A MATHEMATICAL MODEL OF COMBINED PRE-EXPOSURE, POST-EXPOSURE VACCINES AND TREATMENT OF TUBERCULOSIS

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Abstract

Due to high prevalence of tuberculosis (TB) in developing countries where HIV prevalence is also high, developing effective TB vaccines that will prevent infection and reactivation of latent infection is a high priority. This is because patients infected with HIV are at increased risk of developing active TB because of the high rate of reactivation of latent infection and high degree of susceptibility to new infection. Three mathematical models with TB vaccines were used to predict the most effective epidemic-control strategy in reducing active TB cases. The first model is with pre-exposure TB vaccines and treatment of TB, the second with post-exposure vaccines and treatment of TB, and the last one with both vaccines and treatment of TB. The comparison of effectiveness was based on the reproduction rates and numerical analysis using the forward fourth order Runge-Kutta scheme. The combined strategy was found to be the most effective as an epidemic-control strategy.

Declaration

No portion of the work in this thesis has been submitted for another degree or qualification of this or any other university or another institution of learning.

DEDICATION

It is a very special dedication to you my lovely son, Busizizwe 'Zie' Emmanuel Malaza. It was two years spent away from you whilst you were very young. May the good Lord richly bless you and give you many more.

'Astalavista baby'

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Chapter 1

Introduction

1.1 Epidemiology

Epidemiology may be defined as the study of the distribution and determinants of disease in human populations. The purpose for which epidemiological investigations are carried out may be considered under the following headings, although a single investigation may serve more than one purpose.

1. Provision of data necessary for planning and evaluating health care.
2. Identification of determinants of disease so as to enable prevention.
3. Evaluation of methods used to control disease.
4. Description of the natural history of disease.
5. Classification of disease.

Mathematical epidemiology involves spatial modelling, (the application of methods on observed spatial data which would be a point, a line polygon or continuous representing some process operating in space), statistical modelling, micro

simulation modelling, (computer based data) and the application of differential equations in these studies.

There are four basic types of epidemiological studies, namely descriptive, analytic, intervention and evaluation studies. Descriptive studies are used to demonstrate the patterns in which diseases are distributed in populations. Analytic studies are planned investigations designed to test specific hypothesis. They aim to define the causes or determinants of disease more precisely than is possible using descriptive studies alone. Intervention studies are essentially experiments designed to measure the efficiency and safety of particular types of health care intervention (e.g treatment, prevention, control and the way in which health care is provided), and evaluation studies attempts to measure the effectiveness of different health services and programmes. They answer the very important questions, like 'have there been any improvement in health status?'

1.2 Basic facts about tuberculosis

Tuberculosis (TB) remains one of the leading causes of illness and death in the world. It is a bacterial infectious disease caused by Mycobacterium tuberculosis (and occasionally by Mycobacterium bovis and Mycobacterium africunum). These are also called tubercle bacilli. One third of the world's population is estimated to be infected with the bacilli [18].

According to [12], tubercle bacilli can remain dormant in the tissues and persist for many years. General sources of information on TB dynamics suggest that TB is hard to transmit. Nonetheless, under the right conditions a single person with active TB can infect many people.

[8] states that transmission occurs by the airborne spread of infectious droplets. The source is a person with TB of the lung who is coughing. Coughing produces

tiny infectious droplets, which under suitable conditions may cause transmission.

Transmission generally occurs indoors where droplet nuclei can stay in the air for a long time. Two factors determine an individual's risk of exposure: the concentration of the droplet nuclei in the air and the length of time he breathes that air. An individual's risk of infection depends on the extent of exposure to the droplet nuclei and his susceptibility to infection. The risk of a susceptible individual is therefore high with close, prolonged, indoor exposure to a person with sputum smear-positive pulmonary TB (tuberculosis of the lung), that is if an individual has evidence of the bacilli in his sputum, and the more bacilli one has the more infectious he becomes.

The spread of HIV infection has led to a dramatic increase in TB cases in eastern and southern Africa and threatens to do so elsewhere. [6]. Current epidemiological studies strongly support the claim that exposed individuals (infected but not yet clinically ill) are unable to transmit the tubercle bacillus but only individuals with active TB (infected and already ill from the disease) are capable of spreading the bacteria.[4]

[9] states that exposed TB individuals may remain in this latent stage (infected but not clinically ill and not infectious) for variable periods of time (in fact, may die without ever developing active TB). Among generally healthy persons, infection with TB is highly likely to be asymptomatic. Data from a variety of sources suggest that the life time risk of developing clinically evident TB after being infected is approximately 10%, with 90% likelihood of the infection remaining latent. According to [4], the longer we carry the bacteria the less likely we are to develop active TB unless our immune system becomes seriously compromised, (weakened) by other diseases , for example HIV/AIDS.

The progression to active TB is not uniform but is closely linked to various other factors such as nutritional status and/or access to decent medical care and living

conditions [2]. The risk of developing active TB is highest within the first two years of infection, although a few individuals (about 14%) do develop active TB within the first two years of infection [17]. Therefore an intervention that targets persons with recent infection, such as identifying contacts of active cases, could be particulary effective as an epidemic control measure.

According to [14] and [13], at greater ages, the immunity of persons who have been previously infected may wane, and they may be then at risk of developing active TB as a consequence of either exogenous re-infection (that is acquiring a new infection from another infectious individual) or endogenous re-activation of latent bacilli (that is re-activation of a pre-existing dormant infection).

Patients infected with HIV are at increased risk of developing active TB because of the high rate of reactivation of latent infection and high degree of susceptibility to new infection. [5] and [16]. TB rate vary with age, gender and race. Advancing age, male gender, and non-white race are all independently associated with an increase incidence of tuberculosis. In addition, in the United States TB disproportionately afflicts certain sub-populations such as American Indians and Blacks [15]. The following groups of populations are also at high risk of TB infection [8]:

- HIV infected individuals

  This group falls under the immuno-compromised population. HIV infection is the strongest risk factor yet identified for progression to active TB.

- Persons with certain medical conditions

  Other medical conditions that produce immune suppression have been associated with TB, presumably by causing reactivation of latent infection.

- Migrant agricultural workers

  Due to prolonged exposure in poor ventilated places, are also at high risk

of infection.

- Homeless persons

  The practice of bad habits, such as abuse of drugs and alcohol, unprotected sex which may lead to HIV infection, contribute to the activation of latent infection in the homeless.

- Patients and health care workers

  The aggregation of people in the homes and hospitals provides conditions for TB transmission.

- Residents and workers in correctional facilities

  This is because of expanding prison population leading to overcrowded prisons, relatively high rates of HIV infection in prison inmates, and high TB rates in the communities from which the majority of inmates originate.

1.3 TB vaccines and treatment

Latent and active TB can be treated with antibiotics. But TB treatment has side effects (sometimes quite serious), like eye problems and insomia, and takes a long time. Carriers of the bacilli who have not developed TB disease can be treated with a single drug INH; unfortunately, it must be taken religiously for 6-9 months. Treatment for those with active TB requires the simultaneous use of three drugs, for example, a combination of INH, Ethambitol and Streptomycin, for a period of at least 12 months. Lack of compliance (i.e patients not finishing the drugs or not taking them at the right time) with these drug treatments (a very serious problem) not only may lead to a relapse but to the development of antibiotic resistant TB - one of the most public health problems facing society today [4].

A TB vaccine called BCG (Bacillus of Calmette and Guerin) has been available for many decades. It is a bovine strain of Mycobacterium tuberculosis that lost its virulence after growth in the laboratory for many years [11]. It is cheap, but its effectiveness in preventing TB infection is controversial [12]. Results of field trials of the vaccine have differed widely, some indicating protection rates as high as 70% to 80%, others indicating the vaccine was completely ineffective in preventing TB [12]. Potential problems associated with the generalized use of the BCG vaccine in some populations are closely associated to the fact that vaccinated individuals will test positive for TB. It becomes therefore nearly impossible to be able to detect the prevalence of a disease in a population (like the Argentina population) where most individuals are vaccinated.

Since TB remains one of the leading causes of death and illness in the world and its treatment has side effects and long, there is a need to develop vaccines that will either prevent infection (pre-exposure) or prevent/slow progression to disease (post-exposure). There is a great need indeed since even the only available vaccine so far (BCG) has a controversial efficiency in preventing infection with TB.

1.4 Previous work done

In 1998, [7] stated that preventive therapy (the use of isoniazid or other anti-TB drugs aiming to sterilize latent infection with Mycobacterium tuberculosis and thus prevent progression to active disease), has been demonstrated by several large-randomized controlled trials that it is effective in preventing TB in individuals dually infected with HIV and Mycobacterium tuberculosis. However, studies of the feasibility of preventive therapy demonstrate that the process required for targeting appropriate individuals to exclude active TB, to deliver preventive therapy and to achieve adherence is complex and insufficient.

In 2000, [17] et al used a mathematical model of a TB epidemic to evaluate the potential effect of an intervention program targeting recently infected persons as an epidemic-control measure. They used one mathematical model which showed the transmission of TB between susceptible individuals, exposed (infected) individuals, who were divided into those who progress to early latent period and those who progress to long-term latent period, and the active TB cases.

From the model equations they calculated the reproductive rate, R_0 (a very useful summary parameter that quantifies the transmission potential of a pathogen, defined as the number of secondary infectious cases produced when one infectious individual is introduced into a population where everyone is susceptible.) By setting Ro=1, they were able to calculate the rates of effective treatment for active TB, effective treatment of early latent infection, and effective treatment for long-term latent infection that would eliminate the epidemic.

They concluded that the impact of therapy for early latent TB infection is greatest when treatment rates for active TB are lower. If the treatment rate for active TB is increased from 50% to 60%, adding therapy for latent TB infection substantially reduces TB incidence. In contrast, if the treatment rate for active TB is increased from 50% to 80%, the additional impact of increasing therapy for early latent infection is less important in determining the decline in TB incidence. However, even when treatment rates for active TB are high, treatment for early latent TB infection may be necessary to eliminate tuberculosis.

Due to one of the complexities of tuberculosis (vaccinated individuals but not yet infected may test positive to TB) this results may not be reliable because in most cases one may target the wrong people who have no effect at the end. [10] and [3] improved this work.

[10] and [3] used two simple mathematical models (one a pre-exposure vaccine and the other a post-exposure vaccine model) to provide general insight into the

effects of vaccination on TB epidemics. They discussed how these models can be used as health policy tools to identify which vaccines are 'equivalent' (in terms of their potential epidemic-control effects), to design control strategies and to predict the epidemiological impact of different vaccination strategies.

Their model analysis was based on the R_0 value. They also included three mechanisms in their models in which a vaccine could fail. They were the 'take', the 'degree' and the 'duration' mechanisms.

The term 'take' specifies the fraction of vaccinated individuals in whom some level of protective immunologic response is induced by the vaccine. The term 'degree' specifies the degree of vaccine-induced protection assumed the vaccine could confer in those individuals in whom the vaccine 'took'. 'Duration' was the time taken by the vaccine-induced immunity before decaying exponentially with time in those vaccinated individuals in whom the vaccine 'took' and induced a certain degree of protection.

Their results showed that even moderately effective vaccines could have a significant effect on reducing TB epidemics if they can be coupled with moderate to high treatment rates of active disease. We see that this work improves the above work by [17] and company in July 2000. Their results agree. They also suggested that it is necessary to develop both vaccines.

In many developing countries where the prevalence of latently infected individuals is high, post-exposure vaccines will be the most effective in quickly and dramatically reducing the incidence of tuberculosis. However, a pre-exposure vaccine is necessary to prevent a substantial increase in new infections and may be more effective than a post-exposure vaccine for the elimination of tuberculosis. It is likely that the combination of a pre-exposure vaccine, a post-exposure vaccine and treatment of active TB would be the most effective epidemic-control strategy for tuberculosis elimination in developing countries. In developed countries, where

the prevalence of latently infected individuals is low, then only a pre-exposure vaccine (used in combination with a high level of treatment) will be necessary to eliminate tuberculosis. [18] et al improved this work by considering other aspects not just efficiency only, like cumulative percentage of infections prevented and cumulative percentage of TB cases prevented.

[18] et al used mathematical models to compare the potential public health impact of mass vaccination campaigns that used either pre- or post-exposure vaccines. They assessed the public health impact in terms of the cumulative percentage of infections prevented and the cumulative percentage of TB cases prevented. They modelled the potential effect of vaccines in developing countries with a high incidence and prevalence of infection.

They used two separate mathematical models to assess the effect of vaccination: a pre-exposure and a post-exposure vaccine model. Their models are similar to those developed by Lietman and Blower in 1999 but they extended them to include the possibility of re-infection of latently infected persons. Their model analysis included quantifying the effect of vaccine efficiency, duration of vaccine-induced immunity, and vaccination coverage rates on the cumulative percentage of infections and TB cases prevented, based on uncertainty and sensitivity analysis.

After the analysis of the two models, they concluded that pre-exposure vaccines would be almost twice as effective as post-exposure vaccines in reducing the number of new infections. Post-exposure vaccines would initially have a substantially greater impact, compared to pre-exposure vaccines, on reducing the number of new cases of disease. However the effectiveness of post-exposure vaccines would diminish over time, whereas the effectiveness of pre-exposure vaccines would increase. Thus after 20 to 30 years, post- or pre-exposure vaccination campaigns would be almost equally effective in terms of cumulative TB cases prevented.

Even widely deployed and highly effective (50% - 90% efficiency) pre- or post-exposure vaccines would only be able to reduce the number of TB cases by one third. Finally they suggested that to achieve global control of TB, developing a single TB vaccine that function as both a pre- and a post-exposure vaccine is necessary.

This was great work indeed because their models and analysis covered most of the complexities of TB. But I would suggest that they should have considered countries with a high risk of progression to disease also not just high risk of infection only as they stated. This would have helped in the numerical analysis of the post-exposure TB vaccine.

Therefore there is a need to incorporate countries with a high prevalence of progression to disease also in such studies.
The project is a motivation from the work of Lietman et al in 2000 and Ziv et al in 2004. They both looked at how TB vaccines and treatment of active disease are effective in eliminating TB cases. They both used separate models as stated in the literature and both suggested that a combination of the three (pre-exposure vaccines, post-exposure vaccines and treatment of active TB) would be the best in eliminating TB cases. We will try to develop a model that will include the three control measures and then from the analysis we will be able to tell whether it is really effective than the individual measures.

1.5 Aims

The main aim of the project is to model, using mathematical models, the effectiveness of the combination of a pre-exposure TB vaccine, a post-exposure TB vaccine and treatment of active TB as an epidemic-control strategy.

1.6 Objectives

The main objectives are:

1. to review previous models on TB vaccines and treatment to find out what has been done and what can be done.
2. to develop the following models:
    - the basic TB transmission model
    - a model with treatment of active TB
    - a model with pre-exposure TB vaccine and treatment of TB
    - a model with post-exposure TB vaccine and treatment of TB
    - a model with pre-exposure, post-exposure TB vaccines and treatment of TB.
3. to analyse the models by
    - calculating the reproduction numbers of the models
    - finding the equilibrium states and classifying them as disease-free or endemic and express them in terms of R_0 where possible.
    - analysing the stability in each state.
    - analysing the R_0
    - carrying out numerical analysis
4. to compare the results with those of previous researches and suggest future work to be done.

Chapter 2

The Basic TB Transmission Model

The model was developed by [3] et al. No major alterations and additions were done for consistency.

2.1 Variables

The host population was divided into:

X_u - Untreated, unvaccinated susceptible individuals (not yet infected but capable when exposed).

L_u - Untreated, unvaccinated latently infected individuals (those that are infected but not yet infectious or clinically ill).

T - Active TB cases (those that are ill from the disease and infectious)

2.2 Parameters

π- The recruitment rate.

β- The probability of transmission.

ν- The rate of developing active TB.

μ- Natural death rate.

μ_T- Death rate due to disease.

p- The probability of progression to active disease.

2.3 Assumptions

- Transmission occurs through contact between a susceptible individual and an infectious individual.

- The net rate at which new infected individuals arise is proportional to the number of susceptible individuals X_u, times the number of infectious individuals T, times the probability of transmission from T to X_u, β, i.e $\beta X_u T$.

- TB is a fatal disease, that is TB kills.

- After being infected, a susceptible individual may either develop active TB immediately after infection at a probability p or become latently infected with probability $1 - p$.

- Active TB cases are due to endogenous re-activation of latent bacilli only, with exogenous cases insignificant.

- There is no natural immunity against infection and against progression to active disease.

We then represent the information above in form of a compartmental model, as shown in figure 2.1.

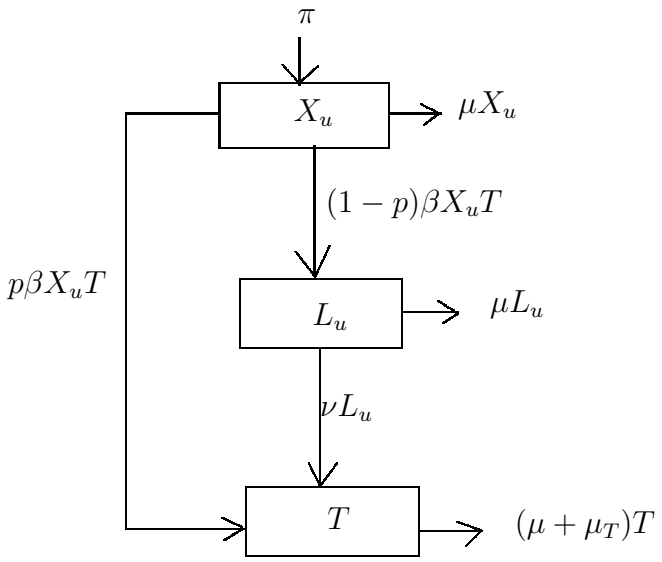

Figure 2.1: Compartmental Model 1

Individuals enter the susceptible population at rate π. Uninfected-unvaccinated individuals (X_u), are infected at rate $\beta T(t)$, and then either progress to active disease (T) immediately after infection with probability p, or progress to latent infection with probability $1-p$. Latently infected individuals (L_u) progress to active disease because of reactivation of latent infection at rate ν. Individuals with active TB die at a rate μ_T due to the disease. All persons die naturally at rate μ.

We then develop time dependent differential equations for each compartment by adding what goes into a compartment and subtracting what comes out as follows:

2.4 Model equations

$$\begin{aligned}
\frac{dX_u}{dt} &= \pi - \mu X_u - \beta X_u T, && (2.1)\\
\frac{dL_u}{dt} &= (1-p)\beta X_u T - (\mu+\nu)L_u, && (2.2)\\
\frac{dT}{dt} &= p\beta X_u T + \nu L_u - (\mu+\mu_T)T. && (2.3)
\end{aligned}$$

2.5 Equilibrium states

These are the solutions of the model equations when equated to zero. From the above system we have:

$$\begin{aligned}
\pi - \mu X_u - \beta X_u T &= 0, && (2.4)\\
(1-p)\beta X_u T - (\mu+\nu)L_u &= 0, && (2.5)\\
p\beta X_u T + \nu L_u - (\mu+\mu_T)T &= 0. && (2.6)
\end{aligned}$$

From equation (2.5) $L_u = \frac{(1-p)\beta X_u T}{\mu+\nu}$.

