DETERMINISTIC MODELLING OF TUBERCULOSIS AND HIV/AIDS

BY

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A Thesis submitted in partial fulfilment of the requirements for the award of the degree of Master of Science in Applied Statistics.

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ABSTRACT

The human immunodeficiency virus (HIV) pandemic presents a massive challenge to the control of recurrent diseases like tuberculosis (TB) at all levels. Tuberculosis is also one of the most common causes of morbidity and one of the leading causes of mortality in people living with HIV/AIDS (PLWHA).

In this study, we have developed a mathematical model that captures the role played by HIV/AIDS in accelerating the infection and hence spread of Tuberculosis. We looked at TB progression among people with HIV and those without. The model is formulated for TB/HIV negative individuals as well as for TB/HIV positive people. The model was developed using the first order partial differential Mackendrick-Von Foster equation.

Further, we reviewed different epidemiological techniques to estimate parameters in the model. These parameters were estimated through extraction of relevant information from data available in the literature. Finally, we were able to present computed numerical solutions of the model using MATLAB.

CHAPTER ONE

INTRODUCTION

1.0 Background Information

The Human Immunodeficiency Virus (HIV) epidemic in Kenya constitutes the most serious health problem and one that we do not fully understand. What makes the matter even more complex is the interaction with the parallel tuberculosis (TB) epidemic which affects both HIV-positive and HIV-negative people. TB and HIV are the leading causes of death from infectious diseases among adults globally and the number of TB cases has risen significantly since the start of the HIV epidemic, particularly in Sub-Saharan Africa where the HIV epidemic is most severe (Stephen D. Lawn, 2006). The World Health Organization (WHO) TB-control strategy, which is based on the directly observed treatment, short course (DOTS) strategy, has failed to contain the TB epidemic in Africa, largely due to the effects of the HIV epidemic in the region (Stephen D. Lawn, 2006). This project reviews the formal mathematical work on deterministic models of this nature and considers the relevance of the modelling approach to the HIV and TB epidemics in Kenya.

The first chapter provides some basic background information on TB and HIV/AIDS. Our main goal here is to understand the basic epidemiology of these two deadly diseases and gain insight into how they affect each other. In Chapter 2, we review related literature on tuberculosis.

In Chapter 3, we present a deterministic compartmental model for the interaction between HIV and TB epidemics. This model is presented as a system of first order linear partial differential equations (age-structured population model).

In Chapter 4, we discuss parameters related to HIV and TB. We further perform numerical simulations to estimate some HIV and TB parameters.

In chapter 5, we discuss the results and give a conclusion.

1.1 What is TB?

Tuberculosis (TB) is a bacterial infection of the lungs (pulmonary tuberculosis) caused by bacterium Mycobacterium tuberculosis. It can also affect the central nervous system, the lymphatic system, the brain, spine and the kidneys. Only people who have pulmonary TB are infectious.

One-third of the world's population is currently infected with the TB bacillus and new infections are occurring at a rate of one per second (WHO, 2007).

Tuberculosis has a vaccine called BCG. Children are vaccinated with BCG at an early age. This has the effect of introducing the bacteria into the system making the child a latent slow rate case.

1.1.1 Exposure to Tubercle Bacilli

Exposure is defined as a contact between two individuals in sufficient proximity to allow conversation between them, or, within confined spaces, where the air exchange (ventilation) of the space has been incomplete between the visits of the two people (Hans .L.R, 1999).

There are three major factors that determine the risk of becoming exposed to tubercle bacilli. They include:

i) The number of incident infectious cases in the community,

ii) The duration of infectiousness, and

iii) The number and nature of interactions between a case and a susceptible contact per unit of time of infectiousness (Hans .L.R, 1999).

TB spreads from person to person through the air as a person with active tuberculosis coughs, sneezes, speaks, spits, kisses. Note that not everyone infected with Mycobacterium tuberculosis becomes sick. After a person becomes infected, the tuberculosis bacteria are controlled by the person's immune system. When this happens, the person moves from latent fast rate to latent slow rate. When the bacteria spread out of control, the infection becomes active.

A person can have active or latent (inactive) TB. Both active and latent TB fast rate are treatable and curable. Active TB means the bacteria are active in the body and they weaken the immune

system, making it impossible to stop them from causing illness. Only people with active TB can spread the disease. People with latent TB do not feel sick and do not have any symptoms.

