An analysis of drug resistant tuberculosis

Louis Nass*, Chinwe Orie, Patrick Brandenburg

Department of Mathematics

Tulane University

New Orleans, LA 70118

December 6, 2020

Abstract

Tuberculosis can be treated and cured with the help of strict antibiotic regiments. However, if one does not fully complete their prescription, the disease can develop a resistance to the treatment. When this happens, individuals can be infected with the resistant form and the disease becomes much harder to fight. Our goal is to develop an infectious disease model that considers both resistant and non-resistant tuberculosis, where the non-resistant strain can develop into the resistant strain if individuals do not complete their medication regiments. We aim to evaluate the effect of the proportion of cases that develop resistance over time.

Key Words: Tuberculosis, drug resistance, mathematical modelling, reproductive number, endemic steady state

*E-mail address: lnass@tulane.edu

Contents

1 Introduction **3**

2 Model **3**

2.1 Model assumptions 3

2.2 Model description 5

2.3 Disease free steady state 8

2.4 Reproductive number 8

2.5 Endemic steady state 10

3 Numerical simulations **11**

4 Conclusion **12**

1 Introduction

Tuberculosis, TB, is an airborne disease that is caused by a bacterial infection that mainly affects the lungs. The disease is spread by inhaling droplets expelled from an infectious individual through sneezes, coughs, and other manners [1]. TB can be treated and cured with a strict regiment of antibiotics.

However, these treatments must be fulfilled to completion to avoid developing resistant strains of TB. If an individual does not complete their prescription of antibiotics, they run the risk of allowing the bacteria to mutate and develop resistance. This is known as acquired resistance [1]. Once the bacteria acquires resistance, they are able to reproduce and mutate further to combat other forms of medication and treatment. This is known as amplified resistance [5]. Finally, the strain is then transmitted and the cycle of resistance continues. This is known as transmitted resistance [1].

TB is especially catastrophic in third-world countries that have limited access to prevention and treatment. In 2019, only 30 countries accounted for 87% of the world's TB cases [3]. What's more, because of the limitations of treatment in various parts of the world, the resistant forms of TB can be extremely difficult to combat and control. To halt resistance, it is essential to ensure full and complete treatments.

This effort, unfortunately, is not always probable or possible. Various factors such as drug prices and availability leave many patients stranded in the battle against TB. Not all people who partially complete treatment will develop the resistant strain, but many will. Our goal should be to lower the proportion of individuals who develop the acquired resistance, before it is amplified and transmitted. Hence, we will utilize an infectious disease model to help analyze this proportion.

2 Model

We will approach the problem of non-resistant and resistant tuberculosis by applying an infectious disease model. This model is made to represent a TB outbreak in a third world country that is receiving external support to control an outbreak. We will consider differential infectivity for the non-resistant strain of TB, and a simple $S - I - R$ model for the resistant strain of TB. However, we first must make a number of assumptions before we begin formally defining our model.

2.1 Model assumptions

We make a number of assumptions in the design of our model in order to simplify the system. We will consider a system of six populations. They are:

- S for individuals who are susceptible to TB infection.
- I_N for individuals who are infected with non-resistant TB that do not pursue treatment.

- I_F for individuals who are infected with non-resistant TB that complete the drug regiment.
- I_P for individuals who are infected with non-resistant TB that partially complete the drug regiment.
- I_R for individuals who are infected with resistant TB.
- R for individuals who have recovered from TB.

To begin, we will assume that there is migration in the system. We will consider an open system, where our individuals are allowed enter or leave. We make this assumption considering third-world countries where people enter and leave the system to aid and assist. However, for simplicity, we will not separate the people entering the system from the natural citizens.

We will also assume random mixing among our individuals. We assume that any infectious person can infect any susceptible person.

We will assume that individuals who are infected with non-resistant TB and fully complete the drug regiment, I_F, will advance to the recovered population, R, with a probability of 1. Contrarily, we assume that individuals who are infected with non-resistant TB and partially complete the drug regiment, I_P, will advance to R with a probability of $P_{I_PR} < 1$. Hence, we observe that individuals in I_P advance to individuals with resistant TB, I_R, with a probability of $P_{I_PI_R} = 1 - P_{I_PR} < 1$. This will be the relationship that we focus our attention the most.

We will assume that death by disease rates only occur for individuals in I_N and I_R. We assume this because treatment or partial treatment will inevitably slow the progression of TB in the non-resistant strains. Not taking any treatment increases the risk of death, but some individuals may recover. Hence members in I_N and I_R may recover or may die from the disease.

We will assume that individuals in the recovered population, R, will be immune to both strains of TB for a period of time, $\hat{\tau}_{Recov}$. Afterwards, they will return to the susceptible population at a rate of $\gamma_{Recov} = 1/\hat{\tau}_{Recov}$.

We denote the number of contacts per year our individuals have in our system as c. For simplicity, we will use a city style model. This means that our number of contacts does not depend on new individuals introduced into the model. Additionally, for simplicity, we will assume that the number of contacts for each population is constant.