Substituting L_u into equation (2.6)$\Rightarrow p\beta X_u T + \nu\frac{(1-p)\beta X_u T}{\mu+\nu} - (\mu+\mu_T)T = 0.$

From above we have after factoring out T that $T^* = 0,$ or

$X_u^* = \frac{(\mu+\mu_T)(\mu+\nu)}{\beta(p\mu+\nu)}$.

Substituting $T^* = 0$ in equation (2.4) gives $X_u^* = \pi/\mu.$

$T^* = 0$ into equation (2.6) $\Rightarrow L_u^* = 0.$

Then our disease free equilibrium state, P_0 is given by

$$P_0 = (X_u^*, 0, 0) = (\pi/\mu, 0, 0).$$

Which exists readily since $\pi/\mu > 0$.

For the endemic equilibrium state we solve as follows:

Using $X_u^* = \frac{(\mu+\mu_T)(\mu+\nu)}{\beta(p\mu+\nu)}$,

from equation (2.4) we have that

$$T = \frac{\pi}{\beta X_u} - \frac{\mu}{\beta}.$$

Substituting X_u^* above gives

$$T^* = \frac{\pi(p\mu+\nu)}{(\mu+\mu_T)(\mu+\nu)} - \frac{\mu}{\beta},$$

$$T^* = \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\mu_T)(\mu+\nu)} - 1.$$

From equation (2.5) we have that

$$L_u = \frac{(1-p)\beta X_u T}{\mu+\nu}.$$

$$\Rightarrow L_u = \frac{(1-p)\beta X_u}{\mu+\nu}(\frac{\pi}{\beta X_u} - \frac{\mu}{\beta}),$$

$$\Rightarrow L_u = \frac{1-p}{\mu+\nu}(\pi - \mu X_u),$$

$$\Rightarrow L_u^* = \frac{1-p}{\mu+\nu}(\pi - \frac{\mu(\mu+\mu_T)(\mu+\nu)}{\beta(p\mu+\nu)}),$$

$$\Rightarrow L_u^* = \frac{1-p}{\mu+\nu}(1 - \frac{\mu(\mu+\mu_T)(\mu+\nu)}{\beta\pi(p\mu+\nu)}).$$

This values gives the endemic (disease persists) equilibrium state P_e.

$$P_e = (X_u^*, L_u^*, T^*) = \Big(\tfrac{(\mu+\mu_T)(\mu+\nu)}{\beta(p\mu+\nu)}, \tfrac{1-p}{\mu+\nu}(1 - \tfrac{\mu(\mu+\mu_T)(\mu+\nu)}{\beta\pi(p\mu+\nu)}), \tfrac{\beta\mu(p\mu+\nu)}{\mu(\mu+\mu_T)(\mu+\nu)} - 1\Big).$$

For existence, the values of L_u^* and T^* should be defined and non zero, that is we should have infected people who will progress to active disease and infect others. We then find the condition for L_u^* and T^* to be positive and greater than zero.

$$L_u^* = \frac{1-p}{\mu+\nu}(1 - \frac{\mu(\mu+\mu_T)(\mu+\nu)}{\beta\pi(p\mu+\nu)}) > 0,$$

$$\Rightarrow 1 - \frac{\mu(\mu+\mu_T)(\mu+\nu)}{\beta\pi(p\mu+\nu)} > 0,$$

$$\Rightarrow 1 > \frac{\mu(\mu+\mu_T)(\mu+\nu)}{\beta\pi(p\mu+\nu)},$$

$$\Rightarrow \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\mu_T)(\mu+\nu)} > 1.$$

And

$$T^* = \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\mu_T)(\mu+\nu)} - 1 > 0,$$

$$\Rightarrow \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\mu_T)(\mu+\nu)} > 1.$$

2.6 The Reproduction Number, R_0

The method used to derive the value of R_0 is the method by Drekmann and Heesterbeek (1990,1992). We arrange the model equations in such a way that the first m equations are involving infected classes. Then we find the matrix $\mathcal{F}_i$, which gives the rate of appearance of new infections in each compartment i. Matrix $\mathcal{V}_i$ gives the rate of transfer of individuals out of compartments i, minus the rate of transfer of individuals into compartments i.

We then find the linearized form or the Jacobian matrix for $\mathcal{F}_i$ and $\mathcal{V}_i$, evaluated at P_0, and denote them as F and V respectively. The generation matrix G is the product of F and the inverse of V.

that is

$$G = FV^{-1}.$$

Then the value of R_0 will be the dominant eigenvalue of G. For the above system of equations,we arrange them as follows:

$$\begin{aligned}
\frac{dL_u}{dt} &= (1-p)\beta X_u T - (\mu+\nu)L_u, \\
\frac{dT}{dt} &= p\beta X_u T + \nu L_u - (\mu+\mu_T)T, \\
\frac{dX_u}{dt} &= \pi - \mu X_u - \beta X_u T.
\end{aligned}$$

so that $m = 2$ and

$$\mathcal{F}_i = \begin{pmatrix} (1-p)\beta X_u T \\ p\beta X_u T \end{pmatrix}, \qquad \mathcal{V}_i = \begin{pmatrix} (\mu+\nu)L_u \\ (\mu+\mu_T)T - \nu L_u \end{pmatrix}.$$

$$F = \begin{pmatrix} 0 & (1-p)\beta\pi/\mu \\ 0 & p\beta\pi/\mu \end{pmatrix}, \qquad V = \begin{pmatrix} (\mu+\nu) & 0 \\ -\nu & (\mu+\mu_T) \end{pmatrix}.$$

$$V^{-1} = \frac{1}{(\mu+\nu)(\mu+\mu_T)} \begin{pmatrix} \mu+\mu_T & 0 \\ \nu & \mu+\nu \end{pmatrix}.$$

$$G = \frac{\beta\pi}{\mu(\mu+\nu)(\mu+\mu_T)} \begin{pmatrix} \nu(1-p) & (1-p)(\mu+\nu) \\ \nu p & p(\mu+\nu) \end{pmatrix}.$$

To solve for the eigenvalues of G, we let

$$\begin{aligned} a &= \nu(1-p), \\ b &= (1-p)(\mu+\nu), \\ c &= \nu p, \\ d &= p(\mu+\nu). \end{aligned}$$

$$\left|G - \lambda I\right| = \frac{\beta\pi}{\mu(\mu+\nu)(\mu+\mu_T)} \begin{vmatrix} a-\lambda & b \\ c & d-\lambda \end{vmatrix} = 0.$$

Solving for λ we get the following equation

$$\lambda^2 - (a+d)\lambda + ad - bc = 0. \tag{2.7}$$

It can be shown that $ad - bc = 0$, so equation(2.7) reduces to

$$\lambda(\lambda - (a+d)) = 0. \tag{2.8}$$

Which solves to

$$\lambda_1 = 0, \tag{2.9}$$

and

$$\lambda_2 = \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\nu)(\mu+\mu_T)}. \tag{2.10}$$

Clearly our dominant eigenvalue is λ_2 which corresponds to our R_0 according to the method.Thus

$$R_0 = \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\nu)(\mu+\mu_T)},$$

$$= \Big[\frac{\beta\pi}{\mu}\Big]\Big[\frac{p\mu+\nu}{\nu+\mu)}\Big]\Big[\frac{1}{\mu+\mu_T}\Big].$$

Now expressing the endemic equilibrium points in terms of R_0 we have,

$$\begin{aligned} X_u^* &= \frac{\pi}{\mu R_0}, \\ L_u^* &= \frac{(1-p)\pi}{\mu+\nu}(1-\frac{1}{R_0}), \\ T^* &= \frac{\mu}{\beta}(R_0-1). \end{aligned}$$

From above it can be noted that X_u^*, L_u^*, T^* are defined for $R_0 > 1$, thus P_e exist if $R_0 > 1$, that is the disease will persist if we have more than one new infectious case produced when one infectious individual is introduced into a population where everyone is susceptible.

2.6.1 Analysis of the reproduction number

We have calculated the value of R_0 above and we found that it is given by:

$$R_0 = \Big[\frac{\beta\pi}{\mu}\Big]\Big[\frac{p\mu+\nu}{\nu+\mu}\Big]\Big[\frac{1}{\mu+\mu_T}\Big].$$

This rate depends linearly on;

- the average number of susceptible individuals that one infectious case infects per unit time,$\frac{\beta\pi}{\mu}$.
- the mean infectious period, $\frac{1}{\mu+\mu_T}$, and
- the probability that an infected individual will develop into an infectious case, $\frac{p\mu+\nu}{\nu+\mu}$, which can be splitted into $p+\frac{\nu(1-p)}{\mu+\nu}$ where p is the probability by which an infected individual develops active TB immediately after infection and $\frac{\nu(1-p)}{\mu+\nu}$ is the probability by which an infected individual will progress to latent infection after infection.

It is the product of the three cases. An epidemic control strategy will target to reduce these values. We shall compare the other values of R_0 for the other models to the above value of R_0 in terms of efficiency in reducing it.

2.7 Stability Analysis of P_0 and P_e by the Linearization Method

We say P_0 or P_e is stable if all the eigenvalues of the linearised matrix of the system evaluated at each equilibrium state are negative.

For the above system of differential equations the Jacobian matrix is as follows:

$$J = \begin{pmatrix} -\mu - \beta T^* & 0 & -\beta X_u^* \\ (1-p)\beta T^* & -(\mu+\nu) & (1-p)\beta X_u^* \\ p\beta T^* & \nu & p\beta X_u^* - (\mu + \mu_T^*) \end{pmatrix}.$$

Evaluating J at $P_0 = (\pi/\mu, 0, 0)$, we have

$$J(P_0) = \begin{pmatrix} -\mu & 0 & -\beta\pi/\mu \\ 0 & -(\mu+\nu) & (1-p)\beta\pi/\mu \\ 0 & \nu & p\beta\pi/\mu - (\mu + \mu_T) \end{pmatrix}.$$

To find the eigenvalues we solve the system

$$\Big| J(P_0) - \lambda I \Big| = 0,$$

which gives us

$$\left|J(P_0) - \lambda I\right| = \begin{vmatrix} -\mu - \lambda & 0 & -\beta\pi/\mu \\ 0 & -(\mu+\nu) - \lambda & (1-p)\beta\pi/\mu \\ 0 & \nu & (p\beta\pi/\mu - (\mu+\mu_T)) - \lambda \end{vmatrix} = 0.$$

Solving the above system leads to

$$(-\mu - \lambda)\begin{vmatrix} -(\mu+\nu) - \lambda & (1-p)\beta\pi/\mu \\ \nu & (p\beta\pi/\mu - (\mu+\mu_T)) - \lambda \end{vmatrix} = 0,$$

$$\Rightarrow -\mu - \lambda = 0 \tag{2.11}$$

or

$$(-(\mu+\nu) - \lambda)((p\beta\pi/\mu - (\mu+\mu_T)) - \lambda) - \nu(1-p)\beta\pi/\mu = 0. \tag{2.12}$$

From equation (2.11) we have that

$$\lambda_1 = -\mu.$$

Solving equation (2.12) for the other two roots, we let

$$\begin{aligned} a &= \mu + \nu, \\ b &= p\beta\pi/\mu - (\mu + \mu_T), \\ c &= \nu(1-p)\beta\pi/\mu. \end{aligned}$$

So that we have (2.12) as

$$(-a - \lambda)(b - \lambda) - c = 0,$$

$$-((a + \lambda)(b - \lambda)) - c = 0,$$

$$\lambda^2 + (a - b)\lambda - (ab + c) = 0,$$

$$\Rightarrow \lambda_{2,3} = \frac{-(a-b) \pm \sqrt{(a-b)^2 + 4(ab+c)}}{2},$$

$$\Rightarrow \lambda_2 = \frac{-(a-b) + \sqrt{(a-b)^2 + 4(ab+c)}}{2},$$

$$\Rightarrow \lambda_3 = \frac{-(a-b) - \sqrt{(a-b)^2 + 4(ab+c)}}{2}.$$

From above, λ_1 is readily negative, and for $\lambda_{2,3}$ to be negative we should have the following situation.

$$\frac{-(a-b) \pm \sqrt{(a-b)^2 + 4(ab+c)}}{2} < 0,$$

$$-(a-b) \pm \sqrt{(a-b)^2 + 4(ab+c)} < 0,$$

$$\pm\sqrt{(a-b)^2 + 4(ab+c)} < a-b,$$

squaring both sides gives

$$(a-b)^2 + 4(ab+c) < (a-b)^2,$$

$$4(ab+c) < 0,$$

$$ab + c < 0.$$

Now substituting for the values of a, b, and c we have that

$$(\mu+\nu)(p\beta\pi/\mu - (\mu+\mu_T)) + \nu(1-p)\beta\pi/\mu < 0,$$

$$(\mu+\nu)\beta\pi/\mu-(\mu+\nu)(\mu+\mu_T)+\nu(1-p)\beta\pi/\mu<0,$$

$$((\mu+\nu)p+\nu(1-p))\beta\pi/\mu<(\mu+\nu)(\mu+\mu_T),$$

$$\frac{(p\mu+\nu)\beta\pi}{\mu(\mu+\nu)(\mu+\mu_T)}<1,$$

$$R_0<1.$$

Thus P_0 is stable for $R_0<1$.

Stability Analysis for P_e.

For the endemic state, we shall use the points expressed in terms of R_0. Substituting the equilibrium points into the Jacobian matrix we have:

$$J(P_e)=\begin{pmatrix} -\mu-\beta\frac{\mu}{\beta}(R_0-1) & 0 & -\mu\beta\frac{\pi}{\mu R_0} \\ (1-p)\beta\frac{\mu}{\beta}(R_0-1) & -(\mu+\nu) & (1-p)\beta\frac{\pi}{\mu R_0} \\ p\beta\frac{\mu}{\beta}(R_0-1) & \nu & p\beta\frac{\pi}{\mu R_0}-(\mu+\mu_T) \end{pmatrix},$$

which reduces to,

$$J(P_e)=\begin{pmatrix} -\mu R_0 & 0 & -\beta\pi/R_0 \\ \mu(1-p)(R_0-1) & -(\mu+\nu) & \frac{(1-p)\beta\pi}{\mu R_0} \\ \mu p(R_0-1) & \nu & \frac{p\beta\mu}{\mu R_0}-(\mu+\mu_T) \end{pmatrix}.$$

Solving for the eigen values of

$$\Big|J(P_e)-\lambda I\Big|=0,$$

we have the following matrix

$$\Big|J(P_e) - \lambda I\Big| = \begin{vmatrix} -\mu R_0 - \lambda & 0 & -\beta\pi/R_0 \\ \mu(1-p)(R_0-1) & -(\mu+\nu)-\lambda & \frac{(1-p)\beta\pi}{\mu R_0} \\ \mu p(R_0-1) & \nu & (\frac{p\beta\mu}{\mu R_0} - (\mu+\mu_T)) - \lambda \end{vmatrix} = 0,$$

$$(-\mu R_0 - \lambda)\begin{vmatrix} -(\mu+\nu)-\lambda & \frac{(1-p)\beta\pi}{\mu R_0} \\ \nu & (\frac{p\beta\pi}{\mu R_0} - (\mu+\mu_T)) - \lambda \end{vmatrix} - \frac{\beta\pi}{R_0}\begin{vmatrix} \mu(1-p)(R_0-1) & -(\mu+\nu+\lambda) \\ \mu p(R_0-1) & \nu| \end{vmatrix} = 0.$$

From above letting

$$\begin{aligned} a &= \mu+\nu, \\ b &= \frac{p\beta\pi}{\mu R_0} - (\mu+\mu_T), \\ c &= \nu\frac{(1-p)\beta\pi}{\mu R_0}, \\ d &= \nu\mu(1-p)(R_0-1). \end{aligned}$$

We have the following equation;

$$\lambda^3 + (\mu R_0 + (a-b))\lambda^2 + (\mu R_0(a-b) - (ab+c) + \gamma)\lambda + (e - (ab+c)\mu R_0) = 0,$$

where

$$\begin{aligned} \gamma &= \frac{\mu p\beta\pi}{R_0}(R_0-1), \\ e &= \frac{\beta\pi d}{R_0} + \frac{\mu p\beta\pi}{R_0}(R_0-1)(\mu+\nu). \end{aligned}$$

If again we let

$$\begin{aligned} a_1 &= \mu R_0 + (a-b), \\ a_2 &= \mu R_0(a-b) - (ab+c) + \gamma, \\ a_3 &= e - (ab+c)\mu R_0. \end{aligned}$$

such that the above equation is

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0.$$

Using the Routh-Hurwitz Stability Criterion which states that if all the eigenvalues of the above equation have strictly negative real parts then

$a_1 > 0, \qquad a_3 > 0, \qquad \text{and} \qquad a_1a_2 - a_3 > 0.$

So we say that Pe is stable if the following are true;

$$\begin{aligned} a_1 = \mu R_0 + a - b &> 0, \\ \mu R_0 + (\mu+\nu) - \Big(\frac{p\beta\pi}{\mu R_0} - (\mu+\mu_T)\Big) &> 0, \\ \frac{(p\mu+\nu)\beta\pi}{(\mu+\nu)(\mu+\mu_T)} + (\mu+\nu) - \Big(\frac{p\beta\pi}{\mu R_0} - (\mu+\mu)\Big) &> 0. \end{aligned}$$

This is possible for;

$$\begin{aligned} \frac{p\beta\pi}{\mu R_0} - (\mu+\mu_T) &< 0, \\ \frac{p\beta\pi}{\mu(\mu+\mu_T)} - R_0 &< 0, \\ \frac{p\beta\pi}{\mu(\mu+\mu_T)} - \frac{(p\mu+\nu)\beta\pi}{\mu(\mu+\nu)(\mu+\mu_T)} &< 0, \\ \frac{\beta\pi}{\mu(\mu+\mu_T)}\Big(p - \frac{p\mu+\nu}{\mu+\nu}\Big) &< 0, \\ \frac{\beta\pi}{\mu(\mu+\mu_T)}\Big(\frac{\nu(p-1)}{\mu+\nu}\Big) &< 0. \end{aligned}$$

The above inequality is possible for

$$p - 1 < 0.$$

$$\Rightarrow \qquad p < 1.$$

$$a_3 = \frac{\beta\pi d}{R_0} + \frac{\mu p\beta\pi}{R_0}(R_0 - 1)(\mu+\nu) - (ab+c)\mu R_0 > 0.$$

For the last term $ab + c$ we find that $p < 1$ as above, so we analyse the first two terms.

$$\frac{\beta\pi}{R_0}\Big[\nu\mu(1-p)(R_0-1)\Big] + \frac{\mu p\beta\pi}{R_0}\Big[(R_0-1)(\mu+\nu)\Big] > 0,$$

$$\begin{aligned}\frac{\beta\pi}{R_0}(R_0-1)\Big[\nu\mu(1-p)+\mu p(\mu+\nu)\Big] &> 0,\\ \beta\pi(1-\frac{1}{R_0})\Big[\mu(p\mu+\nu)\Big] &> 0.\end{aligned}$$

The inequality holds for

$$\begin{aligned}1-\frac{1}{R_0} &> 0,\\ \Rightarrow \qquad R_0 &> 1.\end{aligned}$$

$$a_1a_2-a_3>0,$$

$$\Big[\mu R_0+(a-b)\Big]\Big[\mu R_0(a-b)-(ab+c)+\gamma\Big]-\Big[e-(ab+c)\mu R_0\Big]>0.$$

It can be observed that analysis of the last condition will give the same results as for the first two conditions because of the presence of similar terms.