In some people, Mycobacterium tuberculosis remains inactive for a lifetime without becoming active while others are likely to develop active TB if their immune system is compromised by some deadly disease such as HIV. The early symptoms of active tuberculosis include: coughing up blood, weight loss, fever, loss of appetite, and also shortness of breath indicates an advanced stage of active tuberculosis.

1.1.2 TB Progression

TB progression from latent infection to active disease varies greatly. For instance, people with AIDS are more likely to develop active TB after infection. A patient with AIDS who becomes infected with Mycobacterium tuberculosis has a 50% chance of developing active tuberculosis within 2 months and a 5 to 10% chance of developing active disease each year thereafter (WHO 2007).

According to the World Health Organization (WHO 2007), infants and young children infected with Mycobacterium tuberculosis are also more likely to develop active TB than older people since their immune system is not yet well developed.

1.1.3 MDR-TB and XDR-TB

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis that is resistant to at least isoniazid and rifampicin, the two most powerful first-line anti-TB drugs. The World Health Organization (WHO) defines extensively drug resistant TB (XDR-TB) as MDR-TB plus resistance to any fluoroquinolone and at least 1 of 3 injectable second-line drugs capreomycin, kanamycin and alizarin. People who have active TB usually develop MDR-TB or XDR-TB when they fail to fulfill their prescription of TB medicine as ordered by the Doctor. MDR-TB is dangerous and very difficult to treat. The most important factor in preventing drug resistant TB is to ensure full compliance with anti-TB treatment. As recommended by the WHO, directly observed therapy (DOT) is an effective treatment measure.

Anyone can get TB, but some people are highly susceptible. Those that are at high risk include: people with HIV, people in close contact with infectious individuals, people who are malnourished, health care workers, prison guards, alcoholics, intravenous drug users and the homeless.

1.1.4 TB Skin Test and Treatment

The tuberculin skin testing is the major method of diagnosing the tuberculosis infection. When the test result is positive it implies there is tubercle bacilli. It is normally used to distinguish infected individual from the exposed individual without infection. The infected individuals will then be put on the DOT strategy in order to reduce infections and also treat the disease. An active TB patient can be treated by a combination of anti-tuberculosis therapies such as the ones mentioned in subsection 1.1.3 above. Latent TB fast rate can be treated with isoniazid. The treatment is very effective provided the patients take it for at least six months as prescribed.

1.1.5 HIV/AIDS

AIDS is a life threatening disease caused by HIV which is a sexually transmitted disease. One can become infected with the virus through unprotected sex and sharing of hypodermic needles as well as through blood transfusion. The virus is not transmitted through saliva, spit, sweat, tears, air or insects. HIV in humans is now pandemic. As of January 2006, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that AIDS had killed more than 25 million people since it was first recognized on December 1, 1981, making it one of the most destructive pandemics in recorded history. In 2005 alone, AIDS claimed an estimated 2.4 to 3.3 million lives, of which more than 570,000 were children. It is estimated that about 0.6% of the world's living population is infected with HIV. A third of these deaths are occurring in sub-Saharan Africa, retarding economic growth and increasing poverty.

1.1.6 Stages of HIV Infection

Generally there are four stages of HIV infection. They are briefly described as follows;

• Stage 1: Primary HIV infection: The first stage of infection is extremely infectious. It normally lasts for a few weeks and is often accompanied by a short flu-like illness

• Stage 2: Asymptomatic stage: This stage lasts for an average of ten years and the infected person does not show any symptoms of the disease

• Stage 3: Symptomatic HIV infection: This is the stage where a lot of symptoms (diarrhoea, heavy weight loss, fever, cough and shortness of breath) begin to manifest because the immune system is severely damaged by the virus. It is at this stage that pulmonary TB manifests itself.

• Stage 4: Progression from HIV to AIDS: The final stage occurs when the immune system is extremely weakened. As a result, certain infections called "opportunistic" (infections which cannot attack people with a healthy immune system) take the opportunity to infect the HIV-patients. This is where the patients develop full blown AIDS.