Finally, we will assume that there is no latent stage of TB. We do this for simplicity. This will hopefully make the steady states easier to compute and understand. However, this is a major change in the structure of TB models.

Now that we have made our assumptions, we can describe the structure of our model.

2.2 Model description

As mentioned above in our assumptions, we observe that any individual in S can be infected by any individual in I_N, I_F, I_P, and I_R. We observe that there is only migration into our S stage, but there is migration out of all six of our populations.

We use differential infectivity for the non-resistant strain. This means that individuals infected with the non-resistant strain have some probability of going to I_N, I_F, or I_P. Additionally, any infected individual can advance to R. We observe that individuals in I_P can go to I_R, and individuals in I_N and I_R are at risk of dying from the disease.

Individuals in R return to S after some period of time. We observe a block diagram of our model in figure (1).

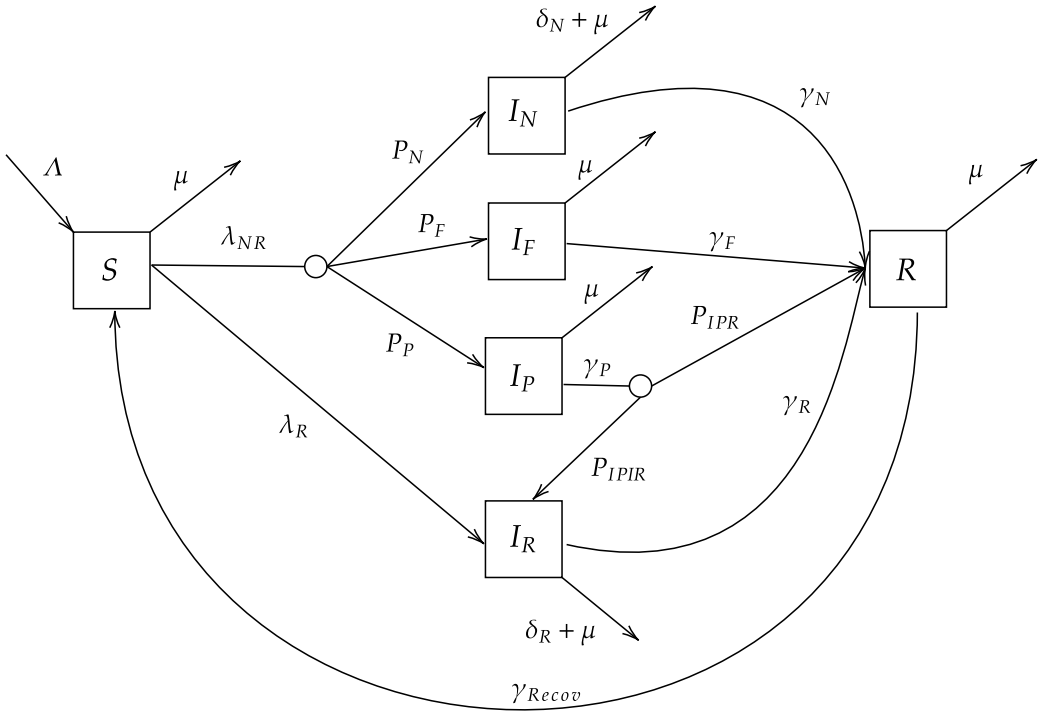

Figure 1: A block diagram of non-resistant and resistant strains of tuberculosis. For simplicity, we remove the latent stages of non-resistant and resistant TB. Additionally, we observe that members in S with the non-resistant strain can go to I_N, I_F, and I_P. Also, I_P can have the disease develop into the resistant strain and migrate into I_R, or can recover and go to R.

Next, we will define the parameters of our system. We let μ be the migration rate in and out of our system. We observe that each population has individuals leaving at a rate μ. Furthermore, S has individuals entering the system at a rate $\Lambda = \mu N(0)$, where $N(0)$ is the initial total population

of our system.

We let δ_N and δ_R be the disease related death rates for non-resistant, non-treatment individuals and resistant individuals respectively.

We let $\hat{\tau}_N$, $\hat{\tau}_F$, $\hat{\tau}_P$, and $\hat{\tau}_R$ be the average number of years it takes for the disease to progress for I_N, I_F, I_P, and I_R respectively. We then let $\gamma_\# = 1/\hat{\tau}_\#$ be the leaving rates from our infectious populations, where $\# = N, F, P, R$ for each population. Because treating the disease will speed up the recovery, we observe that $\hat{\tau}_F < \hat{\tau}_P < \hat{\tau}_N$. Hence, we observe that $\gamma_N < \gamma_P < \gamma_F$. For simplicity, we will assume that $\hat{\tau}_N = \hat{\tau}_R$, and therefore $\gamma_N = \gamma_R$. Similarly, we let $\hat{\tau}_{Recov}$ be the number of years a recovered person is not susceptible to TB, and $\gamma_{Recov} = 1/\hat{\tau}_{Recov}$.