Thus P_e is stable for $R_0>1$ and $p<1$.

Chapter 3

The Transmission Model with Treatment

The model was developed by [4]. The dynamics of treating the latently infected individuals and for those with antibiotic resistant TB were not considered.

3.1 Variables

The host population was divided as above, for the basic model without treatment.

3.2 Parameters

In addition to the parameters for the basic model, we have ϕ, which is the treatment rate of active TB.

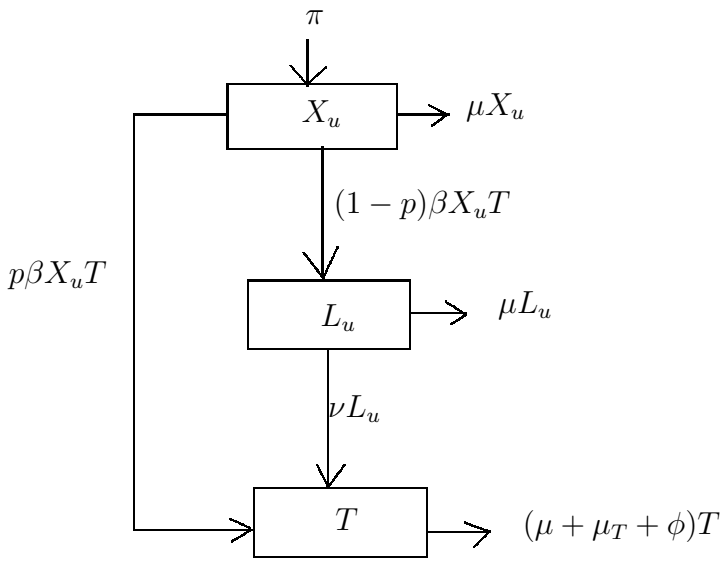

Figure 3.1: Compartmental Model 2

3.3 Assumptions

The assumptions for the model with treatment are the same as before. An additional assumption is that the treated individuals get permanent immunity against TB.

In figure 3.1, we present the data in a compartmental model.

Individuals enter the susceptible population at rate π. Uninfected-unvaccinated individuals (X_u) are infected at rate $\beta T(t)$, and then either progress to active disease (T) immediately after infection with probability p, or progress to latent infection with probability $1-p$. Latently infected individuals (L_u) progress to active disease because of re-activation of latent infection at rate ν. Individuals with active TB either die at a rate μ_T or receive effective treatment at a rate ϕ. All individuals in the different classes die naturally at rate μ. The model equations are as follows.

3.4 Model Equations

$$\begin{aligned}
\frac{dX_u}{dt} &= \pi - \mu X_u - \beta X_u T, && (3.1)\\
\frac{dL_u}{dt} &= (1-p)\beta X_u T - (\mu+\nu)L_u, && (3.2)\\
\frac{dT}{dt} &= p\beta X_u T + \nu L_u - (\mu+\mu_T+\phi)T. && (3.3)
\end{aligned}$$

3.5 Equilibrium states

Like for the basic model, we equate the model equations to zero and solve for X_u, L_u and T.

$$\begin{aligned}
\pi - \mu X_u - \beta X_u T &= 0, && (3.4)\\
(1-p)\beta X_u T - (\mu+\nu)L_u &= 0, && (3.5)\\
p\beta X_u T + \nu L_u - (\mu+\mu_T+\phi)T &= 0. && (3.6)
\end{aligned}$$

From equation(3.5)

$$L_u = \frac{(1-p)\beta X_u T}{\mu+\nu}.$$

Substituting L_u into equation (3.6) we have

$$p\beta X_u T + \nu\frac{(1-p)\beta X_u T}{\mu+\nu} - (\mu+\mu_T+\phi)T = 0.$$

If we factor out T, we get

$$T^* = 0,$$

or

$$X_u^* = \frac{(\mu+\mu_T+\phi)(\mu+\nu)}{\beta(p\mu+\nu)}.$$

Substituting $T^* = 0$ into equation (3.4) and equation (3.5) we get

$$X_u^* = \pi/\mu,$$

and

$$L_u^* = 0.$$

Thus our disease free state P_0,

$$P_0 = (X_u^*, 0, 0) = (\pi/\mu, 0, 0).$$

Which exists readily since $\pi/\mu > 0$.

Next we solve for the endemic equilibrium points.

From equation (3.4)

$$T = \frac{\pi}{\beta X_u} - \frac{\mu}{\beta}.$$

Substituting

$$X_u^* = \frac{(\mu + \mu_T + \phi)(\mu + \nu)}{\beta(p\mu + \nu)},$$

we have that

$$T^* = \frac{\pi(p\mu + \nu)}{(\mu + \nu)(\mu + \mu_T + \phi)} - \frac{\mu}{\beta},$$
$$\Rightarrow T^* = \frac{\beta\pi(p\mu + \nu)}{\mu(\mu + \nu)(\mu + \mu_T + \phi)} - 1.$$

Solving for L_u^* using X_u^* and T^* we have that

$$L_u^* = \frac{(1-p)}{\mu + \nu}(1 - \frac{\mu(\mu + \mu_T + \phi)(\mu + \nu)}{\beta\pi(p\mu + \nu)}).$$

Thus P_e, is given by
$P_e = (X_u^*, L_u^*, T^*) = \Big(\frac{(\mu+\mu_T+\phi)(\mu+\nu)}{\beta(p\mu+\nu)}, \frac{(1-p)}{\mu+\nu}(1 - \frac{\mu(\mu+\mu_T+\phi)(\mu+\nu)}{\beta\pi(p\mu+\nu)}), \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\nu)(\mu+\mu_T+\phi)} - 1\Big).$

P_e exists for

$$T^* = \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\nu)(\mu+\mu_T+\phi)} - 1 > 0,$$

$$\Rightarrow \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\nu)(\mu+\mu_T+\phi)} > 1.$$

And

$$L_u^* = \frac{(1-p)}{\mu+\nu}(1 - \frac{\mu(\mu+\mu_T+\phi)(\mu+\nu)}{\beta\pi(p\mu+\nu)}) > 0,$$

$$\Rightarrow 1 > \frac{\mu(\mu+\mu_T+\phi)(\mu+\nu)}{\beta\pi(p\mu+\nu)},$$

$$\Rightarrow \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\mu_T+\phi)(\mu+\nu)} > 1.$$

Thus unless $\frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\mu_T+\phi)(\mu+\nu)} > 1$, P_e will not exist.

3.6 The Reproduction number, $R_0^{(1)}$

Using the same method as for the basic model, we calculate $R_0^{(1)}$ for the model with treatment.

$$\mathcal{F}_i = \begin{pmatrix} (1-p)\beta X_u T \\ p\beta X_u T \end{pmatrix}, \qquad \mathcal{V}_i = \begin{pmatrix} (\mu+\nu)L_u \\ (\mu+\mu_T+\phi)T - \nu L_u \end{pmatrix}.$$

$$F = \begin{pmatrix} 0 & \frac{(1-p)\beta\pi}{\mu} \\ 0 & \frac{p\beta\pi}{\mu} \end{pmatrix}, \qquad V = \begin{pmatrix} \mu+\nu & 0 \\ -\nu & \mu+\mu_T+\phi \end{pmatrix}.$$

$$G = FV^{-1} = \frac{\beta\pi}{\mu(\mu+\mu_T+\phi)(\mu+\nu)} \begin{pmatrix} (1-p)\nu & (1-p)(\mu+) \\ p\nu & p(\mu+\nu) \end{pmatrix}.$$

Solving $\Big|G - \lambda I\Big| = 0$ we have that

$$\lambda_1 = 0,$$

and

$$\lambda_2 = \frac{\beta\pi(p\mu+\nu)}{\mu(\mu+\mu_T+\phi)(\mu+\nu)}.$$

λ_2 corresponds to the value of $R_0^{(1)}$,

$$R_0^{(1)} = \Big[\frac{\beta\pi}{\mu}\Big]\Big[\frac{1}{\mu+\mu_T+\phi}\Big]\Big[\frac{p\mu+\nu}{\mu+\nu}\Big]$$

3.6.1 Analysis of the Reproduction Number

From above calculations, we have that

$$R_0^{(1)} = \Big[\frac{\beta\pi}{\mu}\Big]\Big[\frac{1}{\mu+\mu_T+\phi}\Big]\Big[\frac{p\mu+\nu}{\mu+\nu}\Big].$$

Expressing $R_0^{(1)}$ in terms of R_0, which is for the basic model, we have

$$R_0^{(1)} = R_0 \frac{(\mu + \mu_T)}{(\mu + \mu_T + \phi)}.$$

$R_0^{(1)}$ has a fraction, $\frac{\mu+\mu_T}{\mu+\mu_T+\phi}$ which reduces R_0. So treatment of active TB reduces the cases of the disease by reducing the infectious period. We can therefore say that, treatment of active TB, as a control strategy, has positive results.

3.7 Stability Analysis of P_0 and P_e by the linearization method

As before, we find the linearized form of the model, then evaluate it at P_0 or at P_e. We then find the eigenvalues of the Jacobian matrix. If they are all negative, then we conclude that P_0 or P_e is stable, or just find the condition when the eigenvalues will be negative.

The Jacobian for the system is as follows:

$$J = \begin{pmatrix} -\mu - \beta T^* & 0 & -\beta X_u^* \\ (1-p)\beta T^* & -(\mu+\nu) & (1-p)\beta X_u^* \\ p\beta T^* & \nu & p\beta X_u^* - (\mu + \mu_T + \phi) \end{pmatrix}.$$

Evaluated at P_0 and solving

$$|J(P_0) - \lambda I| = 0,$$

we have the following

$$|J(P_0) - \lambda I| = \begin{vmatrix} -\mu - \lambda & 0 & -\beta\pi/\mu \\ 0 & -(\mu+\nu) - \lambda & (1-p)\beta\pi/\mu \\ 0 & \nu & (p\beta\pi/\mu - (\mu + \mu_T + \phi)) - \lambda \end{vmatrix} = 0.$$

If we let

$$\begin{aligned} a &= \mu + \nu, \\ b &= p\beta\pi/\mu - (\mu + \mu_T + \phi), \\ c &= \nu(1-p)\beta\pi/\mu. \end{aligned}$$

We get the reduced equation

$$(-\mu - \lambda)(-a - \lambda)(b - \lambda) - c) = 0.$$

$$\Rightarrow \lambda_1 = -\mu.$$

From the above equation we solve for the other two roots and get that

$$\lambda_{2,3} = \frac{-(a-b) \pm \sqrt{(a-b)^2 + 4(ab+c)}}{2},$$

$$\Rightarrow \lambda_2 = \frac{-(a-b) + \sqrt{(a-b)^2 + 4(ab+c)}}{2}.$$

And

$$\Rightarrow \lambda_3 = \frac{-(a-b) - \sqrt{(a-b)^2 + 4(ab+c)}}{2}.$$

λ_1 is negative, we then establish a condition for $\lambda_{2,3}$ to be negative.

$$\lambda_{2,3} = \frac{-(a-b) \pm \sqrt{(a-b)^2 + 4(ab+c)}}{2} < 0,$$

$$\Rightarrow -(a-b) \pm \sqrt{(a-b)^2 + 4(ab+c)} < 0,$$

$$\Rightarrow \pm\sqrt{(a-b)^2 + 4(ab+c)} < (a-b),$$

squaring both sides gives

$$(a-b)^2 + 4(ab+c) < (a-b)^2,$$
$$4(ab+c) < 0,$$
$$ab + c < 0.$$

Substituting back for the values of a, b and c, we have:

$$\begin{aligned}
(\mu+\nu)(p\beta\pi/\mu - (\mu+\mu_T+\phi)) + \nu(1-p)\beta\pi/\mu &< 0, \\
(\mu+\nu)p\beta\pi/\mu - (\mu+\nu)(\mu+\mu_T+\phi) + \nu(1-p)\beta\pi/\mu &< 0, \\
\beta\pi/\mu((\mu+\nu) + \nu(1-p)) &< (\mu+\nu)(\mu+\mu_T+\phi), \\
\frac{(p\mu+\nu)\beta\pi}{\mu(\mu+\nu)(\mu+\mu_T+\phi)} &< 1, \\
R_0 &< 1.
\end{aligned}$$

Thus P_0 is stable if $R_0 < 1$.

Stability Analysis for P_e

For simplicity of our equations, we first express the endemic equilibrium points in terms of R_0 then analyse the stability.

In terms of $R_0^{(1)}$, we have

$$X_u^* = \frac{\pi}{\mu R_0^{(1)}},$$

$$
\begin{aligned}
T^* &= \frac{\mu}{\beta}(R_0^{(1)} - 1), \\
L_u^* &= \frac{(1-p)\pi}{\mu+\nu}(1 - 1/R_0^{(1)}).
\end{aligned}
$$

Clearly P_e exists for $R_0^{(1)} > 1$ that is P_e exists when we have more than one new infectious case produced when one infectious individual is introduced into a population where everyone is susceptible.

The Jacobian matrix

$$
J = \begin{pmatrix}
-\mu - \beta T^* & 0 & -\beta X_u^* \\
(1-p)\beta T^* & -(\mu+\nu) & (1-p)\beta X_u^* \\
p\beta T^* & \nu & p\beta X_u^* - (\mu + \mu_T)
\end{pmatrix},
$$

evaluated at $P_e = (\frac{\pi}{\mu R_0^{(1)}}, \frac{(1-p)\pi}{\mu+\nu}(1 - 1/R_0^{(1)}), \frac{\mu}{\beta}(R_0^{(1)} - 1)$ gives

$$
J(P_e) = \begin{pmatrix}
-\mu R_0^{(1)} & 0 & \frac{-\beta\pi}{\mu R_0^{(1)}} \\
\mu(1-p)(R_0^{(1)} - 1) & -(\mu+\nu) & (1-p)\frac{\beta\pi}{\mu R_0^{(1)}} \\
p\mu(R_0^{(1)} - 1) & \nu & \frac{p\beta\pi}{\mu R_0^{(1)}} - (\mu + \mu_T + \phi)
\end{pmatrix},
$$

$$
|J(P_e) - \lambda I| = \begin{vmatrix}
-\mu R_0^{(1)} - \lambda & o & \frac{-\beta\pi}{\mu R_0^{(1)}} \\
\mu(1-p)(R_0^{(1)} - 1) & -a - \lambda & (1-p)\frac{\beta\pi}{\mu R_0^{(1)}} \\
e & \nu & b - \lambda
\end{vmatrix} = 0.
$$

After letting

$$\begin{aligned} a &= \mu+\nu, \\ b &= \frac{p\beta\pi}{\mu R_0^{(1)}} - (\mu+\mu_T+\phi), \\ c &= \nu(1-p)\frac{\beta\pi}{\mu R_0^{(1)}}, \\ d &= \nu\mu(1-p)(R_0^{(1)}-1), \\ e &= \mu p(R_0^{(1)}-1). \end{aligned}$$

We have the following equation:

$$-(\mu R_0^{(1)}+\lambda)(-(a+\lambda)(b-\lambda)-c) - \frac{\beta\pi}{\mu R_0^{(1)}}(d+(a+\lambda)e) = 0,$$

$$-(\mu R_0^{(1)}+\lambda)(\lambda^2+(a-b)\lambda-(ab+c)) - \frac{\beta\pi d}{\mu R_0^{(1)}} - \frac{\beta\pi ea}{\mu R_0^{(1)}} - \frac{\beta\pi e\lambda}{\mu R_0^{(1)}} = 0,$$

$$-(\mu R_0^{(1)}+\lambda)\lambda^2-(\mu R_0^{(1)}+\lambda)(a-b)\lambda+(\mu R_0^{(1)}+\lambda)(ab+c)-\frac{\beta\pi}{\mu R_0^{(1)}}(d+ae)-\frac{\beta\pi e\lambda}{\mu R_0^{(1)}} = 0,$$

$$\lambda^3+(\mu R_0^{(1)}+a-b)\lambda^2+(\mu R_0^{(1)}(a-b)-(ab+c)+\frac{\beta\pi e}{\mu R_0^{(1)}})\lambda+\frac{\beta\pi}{\mu R_0^{(1)}}(d+ae)-\mu R_0^{(1)}(ab+c) = 0.$$

Let

$$\begin{aligned} a_1 &= \mu R_0^{(1)}+a-b, \\ a_2 &= \mu R_0^{(1)}(a-b)-(ab+c)+\frac{\beta\pi e}{\mu R_0^{(1)}}, \\ a_3 &= \frac{\beta\pi}{\mu R_0^{(1)}}(d+ae)-\mu R_0^{(1)}(ab+c). \end{aligned}$$

We have the following equation

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0.$$

By the Routh-Hurwitz Stability , if the eigenvalues are negative, then;

$$a_1 = \mu R_0^{(1)} + a - b > 0,$$

$$\mu R_0^{(1)} + \mu + \nu - \Big[\frac{p\beta\pi}{\mu R_0^{(1)}} - (\mu + \mu_T + \phi)\Big] > 0.$$

This is possible for:

$$\begin{aligned}
\frac{p\beta\pi}{\mu R_0^{(1)}} - (\mu + \mu_T + \phi) &< 0,\\
\frac{p\beta\pi}{\mu(\mu + \mu_T + \phi)} - R_0^{(1)} &< 0,\\
\frac{p\beta\pi}{\mu(\mu + \mu_T + \phi)} - \frac{(p\mu + \nu)\beta\pi}{\mu(\mu + \nu)(\mu + \mu_T + \phi)} &< 0,\\
\frac{\beta\pi}{\mu(\mu + \mu_T + \phi)}\Big(p - \frac{p\mu + \nu}{\mu + \nu}\Big) &< 0,\\
\frac{\beta\pi}{\mu(\mu + \mu_T + \phi)}\Big(\frac{\nu(p-1)}{\mu + \nu}\Big) &< 0.
\end{aligned}$$

The above inequality is possible for

$$p - 1 < 0.$$

$$\Rightarrow \qquad p < 1.$$

$$a_3 = \frac{\beta\pi}{\mu R_0^{(1)}}(d + ae) - \mu R_0^{(1)}(ab + c) > 0.$$

It can be shown that $ab + c = 0$, then we are left with analyzing

$$\begin{aligned}
\frac{\beta\pi}{\mu R_0^{(1)}}(d + ae) &> 0,\\
\frac{\beta\pi}{\mu R_0}\mu\nu(1-p)(R_0 - 1) + \frac{\beta\pi}{\mu R_0}(\mu + \nu)(R_0 - 1)\mu p &> 0,\\
\frac{\beta\pi}{\mu R_0}(R_0 - 1)\Big[\mu\nu(1-p) + (\mu + \nu)\mu p\Big] &> 0,
\end{aligned}$$

$$\frac{\beta\pi}{\mu R_0}(R_0-1)\Big[\mu(p\mu+\nu)\Big] \;>\; 0.$$

The above inequality holds for

$$R_0 - 1 > 0.$$

$$\Rightarrow \qquad R_0 > 1.$$

$$a_1 a_2 - a_3 > 0,$$

$$\Big[\mu R_0^{(1)}+a-b\Big]\Big[\mu R_0^{(1)}(a-b)-(ab+c)+\frac{\beta\pi\mu p(R_0^{(1)}-1)}{\mu R_0^{(1)}}\Big]-\Big[\frac{\beta\pi}{\mu R_0^{(1)}}(d+ae)-\mu R_0^{(1)}(ab+c)\Big] > 0.$$

It can be observed that analysis of the last condition will give the same results as for the first two conditions because of the presence of similar terms.

