$$
$$\lambda_7 = \lambda_R = \frac{\beta_R \sigma_R (\gamma_{T_R} + \delta_{T_R} + \mu + \phi_R)(\alpha + \delta_{T_{R_I}} - kl(p-1)\tau_R + \mu)}{(\mu + \sigma_R)(\phi_R(\delta_{I_R} + \mu)(\alpha + \delta_{T_{R_I}} + \mu) + (\alpha + \delta_{T_{R_I}} + \mu)(\gamma_{T_R} + \delta_{T_R} + \mu)(\delta_{I_R} + l\tau_R + \mu) - l(p-1)\tau_R\phi_R(\delta_{T_{R_I}} + \mu))}$$

R_c is determined by the spectral radius, ρ, of FV^{-1}. So we obtain $R_c = \rho(FV^{-1})$, where $\rho = \max(\lambda_W, \lambda_R)$.

B Sensitivity Indices of $\mathcal{R}_c$

The normalized sensitivity index is the ratio of the normalized change of the model's output. The sensitivity index for the R_c of a parameter p is given by:

$$SI_p = \frac{p}{R_c}\frac{\partial R_c}{\partial p}$$

B.0.1 Sensitivity Indices of $\mathcal{R}_{c_W}$

$$SI_{\beta_W} = \frac{\sigma_W(\gamma_{T_W} + \delta_{T_W} + \mu + \phi_W)}{(\mu + \sigma_W)\left\{(\gamma_{T_W} + \delta_{T_W} + \mu)(\delta_{I_W} + l\tau_W + \mu) + \phi_W(\delta_{I_W} + lr\tau_W + \mu)\right\}}$$

$$SI_{\sigma_W} = \frac{\mu}{\mu + \sigma_W}$$
$$SI_{\gamma_{T_W}} = \frac{\gamma_{T_W}(r-1)l\tau_W\phi_W}{(\gamma_{T_W} + \delta_{T_W} + \mu)^2(\delta_{I_W} + \mu + l\tau_W) + \phi_W(\gamma_{T_W} + \delta_{T_W} + \mu)(2\delta_{I_W} + 2\mu + rl\tau_W + \tau_W) + {\phi_W}^2(\delta_{I_W} + \mu + rl\tau_W)}$$
$$SI_{\delta_{T_W}} = \frac{\delta_{T_W}(r-1)l\tau_W\phi_W}{(\gamma_{T_W} + \delta_{T_W} + \mu)^2(\delta_{I_W} + \mu + l\tau_W) + \phi_W(\gamma_{T_W} + \delta_{T_W} + \mu)(2\delta_{I_W} + 2\mu + rl\tau_W + \tau_W) + {\phi_W}^2(\delta_{I_W} + \mu + rl\tau_W)}$$
$$SI_\mu = \mu\left(\frac{1}{\gamma_{T_W} + \delta_{T_W} + \mu + \phi_W} - \frac{1}{\mu + \sigma_W} - \frac{\gamma_{T_W} + \delta_{I_W} + \delta_{T_W} + 2\mu + l\tau_W + \phi_W}{(\gamma_{T_W} + \delta_{T_W} + \mu)(\delta_{I_W} + \mu + l\tau_W) + \phi_W(\delta_{I_W} + \mu + rl\tau_W)}\right)$$
$$SI_{\phi_W} = -\frac{(r-1)l\tau_W\phi_W(\gamma_{T_W} + \delta_{T_W} + \mu)}{(\gamma_{T_W} + \delta_{T_W} + \mu)^2(\delta_{I_W} + \mu + l\tau_W) + \phi_W(\gamma_{T_W} + \delta_{T_W} + \mu)(2\delta_{I_W} + 2\mu + rl\tau_W + \tau_W) + {\phi_W}^2(\delta_{I_W} + \mu + rl\tau_W)}$$
$$SI_{\delta_{I_W}} = -\frac{\delta_{I_W}(\gamma_{T_W} + \delta_{T_W} + \mu + \phi_W)}{(\gamma_{T_W} + \delta_{T_W} + \mu)(\delta_{I_W} + \mu + l\tau_W) + \phi_W(\delta_{I_W} + \mu + r\tau_W)}$$
$$SI_{\tau_W} = -\frac{l\tau_W(\gamma_{T_W} + \delta_{T_W} + \mu + r\phi_W)}{(\gamma_{T_W} + \delta_{T_W} + \mu)(\delta_{I_W} + \mu + l\tau_W) + \phi_W(\delta_{I_W} + \mu + rl\tau_W)}$$
$$SI_r = -\frac{rl\tau_W\phi_W}{(\gamma_{T_W} + \delta_{T_W} + \mu)(\delta_{I_W} + \mu + l\tau_W) + \phi_W(\delta_{I_W} + \mu + rl\tau_W)}$$