Next, we let P_N, P_F, and P_P be the probabilities that a person with non-resistant TB goes to I_N, I_F, and I_P respectively. We will observe that $P_N + P_F + P_P = 1$. We also let $P_{I_P R}$ and $P_{I_P I_R}$ be the probabilities that individuals in I_P advance to R and I_R respectively.

Finally, we need to discuss the force from infection and the force of infection. The force from infection is defined as the expected number of new infections per infected person, per year [4]. We denote the force from infection using $\alpha_\#$, and observe that

$$\begin{aligned} \alpha_\# &= \begin{pmatrix}\text{Number of}\\ \text{contacts}\\ \text{per year}\end{pmatrix}\begin{pmatrix}\text{Probability of infection}\\ \text{per contact}\\ \text{from population } I_\#\end{pmatrix}\begin{pmatrix}\text{Probability an}\\ \text{individual is}\\ \text{susceptible}\end{pmatrix} \\ &= \quad c \qquad\qquad\qquad \beta_\# \qquad\qquad\qquad P_S \end{aligned} \tag{1}$$

where c is the number of contacts per year, $\beta_\#$ is the probability of infection per contact where $\# = N, F, P, R$ corresponds to the infectious populations I_N, I_F, I_P, and I_R respectively, and P_S is the probability a contact is susceptible. We denote this as $P_S = S/N$, where $N = S + I_N + I_F + I_P + I_R + R$ is the total population. We observe that P_S is dependent on time, since both S and N are dependent on time. Hence, $\alpha_\#$ is also time dependent. Hence, we can define our system of differential equations, using the forces from infection, as

$$\frac{dS}{dt} = \Lambda + \gamma_{Recov} R - (\alpha_N I_N + \alpha_F I_F + \alpha_P I_P + \alpha_R I_R) - \mu S \tag{2a}$$

$$\frac{dI_N}{dt} = P_N(\alpha_N I_N + \alpha_F I_F + \alpha_P I_P) - (\gamma_N + \delta_N + \mu) I_N \tag{2b}$$

$$\frac{dI_F}{dt} = P_F(\alpha_N I_N + \alpha_F I_F + \alpha_P I_P) - (\gamma_F + \mu) I_F \tag{2c}$$

$$\frac{dI_P}{dt} = P_P(\alpha_N I_N + \alpha_F I_F + \alpha_P I_P) - (\gamma_P + \mu) I_P \tag{2d}$$

$$\frac{dI_R}{dt} = \alpha_R I_R + P_{I_P I_R} \gamma_P I_P - (\gamma_R + \delta_R + \mu) I_R \tag{2e}$$

$$\frac{dR}{dt} = \gamma_N I_N + \gamma_F I_F + P_{I_P R} \gamma_P I_P + \gamma_R I_R - (\gamma_{Recov} + \mu) R \ . \tag{2f}$$

Next, we consider the force of infection. The force of infection is defined as the rate at which the susceptible population becomes infectious [2]. We denote the force of infection for the non-resistant strain of TB as λ_{NR}, and observe that

$$\begin{aligned}\lambda_{NR} &= \begin{pmatrix}\text{Number of}\\ \text{contacts}\\ \text{per year}\end{pmatrix} \sum_{\#} \left[\begin{pmatrix}\text{Probability of infection}\\ \text{per contact}\\ \text{from population } I_{\#}\end{pmatrix} \begin{pmatrix}\text{Probability an}\\ \text{individual is}\\ \text{in } I_{\#}\end{pmatrix} \right] \\ &= \quad c \quad \sum_{\#} \left[\quad \beta_{\#} \quad P_{I_{\#}} \quad \right] \end{aligned} \tag{3}$$

where $P_{I_\#}$ is the probability an infected individual has the non-resistant strain, $I_\#$ for $\# = N, F, P$, and is denoted as $P_{I_\#} = I_\#/N$. We also observe the force of infection of the resistant strain, λ_R, to be

$$\begin{aligned}\lambda_R &= \begin{pmatrix}\text{Number of}\\ \text{contacts}\\ \text{per year}\end{pmatrix} \begin{pmatrix}\text{Probability of infection}\\ \text{per contact}\\ \text{from population } I_R\end{pmatrix} \begin{pmatrix}\text{Probability an}\\ \text{individual is}\\ \text{in } I_R\end{pmatrix} \\ &= \quad c \quad \beta_R \quad P_{I_R} \end{aligned} \tag{4}$$

where $P_{I_R} = I_R/N$ is the probability a contact has the resistant strain of TB. Similar to the force from infection, we observe that the forces of infection, λ_{NR} and λ_R, are also time dependent. We can also define our system of differential equations using the forces of infection as

$$\frac{dS}{dt} = \Lambda + \gamma_{Recov} R - (\lambda_{NR} + \lambda_R + \mu) S \tag{5a}$$

$$\frac{dI_N}{dt} = P_N \lambda_{NR} S - (\gamma_N + \delta_N + \mu) I_N \tag{5b}$$

$$\frac{dI_F}{dt} = P_F \lambda_{NR} S - (\gamma_F + \mu) I_F \tag{5c}$$

$$\frac{dI_P}{dt} = P_P \lambda_{NR} S - (\gamma_P + \mu) I_P \tag{5d}$$

$$\frac{dI_R}{dt} = \lambda_R S + P_{I_P I_R} \gamma_P I_P - (\gamma_R + \delta_R + \mu) I_R \tag{5e}$$

$$\frac{dR}{dt} = \gamma_N I_N + \gamma_F I_F + P_{I_P R} \gamma_P I_P + \gamma_R I_R - (\gamma_{Recov} + \mu) R \; . \tag{5f}$$