Thus P_e is stable for $R_0 > 1$ and $p < 1$.

Chapter 4

Transmission Model with Pre-exposure TB Vaccines and Treatment of Active Disease

The model was developed by [18] et al. The fact that vaccine may wane over time was not considered. It was also assumed that natural immunity is not enough to offer some protection and that TB cases are due to re-activation of latent bacilli not due to exogenous re-infection.

4.1 Variables

The host population was divided into the following groups:

X_u- Unvaccinated susceptible individuals.

X_v- Vaccinated susceptible individuals.

L_u- Unvaccinated latently infected individuals.

L_v- Vaccinated latently infected individuals.

T- Active TB cases.

4.2 Parameters

We have the following parameters used in this model:

π- The recruitment rate.

c- The fraction of the vaccinated susceptible individuals.

μ- The natural death rate.

μ_T - Death rate due to active disease.

β - The probability of transmission.

p - Probability of developing active TB immediately after infection.

ϕ - Effective treatment rate.

ϵ_1 - The probability of protection from infection.

ϵ_2 - The probability of protection from progressing to active TB.

ϵ_3 - The probability of protection from reactivation of latent infection.

4.3 Assumptions

- We assume that vaccine takes quite a long time to wane so vaccine waning will have not much effect on the models.
- Vaccine offers some degree of protection from infection, developing active

disease soon after infection and re-activation of the latent bacilli.

- Not every susceptible individual will be vaccinated, as a result we have the fraction c, which denotes the vaccinated portion of susceptible individuals.

In figure 4.1 we present the above information in a compartmental model.

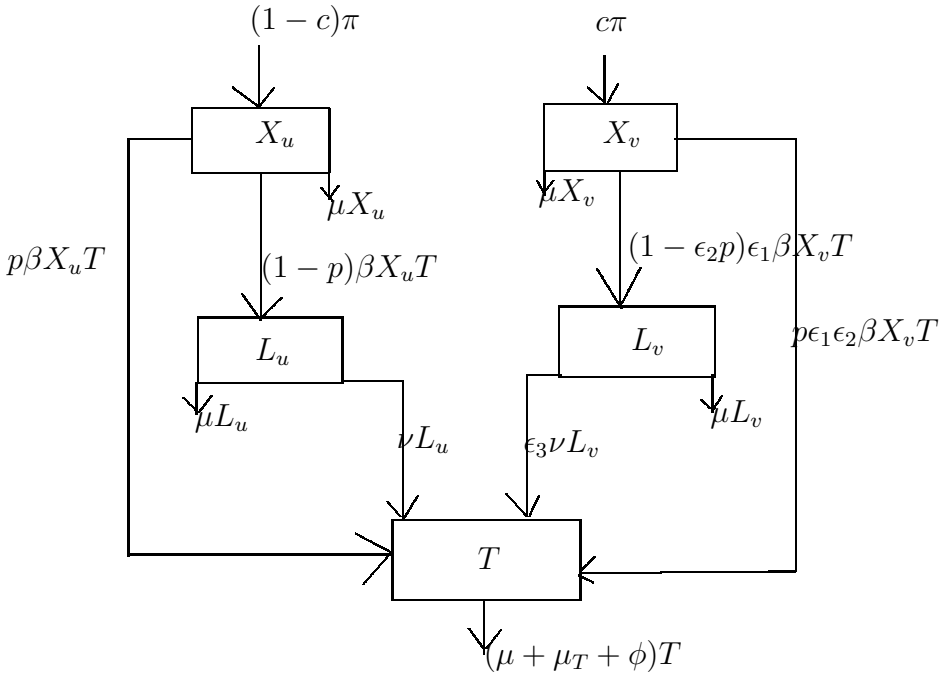

Figure 4.1: Compartmental Model 3

Individuals enter the susceptible population at rate π, and a fraction c of them are vaccinated. Uninfected-unvaccinated individuals (X_u) are infected at rate $\beta T(t)$, and then either progress to active disease (T) immediately after infection with probability p, or progress to latent infection with probability $1-p$. Latently infected individuals (L_u) progress to active disease because of re-activation of latent infection at rate ν. Uninfected-vaccinated persons (X_v) are protected from infection by probability ϵ_1. Vaccinated individuals who become latently infected (L_v) are protected from rapid progression to active disease by probability ϵ_2. It is assumed that the vaccine may offer some protection from re-activation of latent

infection by probability ϵ_3. Individuals with active TB either die at a rate μ_T or receive effective treatment at a rate ϕ.

4.4 Model equations

$$\begin{aligned}
\frac{dX_u}{dt} &= (1-c)\pi - \mu X_u - \beta X_u T, && (4.1)\\
\frac{dX_v}{dt} &= c\pi - \mu X_v - \epsilon_1 \beta X_v T, && (4.2)\\
\frac{dL_u}{dt} &= (1-p)\beta X_u T - (\mu+\nu)L_u, && (4.3)\\
\frac{dL_v}{dt} &= (1-\epsilon_2 p)\epsilon_1 \beta X_v T - (\mu+\epsilon_3\nu)L_v, && (4.4)\\
\frac{dT}{dt} &= p\beta X_u T + \epsilon_1\epsilon_2 p\beta X_v T + \nu L_u + \epsilon_3 \nu L_v - (\mu+\mu_T+\phi)T. && (4.5)
\end{aligned}$$

4.5 Equilibrium States

Equating equation (4.1) to (4.5) to zero, we solve for X_u, X_v, L_u, L_v and T.

$$\begin{aligned}
(1-c)\pi - \mu X_u - \beta X_u T &= 0, && (4.6)\\
c\pi - \mu X_v - \epsilon_1 \beta X_v T &= 0, && (4.7)\\
(1-p)\beta X_u T - (\mu+\nu)L_u &= 0, && (4.8)\\
(1-\epsilon_2 p)\epsilon_1 \beta X_v T - (\mu+\epsilon_3\nu)L_v &= 0, && (4.9)\\
p\beta X_u T + \epsilon_1\epsilon_2 p\beta X_v T + \nu L_u + \epsilon_3 \nu L_v - (\mu+\mu_T+\phi)T &= 0. && (4.10)
\end{aligned}$$

From equation (4.8) and (4.9) we have that:

$$L_u = \frac{(1-p)\beta X_u T}{\mu+\nu},$$

and

$$L_v = \frac{(1-\epsilon_2 p)\epsilon_1 \beta X_v T}{\mu + \epsilon_3 \nu}.$$

Substituting L_u and L_v into equation (4.10) we have:

$$p\beta X_u T + \epsilon_1\epsilon_2 p\beta X_v T + \nu\frac{(1-p)\beta X_u T}{\mu+\nu} + \epsilon_3\nu\frac{(1-\epsilon_2 p)\epsilon_1\beta X_v T}{\mu+\epsilon_3\nu} - (\mu+\mu_T+\phi)T \;=\; 0.$$

Factoring out T from the above equation gives:

$$T^* = 0,$$

or

$$p\beta X_u + \epsilon_1\epsilon_2 p\beta X_v + \frac{\nu(1-p)\beta X_u}{\mu+\nu} + \frac{\epsilon_3\nu(1-\epsilon_2 p)\epsilon_1\beta X_v}{\mu+\epsilon_3\nu} - (\mu+\mu_T+\phi) \;=\; 0.$$

i.e

$$(p+\frac{1-p}{\mu+\nu})\beta X_u + (\epsilon_1\epsilon_2 p + \frac{\epsilon_1\epsilon_3(1-\epsilon_2 p)}{\mu+\epsilon_3\nu})\beta X_v - (\mu+\mu_T+\phi) \;=\; 0. \quad (4.11)$$

With $T^* = 0$, into equation (4.6), we have:

$$X_u^* = \frac{(1-c)\pi}{\mu}.$$

Into equation (4.7) $T^* = 0$ gives:

$$X_v^* = \frac{c\pi}{\mu}.$$

Into equation (4.8), $T^* = 0$ gives:

$$L_u^* = 0,$$

and into equation (4.9),

$$L_v^* = 0.$$

Hence the disease free equilibrium state P_o,

$$P_0 = (X_u^*, X_v^*, 0, 0, 0) = \Big(\frac{(1-c)\pi}{\mu}, \frac{c\pi}{\mu}, 0, 0, 0\Big).$$

Which exists for $0 < c \leq 1$.

We now solve for the endemic equilibrium states.

From equation (4.6)

$$T = \frac{1}{\beta X_u}((1-c)\pi - \mu X_u).$$

Substituting T into equation (4.7), we have;

$$\begin{aligned} c\pi - \mu X_v - \epsilon_1 \beta X_v \frac{1}{\beta X_u}((1-c)\pi - \mu X_u) &= 0, \\ c\pi\beta X_u - \mu\beta X_u X_v - \epsilon_1\beta(1-c)\pi X_v + \mu\epsilon_1\beta X_v X_u &= 0, \end{aligned}$$

$$c\pi\beta X_u - \epsilon_1(1-c)\pi\beta X_v + (\epsilon_1 - 1)\mu\beta X_u X_v = 0. \qquad (4.12)$$

From equation (4.11), let

$$\begin{aligned} q &= p + \frac{\nu(1-p)}{\mu+\nu}, \\ r &= \epsilon_1\epsilon_2 p + \frac{\nu(1-\epsilon_2 p)\epsilon_1\epsilon_3}{\mu+\epsilon_3\nu}, \\ s &= \mu + \mu_T + \phi. \end{aligned}$$

Such that we have

$$q\beta X_u + r\beta X_v - s = 0. \tag{4.13}$$

From (4.13)

$$X_v = \frac{s - q\beta X_u}{r\beta}.$$

Substituting X_v into equation (4.12) we have

$$(\epsilon_1 - 1)\mu q\beta X_u^2 - (c\pi\beta r + \epsilon_1(1-c)\pi q\beta + (\epsilon_1 - 1)\mu s)X_u + \epsilon_1(1-c)\pi s = 0.$$

From above let

$$\begin{aligned} t &= (\epsilon_1 - 1)\mu q\beta, \\ u &= c\pi\beta r + \epsilon_1(1-c)\pi q\beta + (\epsilon_1 - 1)\mu s, \\ v &= \epsilon_1(1-c)\pi s. \end{aligned}$$

So that we have

$$tX_u^2 - uX_u + v = 0.$$

$$\Rightarrow X_u^* = \frac{u \pm \sqrt{u^2 - 4tv}}{2t},$$

$$\Rightarrow X_v^* = \frac{s}{r\beta} - \frac{q(u \pm \sqrt{u^2 - 4tv})}{2rt}.$$

From equation (4.6)

$$T^* = \frac{1}{\beta}(\frac{(1-c)\pi}{X_u^*} - \mu).$$

Substituting for X_u^*, we have

$$T^* = \frac{1}{\beta}(\frac{2(1-c)\pi t}{u \pm \sqrt{u^2 - 4tv}} - \mu).$$

From equation (4.8)

$$L_u^* = \frac{(1-p)\beta X_u T}{\mu + \nu},$$

$$L_u^* = \frac{(1-p)\beta X_u}{\mu + \nu}(\frac{(1-c)\pi}{\beta X_u} - \frac{\mu}{\beta}),$$

$$L_u^* = \frac{(1-p)}{\mu + \nu}((1-c)\pi - \mu X_u),$$

$$L_u^* = \frac{(1-p)}{\mu + \nu}((1-c)\pi - \mu(\frac{u \pm \sqrt{u^2 - 4tv}}{2t})).$$

Doing the same for L_v, we have from equation (4.9)

$$L_v^* = \frac{(1-\epsilon_2 p)\epsilon_1 \beta X_v T}{\mu + \epsilon_3 \nu},$$

$$L_v^* = \frac{(1-\epsilon_2 p)\epsilon_1 \beta X_v}{\mu + \epsilon_3 \nu}\left(\frac{c\pi}{\epsilon_1 \beta X_v} - \frac{\mu}{\epsilon_1 \beta}\right),$$

$$L_v^* = \frac{(1-\epsilon_2 p)}{\mu + \epsilon_3 \nu}(c\pi - \mu X_v),$$

$$L_v^* = \frac{(1-\epsilon_2 p)}{\mu + \epsilon_3 \nu}\Big(c\pi - \mu\Big(\frac{s}{r\beta} - \frac{q(u \pm \sqrt{u^2 - 4tv})}{2rt}\Big)\Big).$$

Hence the coordinates of P_e,
$P_e = \Big(\frac{u \pm \sqrt{u^2-4tv}}{2t}, \frac{s}{r\beta} - \frac{q(u\pm\sqrt{u^2-4tv})}{2rt}, \frac{(1-p)}{\mu+\nu}\Big((1-c)\pi - \mu(\frac{u\pm\sqrt{u^2-4tv}}{2t})\Big), \frac{(1-\epsilon_2 p)}{\mu+\epsilon_3\nu}\Big(c\pi - \mu(\frac{s}{r\beta} - \frac{q(u\pm\sqrt{u^2-4tv})}{2rt})\Big), \frac{1}{\beta}(\frac{2(1-c)\pi t}{u\pm\sqrt{u^2-4tv}} - \mu\Big)$.

P_e exists for

$$\begin{aligned} X_u^* = \frac{u \pm \sqrt{u^2 - 4tv}}{2t} &> 0, \\ u \pm \sqrt{u^2 - 4tv} &> 0, \\ u^2 &> u^2 - 4tv, \\ tv &> 0, \end{aligned}$$

$$\Big[(\epsilon_1 - 1)\mu\Big(\frac{p\mu + \nu}{\mu + \nu}\Big)\beta\Big]\Big[\epsilon_1(1-c)\pi(\mu + \mu_T + \phi)\Big] > 0.$$

The inequality holds for

$\epsilon_1 - 1 > 0$ or $1 - c > 0$.

$\Rightarrow \epsilon_1 > 1$ or $c < 1$.

4.6 The Reproduction Number, $R_0^{(2)}$

We now calculate the reproduction number for the model using the same method as above.

$$\mathcal{F}_i = \begin{pmatrix} (1-p)\beta X_u T \\ (1-\epsilon_2 p)\epsilon_1 \beta X_v T \\ p\beta X_u T + p\epsilon_1\epsilon_2\beta X_v T \end{pmatrix}, \qquad \mathcal{V}_i = \begin{pmatrix} (\mu+\nu)L_u \\ (\mu+\epsilon_3\nu)L_v \\ (\mu+\mu_T+\phi)T - \nu L_u - \epsilon_3\nu L_v \end{pmatrix}.$$

$$F = \begin{pmatrix} 0 & 0 & (1-p)\beta X_u \\ 0 & 0 & (1-\epsilon_2 p)\epsilon_1\beta X_v \\ 0 & 0 & p\beta X_u + p\epsilon_1\epsilon_2\beta X_v \end{pmatrix}, \qquad V = \begin{pmatrix} \mu+\nu & 0 & 0 \\ 0 & \mu+\epsilon_3\nu & 0 \\ -\nu & -\epsilon_3\nu & \mu+\mu_T+\phi \end{pmatrix}.$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu+\nu} & 0 & \frac{\nu}{(\mu+\nu)(\mu+mu_T+\phi)} \\ 0 & \frac{1}{\mu+\epsilon_3\nu} & \frac{-\epsilon_3\nu}{(\mu+\epsilon_3 nu)(\mu+\mu_T+\phi)} \\ 0 & 0 & \frac{1}{\mu+\mu_T+\phi} \end{pmatrix}.$$

$$G = FV^{-1} = \begin{pmatrix} 0 & 0 & \frac{(1-p)(1-c)\beta\pi}{\mu(\mu+\mu_T+\phi)} \\ 0 & 0 & \frac{(1-\epsilon_2 p)\epsilon_1\beta c\pi}{\mu(\mu+\mu_T+\phi)} \\ 0 & 0 & \frac{p\beta(1-c)\pi + p\epsilon_1\epsilon_2\beta c\pi}{\mu(\mu+\mu_T+\phi)} \end{pmatrix}.$$

Solving the equation

$$|G - \lambda I| = 0,$$

we have

$$\lambda_1 = 0,$$

and

$$\lambda_2 = \frac{p\beta(1-c)\pi + p\epsilon_1\epsilon_2\beta c\pi}{\mu(\mu+\mu_T+\phi)}.$$

λ_2 is the dominant eigenvalue which corresponds to the value of R_0. Thus

$$R_0 = \Big[\frac{\beta\pi}{\mu}\Big]\Big[\frac{1}{\mu+\mu_T+\phi}\Big]\Big[1-c+\epsilon_1\epsilon_2 c\Big]\Big[p\Big].$$

4.6.1 Analysis of the Reproduction Number

Expressing $R_0^{(2)}$ in terms of R_0 we have

$$R_0^{(2)} = R_0\frac{(\mu+\nu)(\mu+\mu_T)((1-c)+\epsilon_1\epsilon_2 c)p}{(\mu+\mu_T+\phi)(p\mu+\nu)}.$$

It can be noted that $R_0^{(2)}$ reduces R_0 in three ways. The first one is by reducing the mean infectious period by the factor ϕ. Secondly, the total probability of developing active TB, $\frac{\nu(1-p)}{\nu+\mu}+p$, by that it does not have the term $\frac{\nu(1-p)}{\nu+\mu}$. Thirdly by further reducing p by the factor $1-c+\epsilon_1\epsilon_2 c$. So we may consider the introduction of pre-exposure TB vaccines as a successful epidemic control strategy and more effective than treatment of active disease alone.