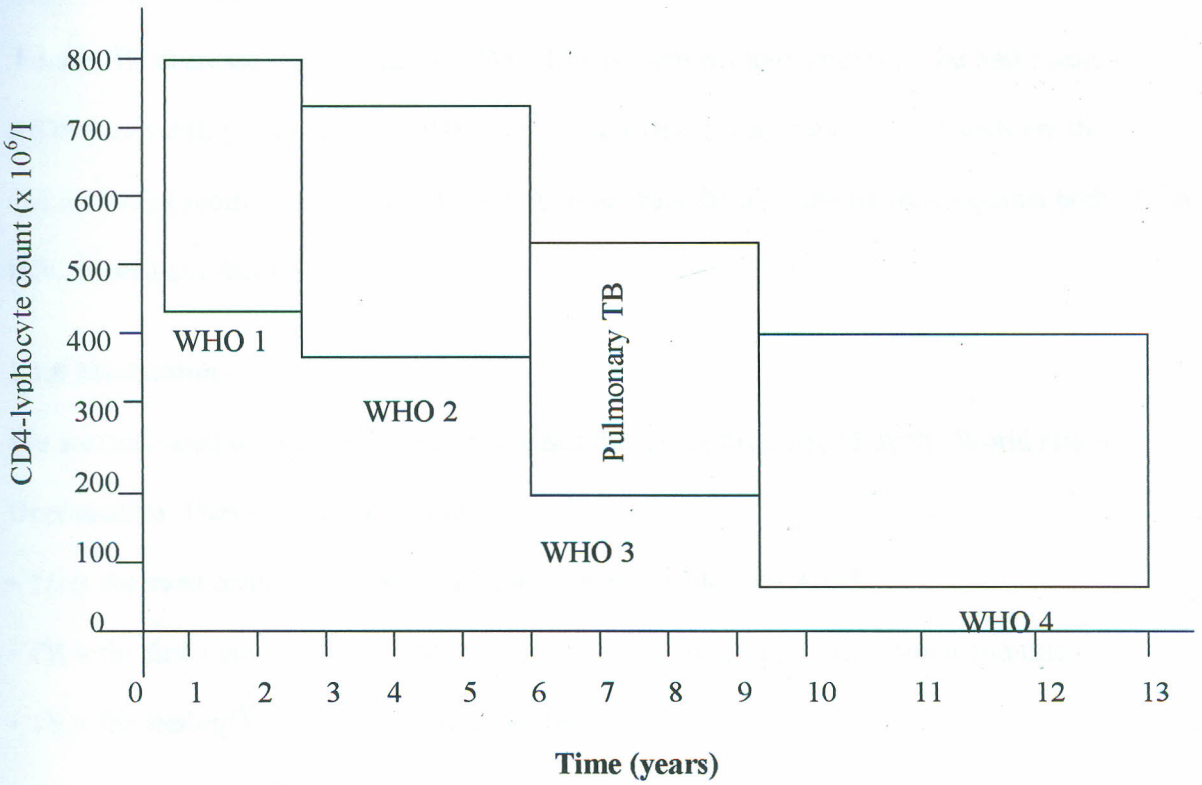


Figure 1.1: WHO (2006). Stages of HIV infection based on CD4 count

1.1.7 How TB and HIV Affect Each Other

Each disease acts as a catalyst in the progression of the other. TB significantly reduces the survival time for people with HIV/AIDS. HIV infection is the largest risk factor for the progression of inactive TB to active TB, and Mycobacterium tuberculosis can speed up the progression of HIV. It is clear that each of these diseases can have a profound impact on the other.

First, there is an increasing interaction between those individuals at high risk for TB and those at high risk for HIV:

Second, TB is the most common HIV-related complication world-wide (Narain et al., 1992).

Third, HIV infected individuals are not only at a greater risk for acquiring TB, but reactivation of latent TB infection is greatly increased due to the fact that the very cells that hold the latent TB in check (the CD4+ T lymphocytes) are precisely the cells that are rendered dysfunctional in HIV-infected individuals (Bryt et al., 1994).

Fourth, TB decreases the number of CD4+ T cells thereby interfering with the best predictor of AIDS survivability (Bryt et al., 1994). This is important, because the CD4+ T cells are the cells that not only become infected with HIV, but orchestrate the immune response against both TB and HIV, as well as other pathogens.

1.1.8 Motivation

We are motivated to model this pair of diseases due to the facts issued by the World Health Organization. They include the following:

- TB is the most common opportunistic infection in people with AIDS
- TB is the first manifestation of AIDS in over 50% of the cases in developing countries
- TB is the leading killer of people with AIDS.