Additionally, we use diagnostic equations to help us further understand the behavior of our system. We consider dN/dt and dT/dt, which are the change in the total population and the total

of new infections per year respectively. We observe that

$$\begin{aligned}\frac{dN}{dt} &= \frac{dS}{dt} + \frac{dI_N}{dt} + \frac{dI_F}{dt} + \frac{dI_P}{dt} + \frac{dI_R}{dt} + \frac{dR}{dt} \\ &= \Lambda - \mu N - \delta_N I_N - \delta_R I_R \qquad (6a)\\ \frac{dT}{dt} &= \alpha_N I_N + \alpha_F I_F + \alpha_P I_P + \alpha_R I_R, \text{ using the force from infection} \qquad (6b)\\ &= \lambda_{NR} S + \lambda_R S, \text{ using the force of infection .} \qquad (6c)\end{aligned}$$

In order to solve for our system, we must include our initial populations $S(0)$, $I_N(0)$, $I_F(0)$, $I_P(0)$, $I_R(0)$, $R(0)$, $N(0) = S(0) + I_N(0) + I_F(0) + I_P(0) + I_R(0) + R(0)$, and $T(0) = I_N(0) + I_F(0) + I_P(0) + I_R(0)$.

A full list of the parameters, and the associated values of the parameters used in our numerical simulation, is found in table (1). Now that we have defined our system, we can analyze the disease free steady state.

2.3 Disease free steady state

The disease free steady state occurs when all of our infected and recovered populations (I_N, I_F, I_P, I_R, R) and our systems of equations observed above are equal to 0. If we apply these conditions to the system of equations seen in equation (2), then for $S^{DFSS} \neq 0$ being the susceptible population at the disease free steady state, we are left with

$$\begin{aligned}0 = \frac{dS^{DFSS}}{dt} &= \Lambda - \mu S^{DFSS} \\ &\Rightarrow \\ S^{DFSS} &= \frac{\mu N(0)}{\mu} \\ &= N(0) \ . \qquad (7)\end{aligned}$$

Hence, we observe the disease free steady state where our susceptible population, S^{DFSS}, is equal to our initial population $N(0)$. Now that we have our disease free steady state, we can now solve for the reproductive number.

2.4 Reproductive number

The reproductive number is a dimensionless value that indicates the stability of the system. There are two forms of the reproductive number that we will analyze, the basic reproductive number, $\mathcal{R}_0$, and the effective reproductive number, $\mathcal{R}_e$. The basic reproductive number, $\mathcal{R}_0$, represents the number of expected new infections generated by one infection in an entirely susceptible population. The effective reproductive number, $\mathcal{R}_e$, is the expected new infections generated by one infection

in a partially susceptible population at time t [4]. We recognize if the reproductive number is less than 1 then disease will die out, if it is equal to 1 then we achieve equilibrium, and if it is greater than 1 then the disease grows without bound.

To compute the reproductive number, we will use the next generation matrix method [4]. We do this by first defining $\mathbf{X}$ as a vector of our infectious populations, $\mathbf{X} = [I_N, I_F, I_P, I_R]^T$. We then redefine our system of equations for the infectious states as

$$\frac{d\mathbf{X}}{dt} = F(\mathbf{X}) - V(\mathbf{X})$$

where $F(\mathbf{X})$ represents the new infections and $V(\mathbf{X})$ represents the disease progression. In our system, using the force from infection system in equation (2), we observe that,

$$F(\mathbf{X}) = \begin{pmatrix} P_N(\alpha_N I_N + \alpha_F I_F + \alpha_P I_P) \\ P_F(\alpha_N I_N + \alpha_F I_F + \alpha_P I_P) \\ P_P(\alpha_N I_N + \alpha_F I_F + \alpha_P I_P) \\ \alpha_R I_R \end{pmatrix} \tag{8}$$

$$V(\mathbf{X}) = \begin{pmatrix} (\gamma_N + \delta_N + \mu) I_N \\ (\gamma_F + \mu) I_F \\ (\gamma_P + \mu) I_P \\ -P_{I_P I_R} \gamma_P I_P + (\gamma_R + \delta_R + \mu) I_R \end{pmatrix} . \tag{9}$$