4.7 Stability Analysis of P_0 and P_e by the linearization Method.

P_0 is stable if the eigenvalues of the linearized form of the system evaluated at P_0 are all negative.

The linearized form J, for the third model is as follows:

$$J = \begin{pmatrix} -\mu - \beta T^* & 0 & 0 & 0 & -\beta X_u^* \\ 0 & -\mu - \epsilon_1 \beta T^* & 0 & 0 & -\epsilon_1 \beta X_v^* \\ (1-p)\beta T^* & 0 & -(\mu+\nu) & 0 & (1-p)\beta X_u^* \\ 0 & (1-\epsilon_2 p)\epsilon_1 \beta T^* & 0 & -(\mu+\epsilon_3\nu) & (1-\epsilon_2 p)\epsilon_1 \beta X_v^* \\ p\beta T^* & p\beta\epsilon_1\epsilon_2 T^* & \nu & \epsilon_3\nu & p\beta X_u^* + p\epsilon_1\epsilon_2\beta X_v^* - (\mu+\mu_T+\phi) \end{pmatrix}.$$

Evaluated at $P_0 = (\frac{(1-c)\pi}{\mu}, \frac{c\pi}{\mu}, 0, 0, 0)$ we get:

$$J(P_0) = \begin{pmatrix} -\mu & 0 & 0 & 0 & \frac{-\beta(1-c)\pi}{\mu} \\ 0 & -\mu & 0 & 0 & \frac{-\epsilon_1\beta c\pi}{\mu} \\ 0 & 0 & -(\mu+\nu) & 0 & \frac{(1-p)\beta(1-c)\pi}{\mu} \\ 0 & 0 & 0 & -(\mu+\epsilon_3\nu) & \frac{(1-\epsilon_2 p)\epsilon_1\beta c\pi}{\mu} \\ 0 & 0 & \nu & \epsilon_3\nu & \frac{p\beta(1-c)\pi}{\mu} + \frac{p\epsilon_1\epsilon_2\beta c\pi}{\mu} - (\mu+\mu_T+\phi) \end{pmatrix}.$$

If we let,

$$\begin{aligned} a &= \mu + \nu, \\ b &= \frac{(1-p)\beta(1-c)\pi}{\mu}, \\ c &= \mu + \epsilon_3\nu, \\ d &= \frac{(1-\epsilon_2 p)\epsilon_1\beta c\pi}{\mu}, \\ \gamma &= \frac{p\beta(1-c)\pi}{\mu} + \frac{p\epsilon_1\epsilon_2\beta c\pi}{\mu} - (\mu+\mu_T+\phi). \end{aligned}$$

and solve

$$|J(P_0) - \lambda I| = 0,$$

we get:

$$|J(P_0) - \lambda I| = \begin{vmatrix} -\mu-\lambda & 0 & 0 & 0 & \frac{-\beta(1-c)\pi}{\mu} \\ 0 & -\mu-\lambda & 0 & 0 & \frac{-\epsilon_1\beta c\pi}{\mu} \\ 0 & 0 & -a-\lambda & 0 & b \\ 0 & 0 & 0 & -c-\lambda & d \\ 0 & 0 & \nu & \epsilon_3\nu & \gamma-\lambda \end{vmatrix} = 0,$$

$$(-\mu-\lambda)(-\mu-\lambda)\begin{vmatrix} -a-\lambda & 0 & b \\ 0 & -c-\lambda & d \\ \nu & \epsilon_3\nu & \gamma-\lambda \end{vmatrix} = 0,$$

$-\mu-\lambda = 0$, $-\mu-\lambda = 0$,

$$\Rightarrow \lambda_1 = \lambda_2 = -\mu.$$

$$(-a-\lambda)\begin{vmatrix} -c-\lambda & d \\ \epsilon_3\nu & \gamma-\lambda \end{vmatrix} + b\begin{vmatrix} 0 & -(c+\lambda) \\ \nu & \epsilon_3\nu \end{vmatrix} = 0,$$

$$\begin{aligned} -(a+\lambda)(-(c+\lambda)(\gamma-\lambda) - d\epsilon_3\nu) + b\nu(c+\lambda) &= 0, \\ (a+\lambda)(c+\lambda)(\gamma-\lambda) + (a+\lambda)d\epsilon_3\nu + bc\nu + b\nu\lambda &= 0, \\ (a+\lambda)(-\lambda^2 + (\gamma-c)\lambda + c\gamma) + ad\epsilon_3\nu + d\epsilon_3\nu\lambda + bc\nu + b\nu\lambda &= 0, \\ \lambda^3 + (a-\gamma+c)\lambda^2 + (a(c-\gamma) - c\gamma - b\nu - \epsilon_3\nu d)\lambda + (-bc\nu - ad\epsilon_3\nu - ac\gamma) &= 0. \end{aligned}$$

Let

$$\begin{aligned} a_1 &= a - \gamma + c, \\ a_2 &= a(c-\gamma) - c\gamma - b\nu - \epsilon_3 \nu d, \\ a_3 &= -bc\nu - ad\epsilon_3\nu - ac\gamma. \end{aligned}$$

So that we have

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0.$$

By the Rourth-Hurwitz Stability Criterion, if the eigenvalues above have negative real parts, then

$$a_1 = a + c - \gamma > 0,$$

$$(\mu+\nu) + (\mu + \epsilon_3\nu) - \left[\tfrac{p\beta\pi(1-c+\epsilon_1\epsilon_2 c)}{\mu} - (\mu + \mu_T + \phi)\right] > 0.$$

The above inequality is satisfied for

$$\begin{aligned} \frac{p\beta\pi(1-c+\epsilon_1\epsilon_2 c)}{\mu} - (\mu+\mu_T+\phi) &< 0, \\ \frac{p\beta\pi(1-c+\epsilon_1\epsilon_2 c)}{\mu} &< (\mu+\mu_T+\phi), \\ \frac{p\beta\pi(1-c+\epsilon_1\epsilon_2 c)}{\mu(\mu+\mu_T+\phi)} &< 1, \\ R_0 &< 1. \end{aligned}$$

$$a_3 = -(bc\nu + ad\epsilon_3\nu + ac\gamma) > 0,$$

$$a_3 = bc\nu + ad\epsilon_3\nu + ac\gamma < 0,$$

$\left[\frac{(1-p)(1-c)\beta\pi\nu}{\mu}(\mu+\epsilon_3\nu)\right]+\left[(\mu+\nu)(\frac{(1-\epsilon_2 p)c\epsilon_1\beta\pi}{\mu})\epsilon_3\nu\right]+\left[(\mu+\nu)(\mu+\epsilon_3\nu)(\frac{p\beta\pi(1-c+\epsilon_1\epsilon_2 c)}{\mu}-(\mu+\mu_T+\phi))\right]<0.$

The above is possible if:

$$\frac{p\beta\pi(1-c+\epsilon_1\epsilon_2 c)}{\mu}-(\mu+\mu_T+\phi)<0$$
$$\Rightarrow \qquad R_0<1$$

The same conditions are observed for the third condition of the criterion because of the presence of similar terms.

Analysis for P_e

The equilibrium points for the endemic state are too big and manual analysis is a bit tricky and too long. So we will not use numerics at this point.

Chapter 5

Transmission Model with Post-exposure TB Vaccines and Treatment of active TB

The model was developed from the work of [18] et al, where the following cases were not considered, vaccine waning, natural immunity and re-infection of latently infected individuals.

5.1 Variables

The host population was divided into the following groups:

X_u - Unvaccinated susceptible individuals.

L_u - Unvaccinated latently infected individuals.

L_v - Vaccinated latently infected persons.

T - Active TB cases.

5.2 Parameters

The parameters used are as follows:

χ - The rate at which the latently infected individuals are vaccinated.

π- The recruitment rate.

μ- The natural death rate.

β- The probability of transmission.

ϵ_3 - The probability of protection from reactivation of latent infection.

p- The probability of progressing to active disease immediately after infection.

ν- The rate of reactivation of latent bacilli.

μ_T- Death rate due to TB.

ϕ - Effective treatment rate.

5.3 Assumptions

The assumptions for the model are the same as for the model with pre-exposure vaccines, with an exception of those assumptions about vaccinated susceptible individuals because we do not have them.

In figure 5.1 is the compartmental model representing the above information about the model.

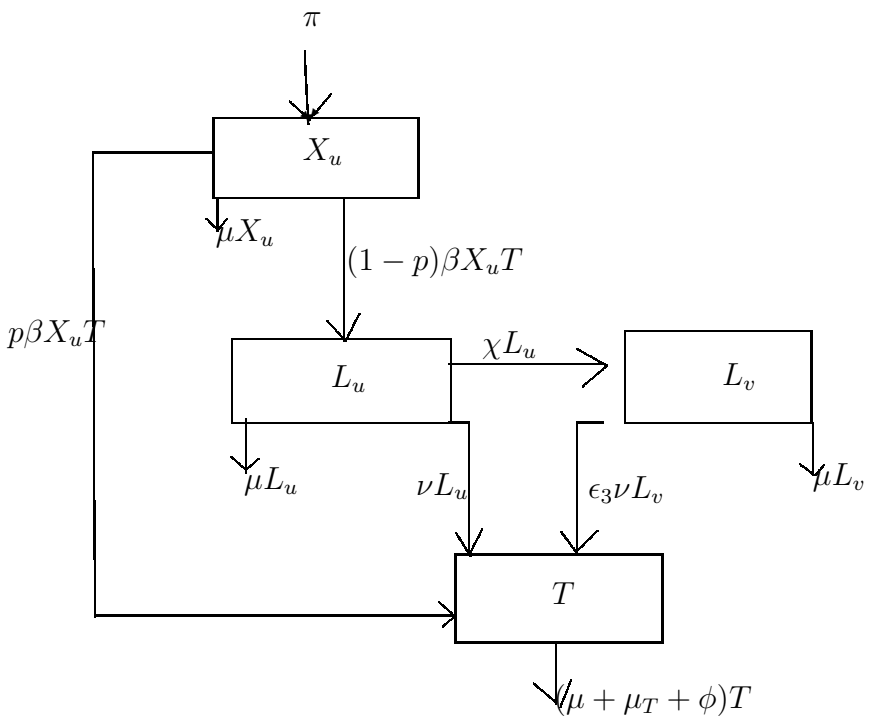

Figure 5.1: Compartmental Model 4

Individuals enter the population at rate π. They become infected at rate $\beta T(t)$ and then either progress rapidly to active disease with probability p or progress to latent infection (L_u) with probability $1-p$. latently infected individuals (L_u) progress to active disease at rate ν due to re-activation of latent infection. Latently infected individuals may also be vaccinated at a rate χ. Vaccinated-latently infected individuals (L_v) are protected from re-activation of latent infection by probability ϵ_3. Individuals with active TB either die at rate μ_T or receive effective treatment at a rate ϕ. The average life expectancy is $1/\mu$.

5.4 Model Equations

$$\begin{aligned}
\frac{dX_u}{dt} &= \pi - \mu X_u - \beta X_u T, && (5.1)\\
\frac{dL_u}{dt} &= (1-p)\beta X_u T - (\chi + \mu + \nu)L_u, && (5.2)\\
\frac{dL_v}{dt} &= \chi L_u - (\mu + \epsilon_3 \nu)L_v, && (5.3)\\
\frac{dT}{dt} &= p\beta X_u T + \nu L_u + \epsilon_3 \nu L_v - (\mu + \mu_T + \phi)T. && (5.4)
\end{aligned}$$

5.5 Equilibrium Points

At equilibrium we have the following solutions of the above system:

$$\begin{aligned}
\pi - \mu X_u - \beta X_u T &= 0, && (5.5)\\
(1-p)\beta X_u T - (\chi + \mu + \nu)L_u &= 0, && (5.6)\\
\chi L_u - (\mu + \epsilon_3 \nu)L_v &= 0, && (5.7)\\
p\beta X_u T + \nu L_u + \epsilon_3 \nu L_v - (\mu + \mu_T + \phi)T &= 0. && (5.8)
\end{aligned}$$

From equation (5.6) and (5.7) we have the following respectively:

$$L_u = \frac{(1-p)\beta X_u T}{\chi + \nu + \mu},$$

$$L_v = \frac{\chi L_u}{\mu + \epsilon_3 \nu},$$

$$= \frac{\chi(1-p)\beta X_u T}{(\mu + \epsilon_3 \nu)(\chi + \nu + \mu)}.$$

Substituting L_u and L_v into equation (5.8) we have

$$p\beta X_u T + \nu\frac{(1-p)\beta X_u T}{\chi+\nu+\mu} + \epsilon_3\nu\frac{\chi(1-p)\beta X_u T}{(\mu+\epsilon_3\nu)(\chi+\nu+\mu)} - (\mu+\mu_T+\phi)T = 0.$$

If we factor out T from above we get

$$T^* = 0,$$

and

$$(p + \nu\frac{(1-p)}{\chi+\nu+\mu} + \epsilon_3\nu\frac{\chi(1-p)}{(\mu+\epsilon_3\nu)(\chi+\nu+\mu)})\beta X_u - (\mu+\mu_T+\phi) = 0. \quad (5.9)$$

With $T^* = 0$ into equation (5.5) we have that

$$X_u^* = \pi/\mu.$$

In equation (5.6)

$$L_u^* = 0.$$

In equation (5.7)

$$L_v^* = 0.$$

Hence we have our P_0 given by

$$P_0 = (X_u^*, 0, 0, 0) = (\pi/\mu, 0, 0, 0).$$

Which exists readily since $\pi/\mu > 0$.

Now solving for the endemic equilibrium points, from equation (5.9) let

$q = p + \nu\frac{(1-p)}{\chi+\nu+\mu} + \epsilon_3\nu\frac{\chi(1-p)}{(\mu+\epsilon_3\nu)(\chi+\nu+\mu)}$,

$r = \mu + \mu_T + \phi$.

Then we have

$q\beta X_u - r = 0$.

$$\Rightarrow \quad X_u = \frac{r}{q\beta}.$$

From equation (5.5)

$$T^* = \frac{\pi}{\beta X_u^*} - \frac{\mu}{\beta}$$

$$\Rightarrow \quad T^* = \frac{q\pi}{r} - \frac{\mu}{\beta}.$$

From equation (5.6)

$$L_u^* = \frac{(1-p)\beta X_u^* T^*}{\chi+\nu+\mu},$$

$$= \frac{(1-p)\beta X_u^*}{\chi+\nu+\mu}(\frac{\pi}{\beta X_u^*} - \frac{\mu}{\beta}),$$

$$= \frac{1-p}{\chi+\mu+\nu}(\pi - \mu X_u^*),$$

$$= \frac{1-p}{\chi+\nu+\mu}(\pi - \frac{\mu r}{\beta q}).$$

From equation (5.7)

$$L_v^* = \frac{\chi L_u^*}{\mu+\epsilon_3\nu},$$

$$= \frac{\chi(1-p)}{(\mu+\epsilon_3\nu)(\chi+\nu+\mu)}(\pi - \frac{\mu r}{q\beta}).$$

Thus
$P_e = (X_u^*, L_u^*, L_v^*, T^*) = \left(\frac{r}{q\beta}, \frac{1-p}{\chi+\nu+\mu}(\pi - \frac{\mu r}{\beta q}), \frac{\chi(1-p)}{(\mu+\epsilon_3\nu)(\chi+\nu+\mu)}(\pi - \frac{\mu r}{q\beta}), \frac{q\pi}{r} - \frac{\mu}{\beta}\right).$

Next we establish the conditions for the equilibrium points to be defined.

X_u^* is readily defined because $r > 0$.

$T^* = \frac{q\pi}{r} - \frac{\mu}{\beta} > 0,$

$\Rightarrow \frac{q\pi}{r} > \frac{\mu}{\beta}$,

$\Rightarrow (\frac{\beta\pi}{\mu})(\frac{1}{\mu+\mu_T+\phi})q > 1.$

$L_u^* = \frac{1-p}{\chi+\nu+\mu}(\pi - \frac{\mu r}{\beta q}) > 0,$

$\Rightarrow \pi > \frac{\mu r}{\beta q}$,

$\Rightarrow \frac{\beta\pi q}{\mu r} > 1,$

$\Rightarrow (\frac{\beta\pi}{\mu})(\frac{1}{\mu+\mu_T+\phi})q > 1.$

$L_v^* = \frac{\chi(1-p)}{(\mu+\epsilon_3\nu)(\chi+\nu+\mu)}(\pi - \frac{\mu r}{q\beta}) > 0,$

$\Rightarrow \pi - \frac{\mu r}{q\beta} > 0,$

$\Rightarrow (\frac{\beta\pi}{\mu})(\frac{1}{\mu+\mu_T+\phi})q > 1.$

Where

$$q = \frac{p(\chi+\mu)+}{\chi+\nu+\mu} + \frac{\chi\epsilon_3\nu(1-p)}{(\mu+\epsilon_3\nu)(\chi+\mu+\nu)}.$$

5.6 The Reproduction Number, $R_0^{(3)}$

As for the previous models, we calculate $R_0^{(3)}$ for this model.

$$\mathcal{F}_i = \begin{pmatrix} (1-p)\beta X_u T \\ 0 \\ p\beta X_u T \end{pmatrix}, \qquad \mathcal{V}_i = \begin{pmatrix} (\chi+\nu+\mu)L_u \\ (\mu+\epsilon_3\nu)L_v - \chi L_u \\ (\mu+\mu_T+\phi)T - \nu L_u - \epsilon_3\nu L_v \end{pmatrix}.$$

$$F = \begin{pmatrix} 0 & 0 & (1-p)\beta X_u \\ 0 & 0 & 0 \\ 0 & 0 & p\beta X_u \end{pmatrix}, \qquad V = \begin{pmatrix} \chi+\nu+\mu & 0 & 0 \\ -\chi & \mu+\epsilon_3\nu & 0 \\ -\nu & -\epsilon_3\nu & \mu+\mu_T+\phi \end{pmatrix}.$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\chi+\nu+\mu} & \frac{-\chi}{(\chi+\nu+\mu)(\epsilon_3\nu+\mu)} & \frac{\chi\epsilon_3\nu+\nu(\mu+\epsilon_3\nu)}{(\chi+\mu+\nu)(\mu+\epsilon_3\nu)(\mu+\mu_T+\phi)} \\ 0 & \frac{1}{\mu+\epsilon_3\nu} & \frac{-\epsilon\nu}{(\mu+\epsilon_T\nu)(\mu+\mu_T+\phi)} \\ 0 & 0 & \frac{1}{\mu+\mu_T+\phi} \end{pmatrix}.$$

$$G = FV^{-1} = \begin{pmatrix} 0 & 0 & \frac{(1-p)\beta\pi}{\mu(\mu+\mu_T+\phi)} \\ 0 & 0 & 0 \\ 0 & 0 & \frac{p\beta\pi}{\mu(\mu+\mu_T+\phi)} \end{pmatrix}.$$

Solving $|G - \lambda I| = 0$,

we have

$$\lambda_1 = \lambda_2 = 0,$$

and

$$\lambda_3 = \frac{p\beta\pi}{\mu(\mu+\mu_T+\phi)}.$$

λ_3 is the dominating eigenvalue and therefore equal to $R_0^{(3)}$.

i.e

$$R_0^{(3)} = \Big(\frac{\beta\pi}{\mu}\Big)\Big(\frac{1}{\mu+\mu_T+\phi}\Big)\Big(p\Big).$$

5.6.1 Analysis of the Reproduction Number

The Reproduction number for this model depends linearly on the average number of susceptible individuals that one infectious case infects per unit time,$\beta\pi/\mu$, the mean infectious period, $\frac{1}{\mu+\mu_T+\phi}$, and the probability that an infected individual will develop into an infectious case p. It does not depend on the probability of progressing to latent infection which reduces the total probability that an infected individual will develop into an infectious case.