1.2 Modeling Disease Propagation

In recent years there has been increasing interest in the use of epidemic models for the analysis of real life epidemics. The need for accurate modelling of the epidemic process is vital, particularly because the financial consequences of infectious disease outbreaks are prohibitive, two important recent examples being the foot and mouth disease (FMD) outbreak in the UK and the severe acute respiratory syndrome (SARS) epidemic in the spring of 2003 in UK. In order to study the development and spread of a disease, we need models that can accurately capture the main characteristics of the disease in question since understanding disease propagation is vital for the most effective reactive measures. Additionally, if we want to adopt a proactive approach and model vaccination strategies, we need methodology for performing statistical inference for the parameters of epidemiological interest. Hence, it readily becomes apparent that it is vital that epidemic models of general applicability and methodology for their statistical analysis should be developed.

1.3 The Need for Epidemic Modelling

The statistical analysis of infectious disease data usually requires the development of problem-specific methodology. There are a number of reasons for this but the main features that distinguish outbreak data are the high dependence that is inherently present and the fact that we can never observe the entire infection process. In many cases the data from the incidence of an infectious disease consist of only the final numbers of infected individuals. Thus, the analysis should take into account all the possible ways that these individuals could be infected. Moreover, even when the data contain the times that the symptoms occur, we cannot observe the actual infection times. These reasons suggest that in order to accurately analyse outbreak data, we need a model that describes a number of aspects of the underlying infection pathway. Hence, inference about the data generating process can provide us with an insight about the quantitative behavior of the most important features of the disease propagation. Additionally, the design of control measures against a disease can be improved through a quantitative analysis based on an epidemic model.

1.4 Assumptions

1. We assume that there is no mother to child transmission of HIV/AIDS.

2. The rate of movement from latent TB fast rate to latent TB slow rate is the same both for HIV negative and HIV positive cases i.e. $\sigma = \sigma^*$, where is the transmission rate from latent TB fast rate to latent TB slow rate for HIV negative individuals whereas σ^* is the corresponding transmission rate from latent TB fast rate to latent TB slow rate for HIV positive people

3. The dynamics for TB and HIV/AIDS infections are the same for all countries.

1.5 Statement of the problem

HIV/AIDS and tuberculosis (TB) are commonly called the "deadly duo" and referred to as HIV/TB. HIV complicates TB infection and is associated with a more rapid clinical decline. Infection with HIV increases the risk of reactivating latent TB infection, and HIV-infected individuals who acquire new TB infections have high rates of disease progression.

In this study, we sought to establish the rates of clinical decline for tuberculosis in HIV negative as well as for HIV positive individuals.

This calls for a mathematical model that takes into account, HIV/AIDS as a condition that accelerates TB infection and spread.

This epidemic model will provide the Government, health sector and the academic world with a better understanding of the infection process and also with the epidemiologically important quantities of interest.

1.6 Objectives

The Objectives of this study are to:

1. Formulate a hypothesis which investigates infection of TB

2. Get more knowledge and understanding about the epidemic network of TB, HIV/AIDS.

3. Answer research question.

4. Develop a mathematical model for HIV and tuberculosis.

5. To establish the rates of clinical decline for TB/HIV + and TB/HIV-

6. To establish the detection rates for TB in HIV positive and HIV negative people.

1.7 Research Question

What is the rate at which HIV/AIDS accelerate the infection and spread of tuberculosis?

1.8 Hypotheses:

H_0: HIV does not influence the movement from latent TB to active TB i.e. $\rho^* \neq \rho$

H_1: HIV helps activate TB infection by accelerating the movement from latent to active TB

i.e. $\rho^* > \rho$

Where, ρ is the transmission rate from latent TB to active TB in HIV negative individuals and ρ^* is the transmission rate from latent TB to active TB in HIV positive individuals.

1.9 Significance of the study

TB is now the most common opportunistic infection in individuals being treated with antiretroviral therapy in the developing world. It may present itself as the first manifestation of HIV infection. There is therefore need to study the development and spread of these two diseases, and develop a model that can capture the main characteristics of the diseases since understanding disease propagation is vital for the most effective reactive measures.