We next calculate the Jacobian matrices of F and V, and evaluate the matrices at the disease free steady state. From the previous section, we observe that at the disease free steady state $S = N$. Therefore $P_S = S/N = 1$. Hence, at the disease free steady state,

$$\alpha_N = c\beta_N \tag{10}$$

$$\alpha_F = c\beta_F \tag{11}$$

$$\alpha_P = c\beta_P \tag{12}$$

$$\alpha_R = c\beta_R \, . \tag{13}$$

Hence, we observe the Jacobian matrices at the disease free steady states to be

$$J_F = \begin{pmatrix} P_N c\beta_N & P_N c\beta_F & P_N c\beta_P & 0 \\ P_F c\beta_N & P_F c\beta_F & P_F c\beta_P & 0 \\ P_P c\beta_N & P_P c\beta_F & P_P c\beta_P & 0 \\ 0 & 0 & 0 & c\beta_R \end{pmatrix} \tag{14}$$

$$J_V = \begin{pmatrix} \gamma_N + \delta_N + \mu & 0 & 0 & 0 \\ 0 & \gamma_F + \mu & 0 & 0 \\ 0 & 0 & \gamma_P + \mu & 0 \\ 0 & 0 & -P_{I_P I_R}\gamma_P & \gamma_R + \delta_R + \mu \end{pmatrix} . \tag{15}$$

We then define the next generation matrix to be $NGM = J_F J_V^{-1}$. Then, the basic reproductive number is equal to the maximum singular value of the next generation matrix. We observe that

$$\begin{aligned}
NGM &= J_F J_V^{-1} \\
&= \begin{pmatrix} P_N c\beta_N & P_N c\beta_F & P_N c\beta_P & 0 \\ P_F c\beta_N & P_F c\beta_F & P_F c\beta_P & 0 \\ P_P c\beta_N & P_P c\beta_F & P_P c\beta_P & 0 \\ 0 & 0 & 0 & c\beta_R \end{pmatrix} \begin{pmatrix} \frac{1}{\gamma_N+\delta_N+\mu} & 0 & 0 & 0 \\ 0 & \frac{1}{\gamma_F+\mu} & 0 & 0 \\ 0 & 0 & \frac{1}{\gamma_P+\mu} & 0 \\ 0 & 0 & \frac{P_{I_P I_R}\gamma_P}{\gamma_R+\delta_R+\mu} & \frac{1}{\gamma_R+\delta_R+\mu} \end{pmatrix} \\
&= \begin{pmatrix} \frac{P_N c\beta_N}{\gamma_N+\delta_N+\mu} & \frac{P_N c\beta_F}{\gamma_F+\mu} & \frac{P_N c\beta_P}{\gamma_P+\mu} & 0 \\ \frac{P_F c\beta_N}{\gamma_N+\delta_N+\mu} & \frac{P_F c\beta_F}{\gamma_F+\mu} & \frac{P_F c\beta_P}{\gamma_P+\mu} & 0 \\ \frac{P_P c\beta_N}{\gamma_N+\delta_N+\mu} & \frac{P_P c\beta_F}{\gamma_F+\mu} & \frac{P_P c\beta_P}{\gamma_P+\mu} & 0 \\ 0 & 0 & \frac{c\beta_R P_{I_P I_R}\gamma_P}{\gamma_R+\delta_R+\mu} & \frac{c\beta_R}{\gamma_R+\delta_R+\mu} \end{pmatrix} .
\end{aligned} \tag{16}$$

Next, we solve for the singular values by computing the eigenvalues of NGM. Here, let $\hat{\lambda}$ be the eigenvalues of NGM. Observe that

$$\begin{aligned}
0 &= \det|NGM - \hat{\lambda} I| \\
&= \hat{\lambda}^2 \left(\frac{c\beta_R}{\gamma_R+\delta_R+\mu} - \hat{\lambda} \right) \left(\frac{P_N c\beta_N}{\gamma_N+\delta_N+\mu} + \frac{P_F c\beta_F}{\gamma_F+\mu} + \frac{P_P c\beta_P}{\gamma_P+\mu} - \hat{\lambda} \right) \\
&\Rightarrow \\
\hat{\lambda} &= \frac{c\beta_R}{\gamma_R+\delta_R+\mu}, \quad \frac{P_N c\beta_N}{\gamma_N+\delta_N+\mu} + \frac{P_F c\beta_F}{\gamma_F+\mu} + \frac{P_P c\beta_P}{\gamma_P+\mu}, \quad 0 .
\end{aligned} \tag{17}$$

Hence, we observe that

$$\mathcal{R}_0 = \max\left\{ \frac{c\beta_R}{\gamma_R+\delta_R+\mu}, \frac{P_N c\beta_N}{\gamma_N+\delta_N+\mu} + \frac{P_F c\beta_F}{\gamma_F+\mu} + \frac{P_P c\beta_P}{\gamma_P+\mu} \right\} . \tag{18}$$

Then, if $P_S \neq 1$, we observe that

$$\mathcal{R}_e = \max\left\{ \frac{\alpha_R}{\gamma_R+\delta_R+\mu}, \frac{P_N \alpha_N}{\gamma_N+\delta_N+\mu} + \frac{P_F \alpha_F}{\gamma_F+\mu} + \frac{P_P \alpha_P}{\gamma_P+\mu} \right\} . \tag{19}$$

Now that we have our reproductive number, we can analyze the endemic steady state of our system.