That is

$$R_0 = \Big[\frac{\beta\pi}{\mu}\Big]\Big[\frac{1}{\mu+\mu_T+\phi}\Big]\Big[p\Big].$$

The missing term, $\frac{\nu(1-p)}{\mu+\nu}$ of the total probability of developing into an infectious case, reduces the total probability $\frac{p\mu+\nu}{\mu+\nu}$ hence reducing R_0. The mean infectious period $\frac{1}{\mu+\nu}$ is also reduced by a factor ϕ. Expressing $R_0^{(3)}$ in terms of R_0 we have

$$R_0^{(3)} = R_0\frac{(\mu+\nu)(\mu+\mu_T)p}{(\mu+\mu_T+\phi)(p\mu+\nu)}.$$

Compared to $R_0^{(2)}$, we see that it has a missing term that is capable of reducing p, which reduces R_0 further. Thus it is less effective in reducing R_0 than $R_0^{(2)}$, but better than $R_0^{(1)}$. Thus in terms of R_0 only, the pre-exposure vaccine model with treatment is effective than the post-exposure vaccine model with treatment.

5.7 Stability Analysis of P_0 by the Linearization Method

As before, we find the linearized matrix of the system and evaluate it at P_0 and then find the eigenvalues of J. If they are all negative then we conclude that P_0 is stable.

$$J = \begin{pmatrix} -\mu - \beta T^* & 0 & 0 & -\beta X_u^* \\ (1-p)\beta T^* & -(\chi+\nu+\mu) & 0 & (1-p)\beta X_u^* \\ 0 & \chi & -(\mu+\epsilon_3\nu) & 0 \\ p\beta T^* & \nu & \epsilon_3\nu & p\beta X_u^* - (\mu+\mu_T+\phi) \end{pmatrix}.$$

Evaluating J at $P_0 = (\pi/\mu, 0, 0, 0)$ we have

$$J(P_0) = \begin{pmatrix} -\mu & 0 & 0 & -\frac{\beta\pi}{\mu} \\ 0 & -(\chi+\nu+\mu) & 0 & \frac{(1-p)\beta\pi}{\mu} \\ 0 & \chi & -(\mu+\epsilon_3\nu) & 0 \\ 0 & \nu & \epsilon_3\nu & \frac{p\beta\pi}{\mu} - (\mu+\mu_T+\phi) \end{pmatrix}.$$

If we let

$$\begin{aligned} a &= \chi+\nu+\mu, \\ b &= (1-p)\beta\pi/\mu, \\ c &= \mu+\epsilon_3\nu, \\ \gamma &= \frac{p\beta\pi}{\mu} - (\mu+\mu_T+\phi). \end{aligned}$$

and solve

$$|J(P_0) - \lambda I| = 0,$$

we have

$$|J(P_0) - \lambda I| = \begin{vmatrix} -\mu - \lambda & 0 & 0 & \frac{-\beta\pi}{\mu} \\ 0 & -a - \lambda & 0 & b \\ 0 & \chi & -c - \lambda & 0 \\ 0 & \nu & \epsilon_3\nu & \gamma - \lambda \end{vmatrix} = 0,$$

which reduces to

$$(-\mu - \lambda) \begin{vmatrix} -a - \lambda & 0 & b \\ \chi & -c - \lambda & 0 \\ \nu & \epsilon_3\nu & \gamma - \lambda \end{vmatrix} = o.$$

$$-\mu - \lambda = 0 \qquad \Rightarrow \qquad \lambda_1 = -\mu$$

Solving for the other three roots from the 3 by 3 matrix we have

$$\lambda^3 + (c - \gamma + a)\lambda^2 + ((c - \gamma)a - c\gamma - b\nu)\lambda + (-c\gamma a - b\chi\epsilon_3\nu - b\nu c) = 0.$$

Let

$$\begin{aligned} a_1 &= c - \gamma + a, \\ a_2 &= (c - \gamma)a - c\gamma - b\nu, \\ a_3 &= -c\gamma a - b\chi\epsilon_3\nu - b\nu c. \end{aligned}$$

$\Rightarrow \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0.$

By the Routh-Hurwitz Stability Criterion as for above models, if the eigenvalues are negative, then

$$a_1 = c - \gamma + a > 0,$$

$$a_3 = -c\gamma a - b\chi\epsilon_3\nu - b\nu c > 0,$$

$$a_1a_2 - a_3 = \Big(c - \gamma + a\Big)\Big((c-\gamma)a - c\gamma - b\nu\Big) + \Big((c-\gamma)a + c\gamma + b\nu\Big) > 0.$$

Substituting back for the values of a, b, c and γ we have

$$a_1 = (\mu + \epsilon_3\nu) - \Big[\tfrac{p\beta\pi}{\mu} - (\mu + \mu_T + \phi)\Big] + (\chi + \nu + \mu) > 0.$$

This is possible when $\gamma < 0$, that is

$$\begin{aligned} \frac{p\beta\pi}{\mu} - (\mu + \mu_T + \phi) &< 0, \\ \frac{p\beta\pi}{\mu} &< (\mu + \mu_T + \phi), \\ \Rightarrow \quad \frac{p\beta\pi}{\mu(\mu + \mu_T + \phi)} &< 1, \\ \Rightarrow \quad R_0 &< 1. \end{aligned}$$

$$a_3 = \Big[(\mu + \epsilon_3\nu)\Big(\tfrac{p\beta\pi}{\mu} - (\mu + \mu_T + \phi)\Big)(\chi + \nu + \mu)\Big] + \Big[\tfrac{(p-1)\beta\pi\nu}{\mu}(\chi\epsilon_3 + \mu + \epsilon_3\nu)\Big] < 0.$$

We consider $a_3 < 0$ because a_3 is negative.

For $a_3 < 0$ then

$$\begin{aligned} \gamma = \frac{p\beta\pi}{\mu} - (\mu + \mu_T + \phi) &< 0, \\ \Rightarrow \frac{p\beta\pi}{\mu(\mu + \mu_T + \phi)} &< 1, \\ \Rightarrow R_0 &< 1. \end{aligned}$$

The same conditions as above are observed for the third part of the criterion, $a_1a_2 - a_3 > 0$ because of the presence of similar terms.

Analysis for P_e

Due to the size of the endemic equilibrium points, finding the conditions for P_e to be stable manually, will be a bit cumbersome. At this point, we will not consider numerical analysis.

Chapter 6

Model With Combined Pre-exposure Vaccine, Post-exposure Vaccine and Treatment of active disease

The model was developed from the work of [17] and [18] et al from their pre- and post-exposure vaccines models. We tried to combine the two models so that we have vaccination both before and after infection. We shall find out the effect of the two vaccines when combined.

6.1 Variables

The host population for the model is divided into:

- X_u - the unvaccinated susceptible individuals.

- X_v - the vaccinated susceptible individuals.
- L_u - the unvaccinated latently infected individuals.
- L_v - the vaccinated latently infected individuals.
- T - the active tb cases.

6.2 Parameters

We have the following parameters used in this model:

π- The recruitment rate.

c- The fraction of the vaccinated susceptible individuals.

μ- The natural death rate.

μ_T - Death rate due to active disease.

β - The probability of transmission.

p - Probability of developing active TB immediately after infection.

ϕ - Effective treatment rate.

ϵ_1 - The probability of protection from infection.

ϵ_2 - The probability of protection from progressing to active TB.

ϵ_3 - The probability of protection from reactivation of latent infection.

χ - The rate at which the latently infected individuals are vaccinated.

6.3 Assumptions

- Transmission occurs through contact between a susceptible individual and an infectious individual.
- The net rate at which new infected individuals arise is proportional to the number of susceptible individuals X_u, times the number of infectious individuals T, times the probability of transmission from T to X_u, β, i.e $\beta X_u T$.
- TB is a fatal disease, that is TB kills.
- After being infected, a susceptible individual may either develop active TB immediately after infection at a probability p or become latently infected with probability $1 - p$.
- Active TB cases are due to endogenous re-activation of latent bacilli only, with exogenous cases insignificant.
- There is no natural immunity against infection and against progression to active disease.
- Treated individuals get permanent immunity against TB.
- We assume that vaccine takes quite a long time to wane so vaccine waning will have not much effect on the models.
- Vaccine offers some degree of protection from infection, developing active disease soon after infection and re-activation of the latent bacilli.
- Not every susceptible individual will be vaccinated, as a result we have the fraction c, which denotes the vaccinated portion of susceptible individuals.

Figure 6.1 shows the compartmental model.

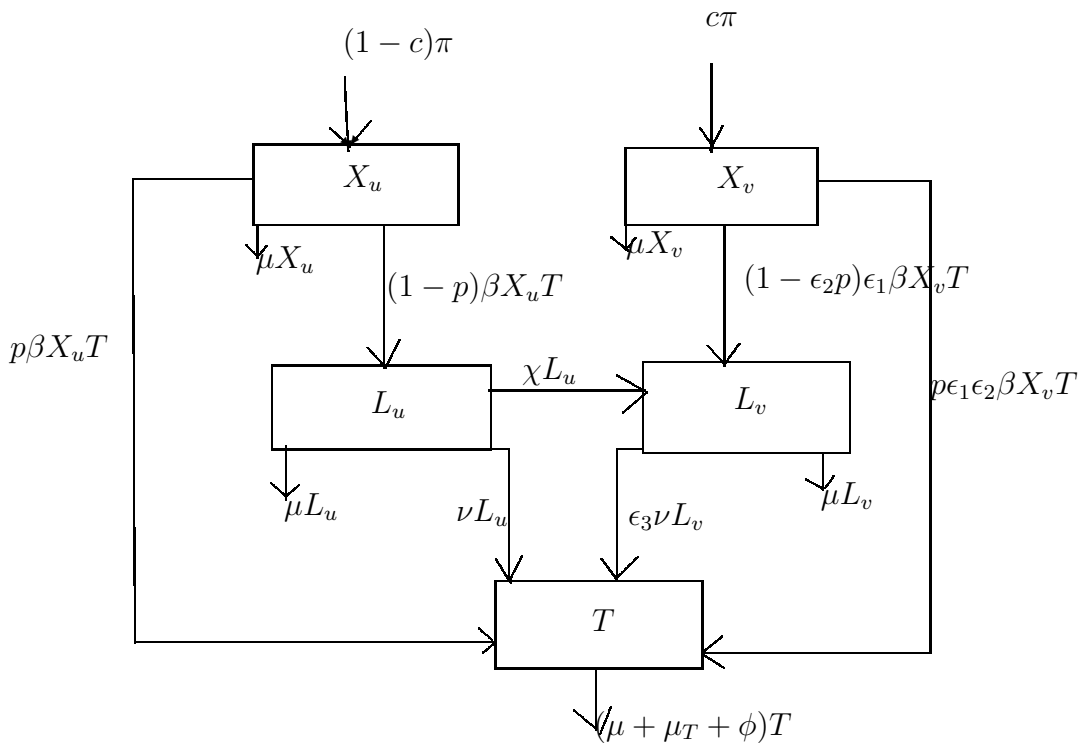

Figure 6.1: Compartmental Model 5

Individuals enter the susceptible population at rate π, and a fraction c of them are vaccinated. Uninfected-unvaccinated persons (X_u) are infected at rate $\beta T(t)$, and then either progress to active disease (T) immediately after infection with probability p, or progress to latent infection with probability $1-p$. Latently infected individuals (L_u) may be vaccinated at a rate χ or progress to active disease because of re-activation of latent infection at rate ν.

Uninfected-vaccinated individuals (X_v) are protected from infection by probability ϵ_1. Vaccinated individuals who become latently infected (L_v) are protected from rapid progression to active disease by probability ϵ_2. It is assumed that the vaccine may offer some protection from re-activation of the latent infection by probability ϵ_3. Persons with active TB either die at a rate μ_T or receive effective treatment at rate ϕ. The average life expectancy is $1/\mu$.

6.4 Model Equations

$$\begin{aligned}
\frac{dX_u}{dt} &= (1-c)\pi - \beta X_u T - \mu X_u, && (6.1)\\
\frac{dX_v}{dt} &= c\pi - \epsilon_1 \beta X_v T - \mu X_v, && (6.2)\\
\frac{dL_u}{dt} &= (1-p)\beta X_u T - (\chi + \nu + \mu) L_u, && (6.3)\\
\frac{dL_v}{dt} &= (1-\epsilon_2 p)\epsilon_1 \beta X_v T + \chi L_u - (\mu + \epsilon_3 \nu) L_v, && (6.4)\\
\frac{dT}{dt} &= p\beta X_u T + p\epsilon_1\epsilon_2 \beta X_v T + \nu L_u + \epsilon_3 \nu L_v - (\mu + \mu_T + \phi) T. && (6.5)
\end{aligned}$$

6.5 Equilibrium Points

We now find the equilibrium points by solving the above system when at equilibrium.

$$\begin{aligned}
(1-c)\pi - \beta X_u T - \mu X_u &= 0, && (6.6)\\
c\pi - \epsilon_1 \beta X_v T - \mu X_v &= 0, && (6.7)\\
(1-p)\beta X_u T - (\chi + \nu + \mu) L_u &= 0, && (6.8)\\
(1-\epsilon_2 p)\epsilon_1 \beta X_v T + \chi L_u - (\mu + \epsilon_3 \nu) L_v &= 0, && (6.9)\\
p\beta X_u T + p\epsilon_1\epsilon_2 \beta X_v T + \nu L_u + \epsilon_3 \nu L_v - (\mu + \mu_T + \phi) T &= 0. && (6.10)
\end{aligned}$$

From equation (6.8)

$$L_u = \frac{(1-p)\beta X_u T}{\chi + \nu + \mu}.$$

From equation (6.9)

$$L_v = \frac{(1-\epsilon_2 p)\epsilon_1 \beta X_v T}{\mu + \epsilon_3 \nu} + \frac{\chi L_u}{\mu + \epsilon_3 \nu},$$

$$\Rightarrow L_v = \frac{(1-\epsilon_2 p)\epsilon_1 \beta X_v T}{\mu + \epsilon_3 \nu} + \frac{\chi(1-p)\beta X_u T}{(\chi+\nu+\mu)(\mu+\epsilon_3\nu)}.$$

Substituting L_u and L_v into equation (6.10) we get

$$p\beta X_u T + p\epsilon_1\epsilon_2\beta X_v T + \nu\tfrac{(1-p)\beta X_u T}{\chi+\nu+\mu} + \epsilon_3\nu(\tfrac{(1-\epsilon_2 p)\epsilon_1\beta X_v T}{\mu+\epsilon_3\nu} + \tfrac{\chi(1-p)\beta X_u T}{(\chi+\nu+\mu)(\mu+\epsilon_3\nu)}) -$$

$$(\mu + \mu_T + \phi)T = 0.$$

From the above equation, if we factor out T we get that

$$T^* = 0,$$

or

$$(p + \tfrac{\nu(1-p)}{\chi+\nu+\mu} + \tfrac{\chi(1-p)}{(\chi+\nu+\mu)(\mu+\epsilon_3\nu)})\beta X_u + (p\epsilon_1\epsilon_2 + \tfrac{\epsilon_3\nu(1-\epsilon_2 p)\epsilon_1}{\mu+\epsilon_3\nu})\beta X_v$$

$$-(\mu + \mu_T + \phi) = 0. \tag{6.11}$$

With $T^* = 0$ into equation

$$(6.6) \Rightarrow X_u^* = \frac{(1-c)\pi}{\mu}.$$

$$(6.7) \Rightarrow X_v^* = \frac{c\pi}{\mu}.$$

$$(6.8) \Rightarrow L_u^* = 0.$$

(6.9) with $L_u^* = 0$

$$\Rightarrow L_v^* = 0.$$

Which gives the value of P_0,

$$P_0 = (X_u^*, X_v^*, 0, 0, 0) = \Big(\frac{(1-c)\pi}{\mu}, \frac{c\pi}{\mu}, 0, 0, 0\Big).$$

Which exists for $0 < c \leq 1$.

We next solve for the endemic equilibrium state.