B.0.2 Sensitivity Indices of $\mathcal{R}_{c_R}$

$$SI_{\beta_R} = \frac{\sigma_R(\gamma_{T_R} + \delta_{T_R} + \mu + \phi_R)(\alpha + \delta_{T_{R_I}} - kl(p-1)\tau_R + \mu)}{(\mu+\sigma_R)\left\{\phi_R(\delta_{I_R}+\mu)(\alpha+\delta_{T_{R_I}}+\mu) + (\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+l\tau_R+\mu) - l(p-1)\tau_R\phi_R(\delta_{T_{R_I}}+\mu)\right\}}$$

$$SI_{\sigma_R} = \frac{\mu}{\mu+\sigma_R}$$

$$SI_{\alpha} = \frac{\alpha(p-1)l\tau_R\left\{k(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R) - \phi_R(-k(\delta_{I_R}+\mu)+\delta_{T_{R_I}}+\mu)\right\}}{(\alpha+\delta_{T_{R_I}}+kl\tau_R+\mu-kpl\tau_R)((\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R)+\alpha\phi_R(\delta_{I_R}+\mu)+\phi_R(\delta_{T_{R_I}}+\mu)(\delta_{I_R}+\mu-pl\tau_R+l\tau_R))}$$

$$SI_{\delta_{T_{R_I}}} = \frac{\delta_{T_{R_I}}(p-1)l\tau_R\left\{k(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R)+\phi_R(\alpha+k(\delta_{I_R}+\mu-pl\tau_R+l\tau_R))\right\}}{(\alpha+\delta_{T_{R_I}}+kl\tau_R+\mu-kpl\tau_R)\left\{(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R)+\alpha\phi_R(\delta_{I_R}+\mu)+\phi_R(\delta_{T_{R_I}}+\mu)(\delta_{I_R}+\mu-pl\tau_R+l\tau_R)\right\}}$$

$$SI_{\mu} = \mu\left(-\frac{(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_R+\delta_{T_R}+\mu)+(\alpha+\delta_{T_{R_I}}+\mu)(\delta_{I_R}+\mu+\tau_R)+\alpha\phi_R+(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R)+\phi_R(\delta_{T_{R_I}}+\mu)+\phi_R(\delta_{I_R}+\mu-pl\tau_R+l\tau_R)}{(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+\tau_R)+\alpha\phi_R(\delta_{I_R}+\mu)+\phi_R(\delta_{T_{R_I}}+\mu)(\delta_{I_R}+\mu-pl\tau_R+\tau_R)}\right)$$
$$+\mu\left(\frac{1}{\gamma_{T_R}+\delta_{T_R}+\mu+\phi_R}-\frac{1}{\mu+\sigma_R}+\frac{1}{\alpha+\delta_{T_{R_I}}+kl\tau_R+\mu-kpl\tau_R}\right)$$