2.5 Endemic steady state

The endemic steady state is an state of equilibrium for our system of differential equations that is not equal to the null case (i.e. where all our populations are 0) [4]. We observe the endemic steady state when the reproductive number equals 1. To solve for the endemic steady state, we set our system of equations equal to 0, and solve the system where the populations are not equal to 0.

We will use $*$ to indicate the population at the endemic steady state. When we evaluate the endemic steady state, we yield

$$S^* = \frac{\gamma_{Recov} R^* + \mu N(0)}{\lambda^*_{NR} + \lambda^*_R + \mu} \tag{20a}$$

$$I^*_N = \frac{P_N(\alpha^*_F I^*_F + \alpha^*_P I^*_P)}{\gamma_N + \delta_N + \mu - P_N \alpha^*_N} \tag{20b}$$

$$I^*_F = \frac{P_F(\alpha^*_N I^*_N + \alpha^*_P I^*_P)}{\gamma_F + \mu - P_F \alpha^*_F} \tag{20c}$$

$$I^*_P = \frac{P_P(\alpha^*_N I^*_N + \alpha^*_F I^*_F)}{\gamma_P + \mu - P_P \alpha^*_P} \tag{20d}$$

$$I^*_R = \frac{P_{I_P I_R} \gamma_P I^*_P}{\gamma_R + \delta_R + \mu - \alpha^*_R} \tag{20e}$$

$$R^* = \frac{\gamma_N I^*_N + \gamma_F I^*_F + P_{I_P R} \gamma_P I^*_P + \gamma_R I^*_R}{\gamma_{Recov} + \mu} \tag{20f}$$

$$N^* = N(0) - \frac{\delta_N I^*_N + \delta_R I^*_R}{\mu} \, . \tag{20g}$$

Although our findings are too complicated to solve analytically, there some takeaways that we can make from our partially solved endemic steady state. First, we observe that the effective reproductive number must be

$$\mathcal{R}_e = \frac{P_N \alpha_N}{\gamma_N + \delta_N + \mu} + \frac{P_F \alpha_F}{\gamma_F + \mu} + \frac{P_P \alpha_P}{\gamma_P + \mu} = 1$$

since, if $\frac{\alpha_R}{\gamma_R + \delta_R + \mu} = 1$, then we observe that equation (20e) would be unstable. Hence, $\frac{\alpha_R}{\gamma_R + \delta_R + \mu} < 1$, and $\mathcal{R}_e = \frac{P_N \alpha_N}{\gamma_N + \delta_N + \mu} + \frac{P_F \alpha_F}{\gamma_F + \mu} + \frac{P_P \alpha_P}{\gamma_P + \mu} = 1$.

Additionally, if we refer again to equation (20e), we observe that the value $P_{I_P I_R}$ directly relates and is positively proportional to I^*_R. The value $P_{I_P I_R} = 1 - P_{I_P R}$ is also negatively proportional to R^*.

Now that we have analyzed our system, we can run numerical simulations.

3 Numerical simulations

We will use *MatLab* to numerically solve our system. We use the numerical ODE solver *ode45()* in *MatLab*.

In our simulations, we aim to observe the effect of changing the probability of allowing non-resistant TB to develop into resistant TB. We will consider a system with 1000 people over a two year period. We will start with 900 susceptible individuals and 100 infected individuals. A full list of the parameters and specific values for each parameter is featured in table (1).