From equation (6.6)

$$T = \frac{(1-c)\pi}{\beta X_u} - \frac{\mu}{\beta}.$$

Substituting T into equation (6.7) we get

$$\begin{aligned} c\pi - \frac{(\epsilon_1\beta X_v)((1-c)\pi - \mu X_u)}{\beta X_u} - \mu X_v &= 0, \\ c\pi\beta X_u - \epsilon_1\beta X_v((1-c)\pi - \mu X_u) - \mu\beta X_u X_v &= 0, \end{aligned}$$

$$c\pi\beta X_u - \epsilon_1(1-c)\pi\beta X_v - (1-\epsilon_1)\mu\beta X_u X_v = 0. \qquad (6.12)$$

From equation (6.11) let

$$\begin{aligned} q &= p + \frac{\nu(1-p)}{\chi+\nu+\mu} + \frac{\chi(1-p)}{(\chi+\nu+\mu)(\mu+\epsilon_3\nu)}, \\ r &= p\epsilon_1\epsilon_2 + \frac{\epsilon_3\nu(1-\epsilon_2 p)\epsilon_1}{\mu+\epsilon_3\nu}, \\ s &= \mu+\mu_T+\phi. \end{aligned}$$

So that (6.11) is

$q\beta X_u + r\beta X_v - s = 0.$

Making X_v the subject from above we get

$$X_v = \frac{s - q\beta X_u}{r\beta}.$$

Substituting X_v into equation (6.12) we have

$c\pi\beta X_u - \frac{(\epsilon_1(1-c)\pi)(s-q\beta X_u)}{r} - (1-\epsilon_1)\mu X_u \frac{s-q\beta X_u}{r} = 0,$

which reduces to

$$(1-\epsilon_1)\mu q\beta X_u^2 + (c\pi r\beta - (1-\epsilon_1)\mu s + \epsilon_1(1-c)\pi q\beta)X_u - \epsilon_1(1-c)\pi s = 0.$$

If we let

$$\begin{aligned} t &= (1-\epsilon_1)\mu q\beta, \\ u &= c\pi r\beta - (1-\epsilon_1)\mu s + \epsilon_1(1-c)\pi q\beta, \\ v &= \epsilon_1(1-c)\pi s. \end{aligned}$$

We have the above equation as

$$tX_u^2 + uX_u - v = 0. \tag{6.13}$$

$$\Rightarrow X_u^* = \frac{-u \pm \sqrt{u^2 + 4tv}}{2t}.$$

Substituting X_u^* into X_v^*

$$\Rightarrow X_v^* = \frac{s - q\beta}{r\beta}(\frac{-u \pm \sqrt{u^2 + 4tv}}{2t}).$$

Substituting X_u^* into equation (6.6) and solving for T^* we get

$$T^* = \frac{2t(1-c)\pi}{\beta(-u \pm \sqrt{u^2 + 4tv})} - \frac{\mu}{\beta}.$$

With X_u^* and T^* into equation (6.8) we solve for L_u^*

$$\Rightarrow L_u^* = \frac{1-p}{\chi + \nu + \mu}((1-c)\pi - \mu(\frac{-u \pm \sqrt{u^2 + 4tv}}{2t})).$$

With X_u^*, X_v^*, L_u^* and T^* we solve for L_v^*

$$\Rightarrow L_v^* = \tfrac{1-\epsilon_2 p}{\mu+\epsilon_3\nu}(c\pi - \mu(\tfrac{s-q\beta}{r\beta}(\tfrac{-u\pm\sqrt{u^2+4tv}}{2t}))) + \tfrac{\chi(1-p)}{(\chi+\nu+\mu)(\mu+\epsilon_3\nu)}((1-c)\pi - \mu(\tfrac{-u\pm\sqrt{u^2+4tv}}{2t})).$$

Thus the corresponding coordinates of P_e.

$P_e = (X_u^*, X_v^*, Lu^*, Lv^*, T^*) = \Big(\frac{-u \pm \sqrt{u^2+4tv}}{2t}, \frac{s-q\beta}{r\beta}(\frac{-u \pm \sqrt{u^2+4tv}}{2t}),$
$\frac{1-p}{\chi+\nu+\mu}((1-c)\pi - \mu(\frac{-u \pm \sqrt{u^2+4tv}}{2t})),$
$\frac{1-\epsilon_2 p}{\mu+\epsilon_3\nu}(c\pi - \mu(\frac{s-q\beta}{r\beta}(\frac{-u \pm \sqrt{u^2+4tv}}{2t}))) + \frac{\chi(1-p)}{(\chi+\nu+\mu)(\mu+\epsilon_3\nu)}((1-c)\pi - \mu(\frac{-u \pm \sqrt{u^2+4tv}}{2t})),$
$\frac{2t(1-c)\pi}{\beta(-u \pm \sqrt{u^2+4tv})} - \frac{\mu}{\beta}\Big).$

Which exists when the equilibrium points are defined.

$$\begin{aligned} X_u^* = \frac{-u \pm \sqrt{u^2+4tv}}{2t} &> 0, \\ \Rightarrow -u \pm \sqrt{u^2+4tv} &> 0, \\ \Rightarrow u \pm \sqrt{u^2+4tv} &< 0, \\ \Rightarrow u^2 &< u^2 + 4tv, \\ \Rightarrow tv &> 0. \end{aligned}$$

$$\Big[(1-\epsilon_1)\mu q\beta\Big]\Big[(1-c)\epsilon_1\pi s\Big] > 0,$$

$$\Big[(1-\epsilon_1)\mu\beta\Big(\frac{p(\chi+\mu)+\nu}{\chi+\mu+\nu} + \frac{\chi(1-p)}{(\chi+\nu+\mu)(\mu+\epsilon_3\nu)}\Big)\Big]\Big[(1-c)\epsilon_1\pi(\mu+\mu_T+\phi)\Big] > 0.$$

This occurs when

$$1-\epsilon_1 > 0, \qquad 1-p > 0, \qquad 1-c > 0$$

$$\Rightarrow \epsilon_1 < 1, p < 1 \qquad and \qquad c < 1.$$

$$\begin{aligned} X_v^* = \frac{s-q\beta}{r\beta}(\frac{-u \pm \sqrt{u^2+4tv}}{2t}) > 0, \\ \Rightarrow \frac{-u \pm \sqrt{u^2+4tv}}{2t} > 0. \end{aligned}$$

which will be positive for the same conditions as for X_u^* above.

$$L_u^* = \frac{1-p}{\chi+\nu+\mu}((1-c)\pi - \mu(\frac{-u \pm \sqrt{u^2+4tv}}{2t})) > 0,$$

$$\frac{(1-c)\pi}{\mu} - (\frac{-u \pm \sqrt{u^2+4tv}}{2t}) > 0,$$

$$\frac{2t(1-c)\pi}{\mu} > -u \pm \sqrt{u^2+4tv},$$

$$(\frac{2t(1-c)\pi}{\mu})^2 + \frac{4t(1-c)\pi u}{\mu} + u^2 > u^2 + 4tv,$$

$$(\frac{2t(1-c)\pi}{\mu})^2 + \frac{4t(1-c)\pi u}{\mu} - 4tv > 0,$$

The term $(\frac{2t(1-c)\pi}{\mu})^2$ is readily positive, we then analyze the other two terms.

$$\frac{4t(1-c)\pi u}{\mu} - 4tv > 0,$$

$$4t\Big(\frac{(1-c)\pi u}{\mu} - v\Big) > 0,$$

$$\frac{(1-c)\pi u}{\mu} - v > 0,$$

$$(1-c)\Big[\pi/\mu(c\pi r\beta - (1-\epsilon_1)\mu s + \epsilon_1(1-c)\pi q\beta) - \epsilon_1\pi(\mu+\mu_T+\phi)\Big] > 0.$$

The above holds if

$$1-c>0 \qquad \Rightarrow c<1$$

$$\epsilon_1 - 1 > 0 \qquad \Rightarrow \epsilon_1 > 1$$

$$1-\epsilon_2 p > 0 \qquad \Rightarrow \epsilon_2 p < 1$$

$$1-p>0 \qquad \Rightarrow p<1$$

Analysis of the other terms give the same conditions as above.

6.6 The Reproduction Number, $R_0^{(4)}$

$$\mathcal{F}_i = \begin{pmatrix} (1-p)\beta X_u T \\ (1-\epsilon_2)\epsilon_1\beta X_u T \\ p\beta X_u T + p\epsilon_1\epsilon_2\beta X_u T \end{pmatrix}, \qquad \mathcal{V}_i = \begin{pmatrix} (\chi+\nu+\mu)L_u \\ (\mu+\epsilon_3\nu)L_v - \chi L_u \\ (\mu+\mu_T+\phi)T - \nu L_u - \epsilon_3\nu L_v \end{pmatrix}.$$

$$F = \begin{pmatrix} 0 & 0 & (1-p)\beta X_u \\ 0 & 0 & 0(1-\epsilon_2 p)\epsilon_1\beta X_v \\ 0 & 0 & p\beta X_u + p\epsilon_1\epsilon_2\beta X_v \end{pmatrix}, V = \begin{pmatrix} \chi+\nu+\mu & 0 & 0 \\ -\chi & \mu+\epsilon_3\nu & 0 \\ -\nu & -\epsilon_3\nu & \mu+\mu_T+\phi \end{pmatrix}.$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\chi+\nu+\mu} & \frac{\chi}{(\chi+\nu+\mu)(\mu+\epsilon_3\nu)} & \frac{-\epsilon_3\nu+\nu(\mu+\epsilon_3\nu)}{(\chi+\nu+\mu)(\mu+\epsilon_3\nu)(\mu+\mu_T+\phi)} \\ 0 & \frac{1}{\mu+\epsilon_3\nu} & \frac{-\epsilon_3\nu}{(\mu+\epsilon_3\nu)(\mu+\mu_T+\phi)} \\ 0 & 0 & \frac{1}{\mu+\mu_T+\phi} \end{pmatrix}.$$

$$G = FV^{-1} = \begin{pmatrix} 0 & 0 & \frac{(1-p)\beta(1-c)\pi}{\mu(\mu+\mu_T+\phi))} \\ 0 & 0 & \frac{(1-\epsilon_2 p)\epsilon_1\beta c\pi}{\mu(\mu+\mu_T+\phi)} \\ 0 & 0 & \frac{(p(1-c)+p\epsilon_1\epsilon_2 c)\beta\pi}{\mu(\mu+\mu_T+\phi)} \end{pmatrix}.$$

$$R_0^{(4)} = \Big[\frac{\beta\pi}{\mu}\Big]\Big[\frac{1}{\mu+\mu_T+\phi}\Big]\Big[(1-c)+\epsilon_1\epsilon_2 c\Big]\Big[p\Big].$$

6.6.1 Analysis of the Reproduction Number

$$R_0^{(4)} = \Big[\frac{\beta\pi}{\mu}\Big]\Big[\frac{1}{\mu+\mu_T+\phi}\Big]\Big[(1-c)+\epsilon_1\epsilon_2 c\Big]\Big[p\Big].$$

This value is equal to $R_0^{(2)}$, which is the reproduction number for the model with pre-exposure TB vaccines. This result might be revealing the importance and effectiveness of pre-exposure vaccines in reducing TB cases. It shows that the average number of TB cases reduced by this strategy is the same as that by the latter. The introduction of post-exposure vaccines does not make a significant

change in the number of TB cases reduced compared to pre-exposure vaccines alone.

6.7 Stability Analysis of P_0 by the Linearization Method

We next establish when P_0 is stable, by finding the eigenvalues of the linearized form evaluated at P_0. If all the eigenvalues are negative, we will then conclude that P_0 is stable, or find the condition for the eigenvalues to be negative.

The linearized form J of the system is as follows:

$$J = \begin{pmatrix} -\beta T - \mu & 0 & 0 & 0 & -\beta X_u \\ 0 & -\epsilon_1 \beta T - \mu & 0 & 0 & -\epsilon_1 \beta X_v \\ (1-p)\beta T & 0 & -(\chi + \nu + \mu) & 0 & (1-p)\beta X_u \\ 0 & (1-\epsilon_2 p)\epsilon_1 \beta T & \chi & -(\mu + \epsilon_3 \nu) & (1-\epsilon_2 p)\epsilon_1 \beta X_v \\ p\beta T & p\epsilon_1 \epsilon_2 \beta T & \nu & \epsilon_3 \nu & p\beta X_u + p\epsilon_1 \epsilon_2 \beta X_v - (\mu + \mu_T + \phi) \end{pmatrix}.$$

Evaluating J at $P_0 = (\frac{(1-c)\pi}{\mu}, \frac{c\pi}{\mu}, 0, 0, 0)$ we get

$$J(P_0) = \begin{pmatrix} -\mu & 0 & 0 & 0 & \frac{-\beta(1-c)\pi}{\mu} \\ 0 & -\mu & 0 & 0 & \frac{-\epsilon_1 \beta c \pi}{\mu} \\ 0 & 0 & -(\chi + \nu + \mu) & 0 & \frac{(1-p)\beta(1-c)\pi}{\mu} \\ 0 & 0 & \chi & -(\mu + \epsilon_3 \nu) & \frac{(1-\epsilon_2 p)\epsilon_1 \beta c \pi}{\mu} \\ 0 & 0 & \nu & \epsilon_3 \nu & \frac{p\beta(1-c)\pi}{\mu} + \frac{p\epsilon_1 \epsilon_2 \beta c \pi}{\mu} - (\mu + \mu_T + \phi) \end{pmatrix}.$$

For simplicity we let

$$\begin{aligned} a &= \chi + \nu + \mu, \\ b &= \frac{(1-p)\beta(1-c)\pi}{\mu}, \\ c &= \mu + \epsilon_3\nu, \\ d &= \frac{(1-\epsilon_2 p)\epsilon_1\beta c\pi}{\mu}, \\ \gamma &= \frac{p\beta(1-c)\pi}{\mu} + \frac{p\epsilon_1\epsilon_2\beta c\pi}{\mu} - (\mu + \mu_T + \phi). \end{aligned}$$

And then solve for the eigenvalues of $J(P_0)$

$$|J(P_0) - \lambda I| = \begin{vmatrix} -\mu-\lambda & 0 & 0 & 0 & \frac{-\beta(1-c)\pi}{\mu} \\ 0 & -\mu-\lambda & 0 & 0 & \frac{-\epsilon_1\beta c\pi}{\mu} \\ 0 & 0 & -a-\lambda & 0 & b \\ 0 & 0 & \chi & -c-\lambda & d \\ 0 & 0 & \nu & \epsilon_3\nu & \gamma-\lambda \end{vmatrix} = 0.$$

$$\Rightarrow (-\mu-\lambda)(-\mu-\lambda)\begin{vmatrix} -a-\lambda & 0 & b \\ \chi & -c-\lambda & d \\ \nu & \epsilon_3\nu & \gamma-\lambda \end{vmatrix} = 0.$$

$$\Rightarrow \lambda_1 = \lambda_2 = -\mu.$$

And

$(-a-\lambda)((-c-\lambda)(\gamma-\lambda) - d\epsilon_3\nu) + b(\chi\epsilon_3\nu + \nu(c+\lambda)) = 0,$

which reduces to

$\lambda^3 + (c+a-\gamma)\lambda^2 + (ac - d\epsilon_3\nu + -b\nu - c\gamma - \gamma a)\lambda - (ac\gamma + ad\epsilon_3\nu + b\chi\epsilon_3\nu + bc\nu) = 0.$

Let

$$\begin{aligned} a_1 &= c + a - \gamma, \\ a_2 &= ac - d\epsilon_3\nu + -b\nu - c\gamma - \gamma a, \\ a_3 &= -(ac\gamma + ad\epsilon_3\nu + b\chi\epsilon_3\nu + bc\nu). \end{aligned}$$

$$\Rightarrow \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0.$$

By the Routh-Hurwitz Stability Criterion used before,

$$a_1 = c + a - \gamma > 0,$$

$$\Rightarrow \Big[\mu + \epsilon_3\nu\Big] + \Big[\chi + \nu + \mu\Big] - \Big[\frac{p\beta\pi(1 - c + \epsilon_1\epsilon_2 c)}{\mu} - (\mu + \mu_T + \phi)\Big] > 0.$$

The inequality holds if

$$\begin{aligned} \frac{p\beta\pi(1 - c + \epsilon_1\epsilon_2 c)}{\mu} - (\mu + \mu_T + \phi) &< 0, \\ \frac{p\beta\pi(1 - c + \epsilon_1\epsilon_2 c)}{\mu(\mu + \mu_T + \phi)} &< 1, \\ R_0 &< 1. \end{aligned}$$

$$a_3 = -(ac\gamma + ad\epsilon_3\nu + b\chi\epsilon_3\nu + bc\nu) > 0$$

$$\Rightarrow ac\gamma + ad\epsilon_3\nu + b\chi\epsilon_3\nu + bc\nu < 0$$

$$\Rightarrow ac\gamma + ad\epsilon_3\nu + b\nu(\chi\epsilon_3 + c) < 0$$

$$\Rightarrow \Big[(\chi+\nu+\mu)(\mu+\epsilon_3\nu)\Big(\tfrac{p\beta\pi(1-c+\epsilon_1\epsilon_2 c)}{\mu} - (\mu+\mu_T+\phi)\Big)\Big] + \Big[(\chi+\nu+\mu)\Big(\tfrac{(1-\epsilon_2 p)\epsilon_1\beta c\pi}{\mu}\Big)\epsilon_3\nu\Big] +$$

$$\Big[\tfrac{(1-p)(1-c)\beta\pi\nu}{\mu}(\chi\epsilon_3 + (\mu + \epsilon_3\nu))\Big] < 0$$

The summation of the three terms above is negative if we have the following

conditions

$$\begin{aligned}
\gamma = \frac{p\beta\pi(1-c+\epsilon_1\epsilon_2)}{\mu} - (\mu+\mu_T+\phi) &< 0 \\
\Rightarrow \frac{p\beta\pi(1-c+\epsilon_1\epsilon_2)}{\mu} &< \mu+\mu_T+\phi \\
\Rightarrow \frac{p\beta\pi(1-c+\epsilon_1\epsilon_2)}{\mu(\mu+\mu_T+\phi)} &< 1 \\
\Rightarrow R_0 &< 1
\end{aligned}$$

$$d = \frac{(1-\epsilon_2 p)\epsilon_1\beta c\pi}{\mu} < 0, \qquad \Rightarrow \qquad 1 < \epsilon_2 p$$

$$b = \frac{(1-p)\beta(1-c)\pi}{\mu} < 0 \qquad \Rightarrow \qquad 1 < p \qquad or \qquad 1 < c$$

.

$$\begin{aligned}
a_1a_2 - a_3 &> 0 \\
\Big(c+a-\gamma\Big)\Big(ac - d\epsilon_3\nu - \gamma(c+a) - b\nu\Big) + \Big(ac\gamma + ad\epsilon_3\nu + b\nu(\chi\epsilon_3 + c)\Big) &> 0
\end{aligned}$$

It can be observed that for the product a_1a_2 to be positive, γ ,d and b has to be negative. We have already analyzed the conditions for $\gamma < 0$,$d < 0$, $b < 0$ above. It can be noted also that if $a_3 < 0$, the inequality holds, and a_3 is readily negative. Thus we have the same conditions as above for $a_1 > 0$ and $a_3 > 0$ for the third part of the criterion to hold.

Analysis of P_e

Due to the size of the endemic equilibrium points, finding the conditions for P_e to be stable manually, will be a bit cumbersome. At this point, we will not consider numerical analysis.