$$SI_k = \frac{(1-p)kl\tau_R}{\alpha+\delta_{T_{R_I}}+\mu+(1-p)kl\tau_R}$$

$$SI_{\tau_R} = \frac{\beta_{T_R}l\sigma_{I_R}a_R(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu+\phi_R)\left\{(p-1)\phi_R(-k(\delta_{I_R}+\mu)+\delta_{T_{R_I}}+\mu)-(\gamma_{T_R}+\delta_{T_R}+\mu)(\alpha+\delta_{T_{R_I}}+\mu+k(p-1)(\delta_{I_R}+\mu))\right\}}{(\mu+\sigma_R)(\phi_R(\delta_{I_R}+\mu)(\alpha+\delta_{T_{R_I}}+\mu)+(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+l\tau_R+\mu)-l(p-1)\tau_R\phi_R(\delta_{T_{R_I}}+\mu))^2}$$

$$SI_p = \frac{pl\tau_R(\alpha+\delta_{T_{R_I}}+\mu)(\phi_R(-k(\delta_{I_R}+\mu)+\delta_{T_{R_I}}+\mu)-k(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R))}{(\alpha+\delta_{T_{R_I}}+kl\tau_R+\mu-kpl\tau_R)\left\{(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R)+\alpha\phi_R(\delta_{I_R}+\mu)+\phi_R(\delta_{T_{R_I}}+\mu)(\delta_{I_R}+\mu-pl\tau_R+l\tau_R)\right\}}$$

$$SI_{\gamma_{T_R}} = \frac{\gamma_{T_R}l\tau_R\phi_R(\alpha+p(\delta_{T_{R_I}}+\mu))}{(\gamma_{T_R}+\delta_{T_R}+\mu+\phi_R)\left\{(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R)+\alpha\phi_R(\delta_{I_R}+\mu)+\phi_R(\delta_{T_{R_I}}+\mu)(\delta_{I_R}+\mu-pl\tau_R+l\tau_R)\right\}}$$

$$SI_{\delta_{T_R}} = -\frac{\delta_{T_R}\gamma_{T_R}l\tau_R\phi_R(\alpha+p(\delta_{T_{R_I}}+\mu))}{(\gamma_{T_R}+\delta_{T_R}+\mu+\phi_R)\left\{(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R)+\alpha\phi_R(\delta_{I_R}+\mu)+\phi_R(\delta_{T_{R_I}}+\mu)(\delta_{I_R}+\mu-pl\tau_R+l\tau_R)\right\}}$$

$$SI_{\phi_R} = \frac{l\tau_R\phi_R(\gamma_{T_R}+\delta_{T_R}+\mu)(\alpha+p(\delta_{T_{R_I}}+\mu))}{(\gamma_{T_R}+\delta_{T_R}+\mu+\phi_R)\left\{(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R)+\alpha\phi_R(\delta_{I_R}+\mu)+\phi_R(\delta_{T_{R_I}}+\mu)(\delta_{I_R}+\mu-pl\tau_R+l\tau_R)\right\}}$$

$$SI_{\delta_{I_R}} = -\frac{\delta_{I_R}(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu+\phi_R)}{(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+\mu+l\tau_R)+\alpha\phi_R(\delta_{I_R}+\mu)+\phi_R(\delta_{T_{R_I}}+\mu)(\delta_{I_R}+\mu-pl\tau_R+l\tau_R)}$$

$$SI_{I_l} = \frac{\beta_R\sigma_R l\tau_R(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu+\phi_R)((p-1)\phi_R(-k(\delta_{I_R}+\mu)+\delta_{T_{R_I}}+\mu)-(\gamma_{T_R}+\delta_{T_R}+\mu)(\alpha+\delta_{T_{R_I}}+\mu+k(p-1)(\delta_{I_R}+\mu)))}{(\mu+\sigma_R)(\phi_R(\delta_{I_R}+\mu)(\alpha+\delta_{T_{R_I}}+\mu)+(\alpha+\delta_{T_{R_I}}+\mu)(\gamma_{T_R}+\delta_{T_R}+\mu)(\delta_{I_R}+l\tau_R+\mu)-l(p-1)\tau_R\phi_R(\delta_{T_{R_I}}+\mu))^2}$$