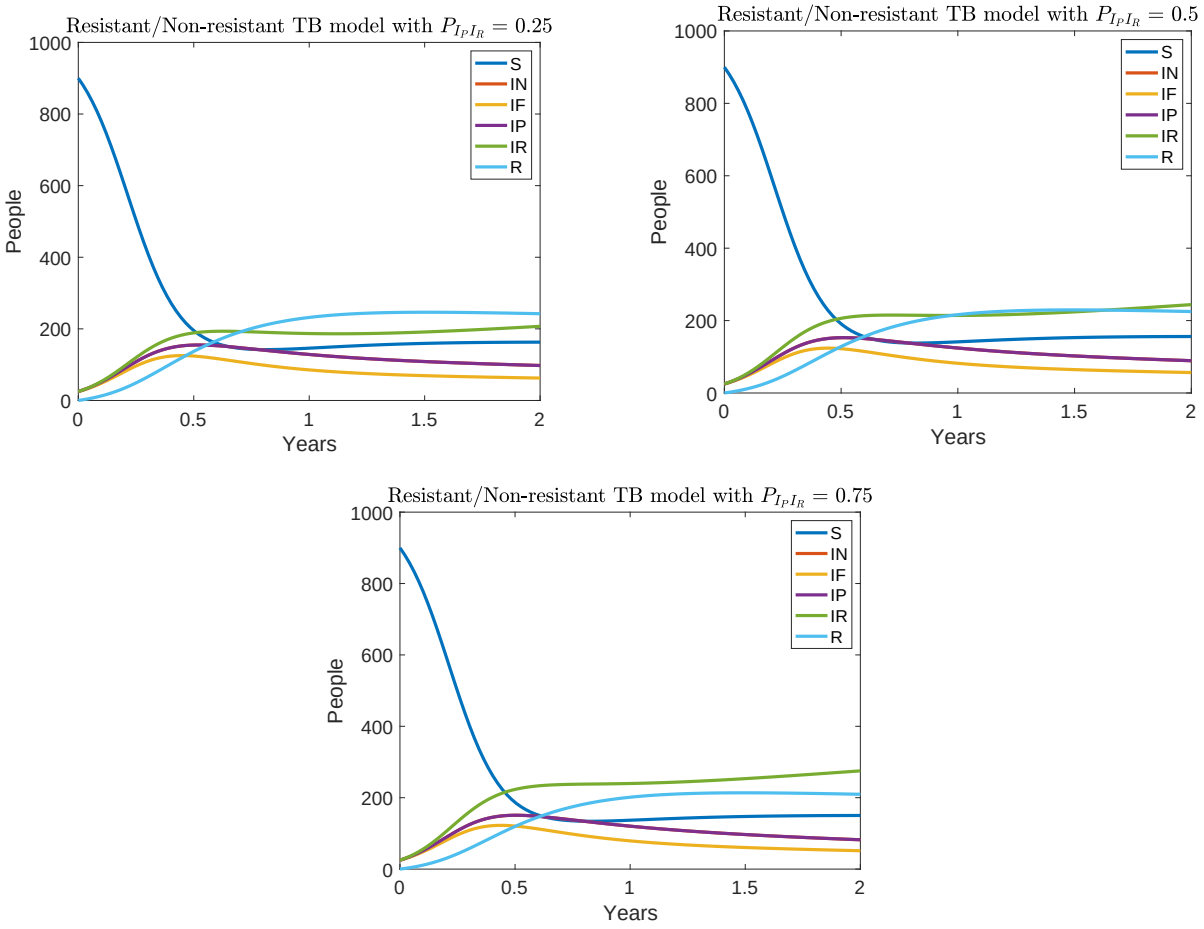

Figure 2: Populations from our system of equations where we vary the probability of allowing non-resistant TB to develop into resistant TB. We observe that as the probability of allowing TB to become resistant increases, the long term steady state of I_R increases as well.

We observe the results of our numerical simulations in figure (2). We see that as $P_{I_P I_R}$ increases, then the long term steady state of I_R increases. This is consistent with our endemic equilibrium findings.

Additionally, we observe that as $P_{I_P I_R}$ increases, the long term steady state of R slightly decreases. Again, this is consistent with our result from the endemic equilibrium.

4 Conclusion

We observe that the proportion of individuals that develop acquired resistance is directly related to the long term stability of tuberculosis. We observed, analytically, that this value directly influences the endemic steady state of both our I_R and R populations. From our numerical simulations, we

qualitatively observe that as this proportion increases, the steady state of I_R increases and the steady state of R decreases. Hence, we recognize the importance of fully treating the non-resistant form TB in order to control and contain a potential resistant form.

However, there are a few problems with our model. For simplicity, we removed the latent stage of TB in order to make some of the calculations of the endemic steady state easier. As a result, we are missing 2 major stages in the construction of our model, non-resistant latent, L_{NR}, and resistant latent, L_R. Furthermore, since we are considering a third-world country receiving external aid, we should separate the populations into natural citizens and foreign help. This will more accurately represent the population that we aim to model.

Despite the shortcomings, this model can be utilized as a basis to further model the effects of tuberculosis. Additionally, our model provides us with some insight on the importance of full treatment of bacterial diseases. Famous physician and expert in antimicrobial research Paul Ehrlich states that treatment of infections should "hit hard and early" in order to reduce the likelihood of developing resistant strains [5]. This advice serves us well not only for tuberculosis, but for any treatable infectious disease.

References

[1] Sally M. Blower and Tom Chou. Modeling the emergence of 'hot zones': tuberculosis and the amplification dynamics of drug resistance. *Natrue Medicine*, 10, 2004.

[2] Wikipedia contributors. Force of infection — Wikipedia, the free encyclopedia, 2020. Online; accessed 2020-12-1.

[3] World Health Organization Contributors. Tuberculosis, Dec 2020. Online; accessed 2020-12-2.

[4] James Hyman and et al. An introduction to using mathematical models for understanding infectious disease transmission. *Tulane Math Archive*, 1, 2020.

[5] Marc Lipsitch and Matthew H. Samore. Antimicrobial use and antimicrobial resistance: a population perspective. *Emerging Infectious Diseases*, 8, 2002.

[6] Marylin Ronoh, Rym Jaroudi, Patrick Fotso, and Victor Kamdoum. A mathematical model of tuberculosis with drug resistance effects. *Scientific Research Publishing*, 1, 2016.