Chapter 7

Numerical Analysis by the Fourth Order Runge-Kutta Scheme

Numerical analysis were carried out for the models using the above mentioned method. Numerical values of the parameters taken from [3] were used and the change in behavior of the graphs noted and discussed. The iterative process by the fourth order Runge-Kutta scheme is given by

$$Y_{n+1} = Y_n + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

where

$$k_1 = hf(x_n, y_n)$$

$$k_2 = hf(x_n + 1/2h, y_n + 1/2k_1)$$

$$k_3 = hf(x_n + 1/2h, y_n + 1/2k_2)$$

$$k_4 = hf(x_n + h, y_n + k_3).$$

The values of the parameters used are given in table 7.1:

parameter	value	parameter	value
π	0.2	ϵ_2	0.4
β	0.005	ϵ_3	0.005
μ	0.013	χ	0.1
μ_T	0.461		
ϕ	0.8		
p	0.001		
c	0.9		
ϵ_1	0.5		

Table 7.1: List of parameter values used in Numerical analysis

The initial populations were estimated in table 7.2 $X_u = 50000$and $L_u = 1000$ were used for the first 2 models. $X_u = 40000$ and $L_u = 800$ were used for models 3 to 5. To maximize convergence, we ran 1000 points. The matlab programmes are given in the appendix.

In figure 7.1 to 7.5, are the graphs of the active TB individuals against time.

From figure 7.1 we can see that the graph is increasing to about 1400 individuals by the second year. It is quite a sharp and fast increase. By the tenth year there were about 2700 individuals. The graph stopped increasing by the seventh year and started to decrease after the tenth year. This is because during the seventh year, the initial susceptible population was almost zero. So there were no more people coming into the active TB class. They started decreasing because of natural death and death due to the disease. We can can see how terrible the endemic can be without any control measures.

When we introduce treatment, the rate at which TB invades the population

variable	value
X_u	50000, 40000
X_v	10 000
L_u	1 000, 800
L_v	200
T	100

Table 7.2: List of variable values used in Numerical Analysis

decreases. There is a small reduction in the total number of TB cases observed during the first year, about 30% decrease. Then the graph rises again. By the second year there were about 750 individuals compared to 1400 for the first model. By the tenth year there were about 1000 individuals which is an improvement compared to the first model. So treatment has a positive effect in reducing TB cases but a very small effect and for a short period of time. Which means treatment needs to be enhanced for better results.

The introduction of pre-exposure vaccines shows a great improvement compared to treatment alone. There is a very significant decrease in the TB cases by about 85% until the fifth year. Which means that the period of effectiveness is now extended to five years instead of two years for the model with treatment, and the TB cases reduced have been increased also. But after the fifth year we notice an increase again in the TB cases. Which means that pre-exposure vaccines with treatment is very effective but the effectiveness diminishes with time. If we extend the time to 30 years the graph will still be increasing.

With post-exposure vaccines and treatment, the graph decreases, reducing about 75% of active TB cases. The number of cases reduced is smaller compared to that of the pre-exposure vaccines. But the good thing about this model is that the graph keeps on approaching zero.If we extend the time to 30 years the graph will still be decreasing. Which means that the effectiveness of the post-exposure vaccines does not diminish with time, but increases.

In figure 7.5, we observe how the two vaccines together with treatment give best results. The TB cases are reduced by about 87%. The graph keeps on approaching zero. Which means that the combination of the three control measures give better results than the individual strategies. While the number of TB cases is kept minimum, the effectiveness also increases with time. If we extend the time to 30 years the graph will still be decreasing.

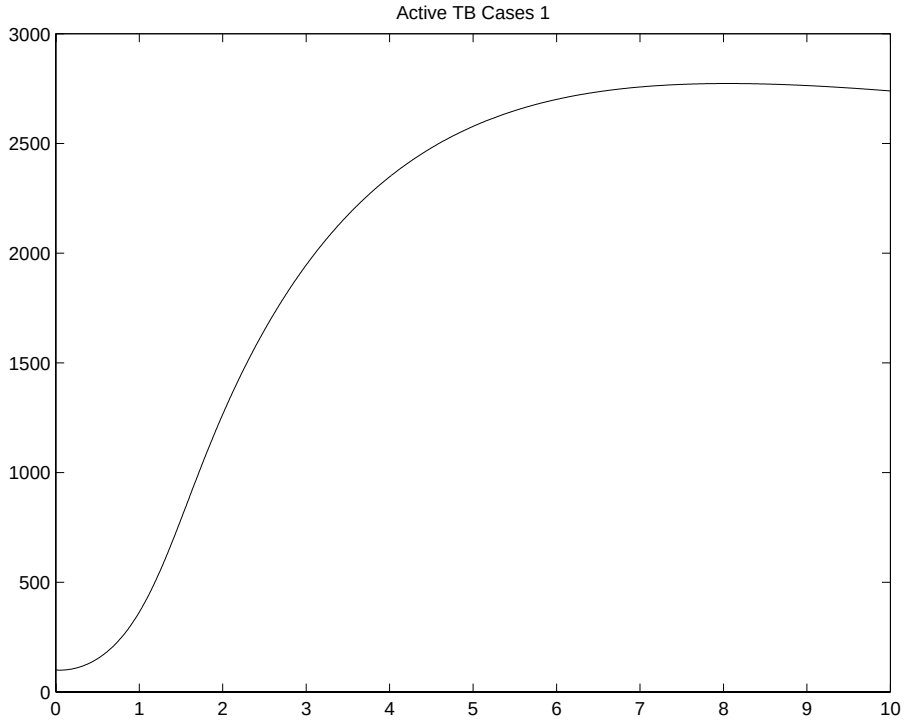

Figure 7.1: Active TB Cases 1

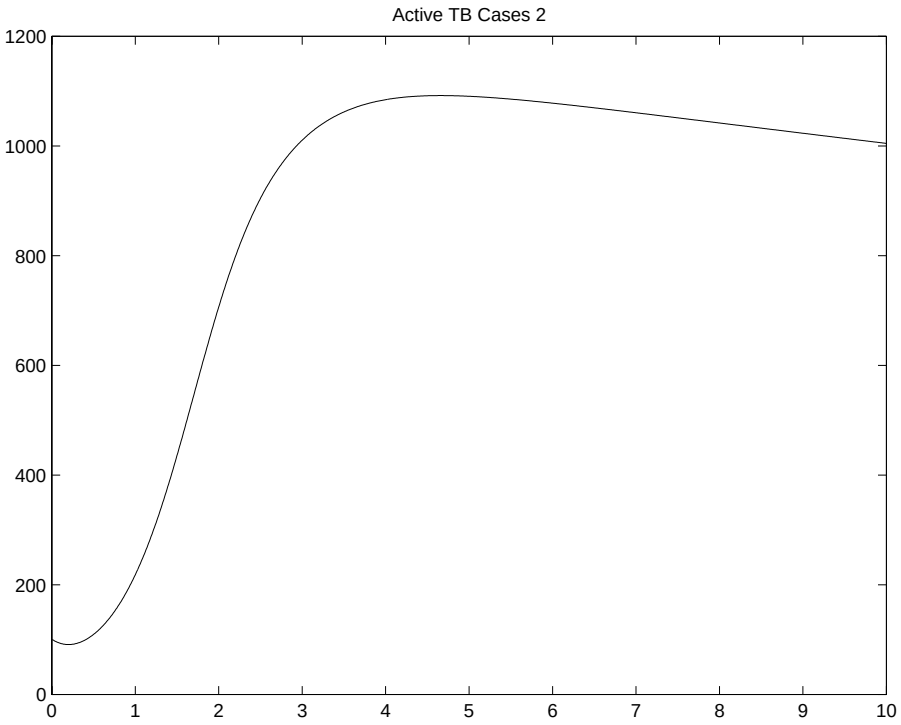

Figure 7.2: Active TB Cases 2

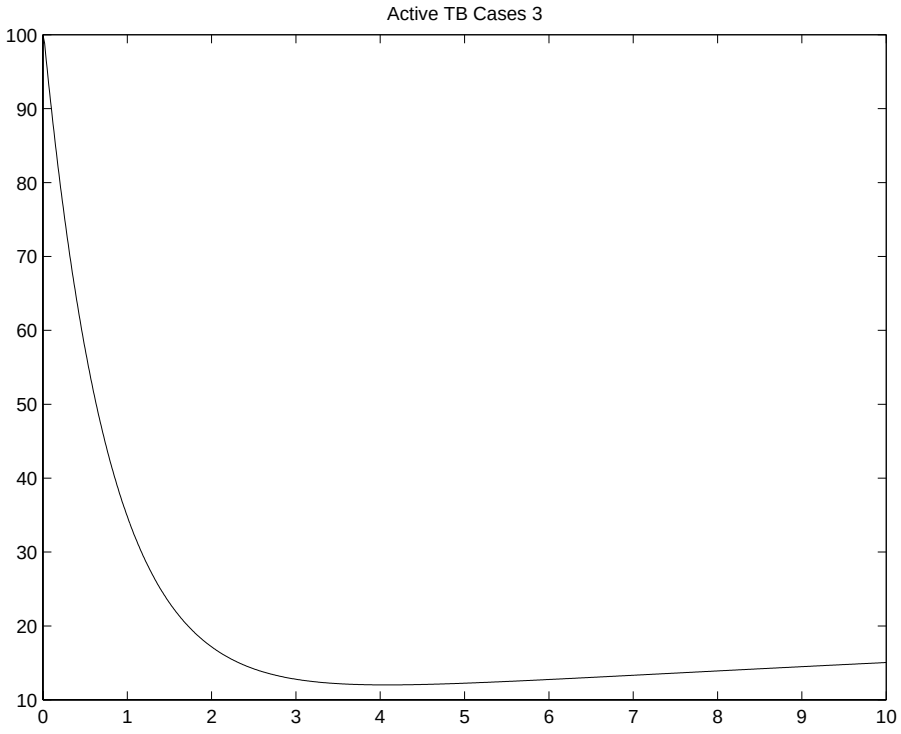

Figure 7.3: Active TB Cases 3

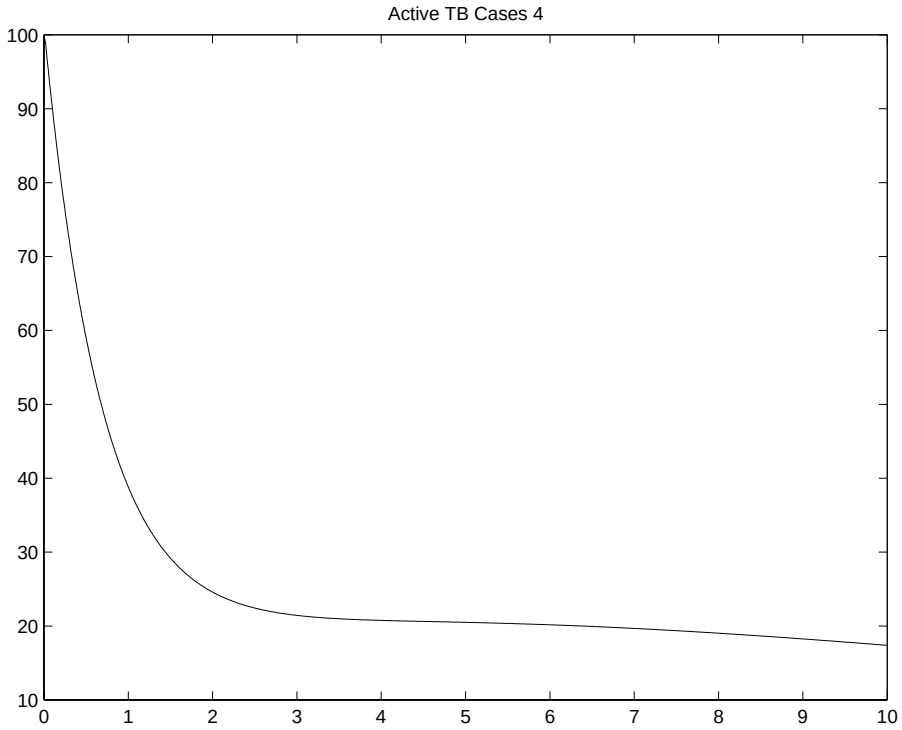

Figure 7.4: Active TB Cases 4

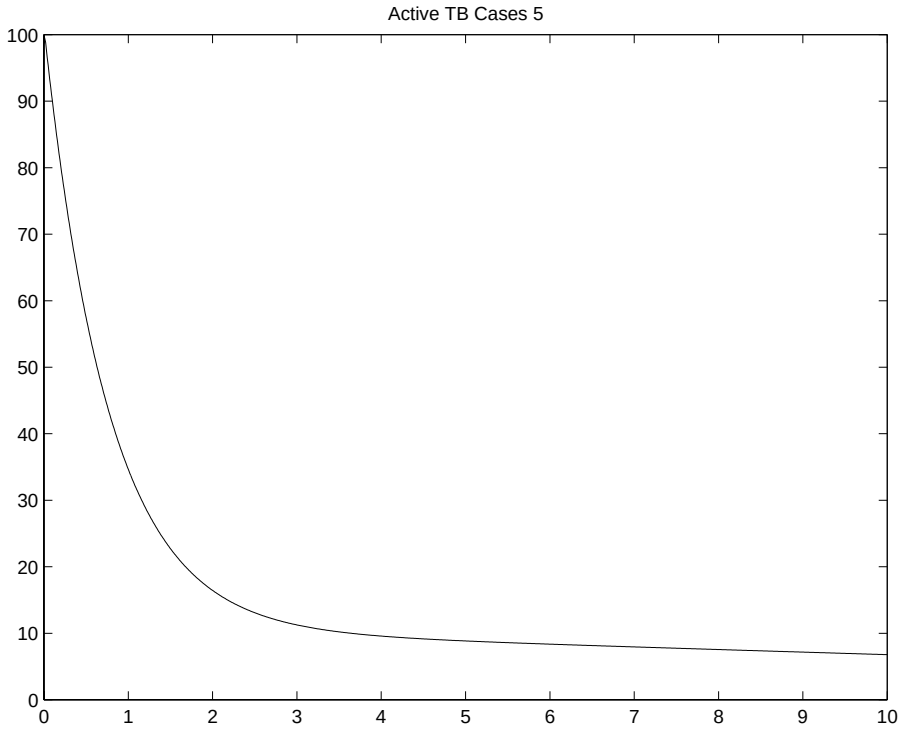

Figure 7.5: Active TB Cases 5

Model Validation and Conclusion

The efficiency of the reproduction numbers of the models have been discussed. Results from numerical analysis also have been interpreted. From the former, it was concluded that pre-exposure vaccines are the most effective since even with the combined model the value of the reproduction number was the same as for the pre-exposure vaccines alone. From the latter, it was revealed that the effectiveness of pre-exposure vaccines diminishes with time while for the post-exposure increases. We observed how the graph of the pre-exposure vaccines started increasing after 5 years and that of the post-exposure decreasing.

In the combined strategy we saw how the two vaccines together gave best results. While the number of TB cases reduced was kept at maximum, the effectiveness was maintained. We noted that the graph kept approaching zero. Thus the combination of the vaccines together with high treatment rates is best in eliminating TB cases.

The results agree with the recommendations of [10]. Indeed the combination of a pre-exposure vaccine, a post-exposure vaccine, and treatment of active TB is the most effective epidemic-control strategy for TB elimination in developing countries, where the prevalence of both infection and reactivation of latent bacilli is high.

[18] et al found that the effectiveness of post-exposure vaccines would diminish over time, whereas that of pre-exposure vaccines would increase. This contrast

might be from the fact that their analysis was based in developing countries with a high incidence and prevalence of infection only. The prevalence of reactivation of latent infection was not considered. As a result the effectiveness of the post-exposure vaccines will become less significant with time because it was assumed there are fewer individuals who needed the post-exposure vaccines. I strongly believe that if both cases (infection and reactivation of latent bacilli) were considered, the results would be different.

Due to the increasing prevalence of HIV infection in developing countries, the models should be developed to include interactions between HIV as future work. Population age-structures included, would make the models more realistic because HIV prevalence vary significantly with age. The assumptions should be extended to allow the occurrence of TB cases more than once, that is recovered individuals becoming susceptible again. This is because of the fact that HIV infection has no cure, thus as long as an individual is HIV positive, he will remain highly susceptible to TB infection even after successful treatment. Such models can be used to identify the best strategies for the elimination of TB where HIV infection rates are high. This is because HIV infection is the strongest risk factor yet identified for progression to active TB and the infected individuals are highly susceptible.

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Appendix

Matlab Programme for the basic TB transmission model

```
clear T = 10; h = 0.01;

Xu0 = 50000; Lu0 = 1000; Tu0 = 100;

pie = 0.2; mu = 0.013; beta = 0.005; p = 0.001; nu = 0.00527; muT = 0.461;

Xu(1) = Xu0; Lu(1) = Lu0; Tu(1) = Tu0;

t(1) = 0; n = T/h;

for i = 2:n

k11 = h * (pie - mu * Xu0 - beta * Xu0 * Tu0);

k21 = h * (pie - mu * (Xu0+h/2) - beta * (Xu0+h/2) * (Tu0+k11/2));

k31 = h * (pie - mu * (Xu0+h/2) - beta*(Xu0+h/2)*(Tu0+k21/2));

k41 = h * (pie - mu *(Xu0 +h) - beta *(Xu0+h) *(Tu0+k31));

k12 = h* ((1-p)* beta * Xu0 * Tu0 - (mu +nu) * Lu0);

k22 = h * ((1-p) * beta *(Xu0+h/2)*(Tu0+k12/2) - (mu+nu)*(Lu0+h/2));

k32 = h * ((1-p) * beta * (Xu0+h/2) *(Tu0+k22/2)-(mu+nu)*(Lu0+h/2));
```

```
k42 = h * ((1-p) * beta*(Xu0+h) *(Tu0+k32) - (mu+nu)* (Lu0+h));

k13 = h*(p*beta*Xu0*Tu0 + nu*Lu0 - (mu+muT)*Tu0);

k23 = h*(p*beta*(Xu0+h/2)*(Tu0+k13/2) + nu*(Lu0+h/2) - (mu + muT)*(Tu0+k13/2));

k33 = h*(p*beta*(Xu0+h/2)*(Tu0+k23/2) + nu*(Lu0+h/2) - (mu + muT)*(Tu0+k23/2));

k43 = h*(p*beta*(Xu0+h)*(Tu0+k33) + nu*(Lu0+h) - (mu+muT)*(Tu0+k33));

t(i) = i*h; Xu(i) = Xu0 + 1/6*(k11 + 2*k21 + 2*k31 + k41);

Lu(i) = Lu0 + 1/6 *(k12 + 2*k22 + 2*k32 + k42);

Tu(i) = Tu0 + 1/6 *(k13 + 2*k23 + 2*k33 + k43);

Xu0 = Xu(i); Lu0 = Lu(i); Tu0 = Tu(i);

end

figure(10) plot(t,Xu,'b') title('Susceptibles 1')

figure(11) plot(t,Lu,'r') title('Latently Infected Individuals 1')

figure(12) plot(t,Tu,'g') title('Active TB Cases 1')
```

Programmes for the other model equations are similar. The only difference is with the k's, which will vary according to the equations.