Parameter	*Description*	*Dimensions*	*Value*	*Reference*
	Variables			
$S(t)$	Susceptible population	people		
$I_N(t)$	Infected population with non-resistant TB, no treatment	people		
$I_F(t)$	Infected population with non-resistant TB, full treatment	people		
$I_P(t)$	Infected population with non-resistant TB, partial treatment	people		
$I_R(t)$	Infected population with resistant TB	people		
	Independent parameters			
$S(0)$	Initial susceptible population	people	900	
$I_N(0)$	Initial infected population with non-resistant TB, no treatment	people	25	
$I_F(0)$	Initial infected population with non-resistant TB, full treatment	people	25	
$I_P(0)$	Initial infected population with non-resistant TB, partial treatment	people	25	
$I_R(0)$	Initial infected population with resistant TB	people	25	
$R(0)$	Initial recovered population	people	0	
c	Average number of contacts per year	contacts years^{-1}	10	
β_N	Probability of infection of non-resistant, no treatment TB per contact	contacts^{-1}	0.22	[6]
β_F	Probability of infection of non-resistant, full treatment TB per contact	contacts^{-1}	0.22	[6]
β_P	Probability of infection of non-resistant, partial treatment TB per contact	contacts^{-1}	0.22	[6]
β_R	Probability of infection of resistant TB per contact	contacts^{-1}	0.22	[6]
$\hat{\tau}_N$	Average number of years non-resistant TB develops without treatment	years	2	[6]
$\hat{\tau}_F$	Average number of years non-resistant TB develops with full treatment	years	0.5	[6]
$\hat{\tau}_P$	Average number of years non-resistant TB develops with partial treatment	years	1	[6]
$\hat{\tau}_R$	Average number of years resistant TB develops	years	2	[6]
$\hat{\tau}_{Recov}$	Average number of years a recovered person is immune to TB	years	2	[6]
δ_N	Death rate of non-resistant TB	years^{-1}	0.01	[6]
δ_R	Death rate of resistant TB	years^{-1}	0.01	[6]
P_N	Probability an infectious person with non-resistant TB does not receive treatment	dimensionless	1/3	survey
P_F	Probability an infectious person with non-resistant TB does receive full treatment	dimensionless	1/3	survey
P_F	Probability an infectious person with non-resistant TB does receive partial treatment	dimensionless	1/3	survey
$P_{I_P I_R}$	Probability an individual with partial treatment of non-resistant TB develops to resistant TB	dimensionless	0.25, 0.5, 0.75	
$P_{I_P R}$	Probability an individual with partial treatment of non-resistant TB recovers	dimensionless	0.75, 0.5, 0.25	
μ	Migration rate	years^{-1}	1	
	Dependent parameters			
$N(t)$	Total population in the system = $S(t) + I_N(t) + I_F(t) + I_P(t) + I_R(t) + R(t)$	people		
$N(0)$	Initial total population = $S(0) + I_N(0) + I_F(0) + I_P(0) + I_R(0) + R(0)$	people	1000	
$T(t)$	Cumulative sum of infectious people	people		
Λ	Incoming migration rate = $\mu N(0)$	people years^{-1}	1000	
γ_N	Rate at which individuals leave $I_N = 1/\hat{\tau}_N$	years^{-1}	0.5	
γ_F	Rate at which individuals leave $I_F = 1/\hat{\tau}_F$	years^{-1}	2	
γ_P	Rate at which individuals leave $I_P = 1/\hat{\tau}_P$	years^{-1}	1	
γ_R	Rate at which individuals leave $I_R = 1/\hat{\tau}_R$	years^{-1}	0.5	
γ_{Recov}	Rate at which individuals leave $R = 1/\hat{\tau}_{Recov}$	years^{-1}	0.5	
P_S	Probability a contact is in $S = S/N$	dimensionless		
P_{I_N}	Probability a contact is in $I_N = I_N/N$	dimensionless		
P_{I_F}	Probability a contact is in $I_F = I_F/N$	dimensionless		
P_{I_P}	Probability a contact is in $I_P = I_P/N$	dimensionless		
P_{I_R}	Probability a contact is in $I_R = I_R/N$	dimensionless		
α_N	Force from infection of non-resistant, no treatment TB = $c\beta_N P_S$	years^{-1}		
α_F	Force from infection of non-resistant, full treatment TB = $c\beta_F P_S$	years^{-1}		
α_P	Force from infection of non-resistant, partial treatment TB = $c\beta_P P_S$	years^{-1}		
α_R	Force from infection of resistant TB = $c\beta_R P_S$	years^{-1}		
λ_{NR}	Force of infection of non-resistant TB = $c(\beta_N P_{I_N} + \beta_F P_{I_F} + \beta_P P_{I_P})$	years^{-1}		
λ_R	Force of infection of resistant TB = $c\beta_R P_{I_R}$	years^{-1}		

Table 1: Table of parameters used in the non-resistant/resistant TB model