CHAPTER TWO
LITERATURE REVIEW

2.1 Introduction

In this chapter, we review related literature on epidemic modelling of infectious diseases.

2.2 Epidemic modelling of infectious diseases.

Early work on epidemics is from the beginning of the 20th century, and perhaps the first really influential mathematical model is a deterministic model due to Kermack and McKendrick from 1927 (May, 1991). Probably the most important stochastic model from that era is the chain-binomial model introduced by Reed and Frost in 1928 (Anderson and Britton 2000).

There is a vast literature on deterministic and stochastic epidemic models. Some of the work on modelling disease transmission prior to 1975 is contained in Bailey (1975). Bailey presents a comprehensive account of both stochastic and deterministic models and illustrates the use of a variety of the models using real outbreak data.

2.2.1 Previous work on TB models

The first model for the transmission dynamics of TB was built in 1962 by Waaler. He divided the population into three epidemiological classes: non-infected (susceptible), infected non-cases (latent TB), and infected cases (infectious). He formulated the infection rate as an unknown function of the number of infectious individuals. He used a particular linear function to model infection rates in the implementation of his model. The incidence (new cases of infections per unit time) was assumed to depend only on the number of infections. Furthermore, the equations for the latent and infectious classes were assumed to be uncoupled from the equation for the susceptible class. The central part of this model is given by the following linear system of difference equations:

$$\begin{aligned} E_{t+1} &= E_t + aI_t - eE_t - d_2E_t + gE_t \\ I_{t+1} &= I_t - gE_t - d_3I_t + eE_t \end{aligned} \qquad (2.1)$$

where the incidence rate aI_t is proportional to the number of infections; e is the per-capita progression rate from latent-TB to infectious-TB cases; g is the per-capita treatment rate (treated individuals will become members of latent-TB class again.); d_2 is the per-capita death rate of the latent-TB class; and d_3 is the per-capita death rate of the infectious-TB class.

Aparicio et al (2002) developed a basic generalized households (cluster) model, which took close and casual contacts into account. They focused on the active-TB cases within their social networks (family members, officemates, classmates, any persons who have prolonged contacts with an active case). Such a generalized household or epidemiologically active cluster was used to study transmission of TB outside and within their social networks. The study indicated that casual contact significantly increases the number of secondary active cases.

In this model the population was divided into two clusters. One of active TB (N_1), which have only one active case and another of inactive TB (N_2) which have no active cases. The clusters were further subdivided into a susceptible group (S_i), an exposed group (E_i) and an infectious group (I_i) according to the progression of TB, where it was assumed that when one person from an inactive cluster develops active TB, the whole cluster becomes an active-TB cluster and vice versa. It was also assumed that casual infection just occurs in N_2 and close infection depends on the life of the cluster (Aparicio et al, 2002). All assumptions lead to the basic household model:

$$\begin{aligned}
\frac{dS_1}{dt} &= -(\beta+\gamma)S_1 + \frac{S_2}{N_2}nkE_2 \\
\frac{dE_1}{dt} &= \beta S_1 - \gamma E_1 + \frac{E_2}{N_2}nkE_2 \\
\frac{dI}{dt} &= kE_2 - \gamma I \\
\frac{dS_2}{dt} &= \lambda - \mu S_2 + \gamma S_1 - \frac{S_2}{N_2}nkE_2 \\
\frac{dE_2}{dt} &= \gamma E_1 - (k+\mu)E_2 - \frac{E_2}{N_2}nkE_2
\end{aligned} \qquad (2.2)$$

where β is transmission rate, n is the size of cluster, λ is the recruitment rate to S_2, μ is natural mortality of N_2, E_2 is the exposed in N_2, γ is the total per-capita removal rate from the I, k is the progression rate to active TB.

The basic reproductive number for the model is

$$R_0 = \left(\frac{n}{1+\frac{\gamma}{\beta}} \right) \left(\frac{1}{\frac{\mu}{k}+1} \right) \tag{2.3}$$

It can be seen that R_0 depends nonlinearly on the parameter β (risk of infection on an epidemiologically active cluster of size n) and linearly on the average generalized household size, n. If $R_0>1$ then there exist endemic equilibrium and disease persists.

Schinazi (2000) introduced a spatial stochastic model for TB and HIV co-existence and showed that casual infection can induce an outbreak of TB independent of the active cluster.

Song et al (2002) extended the basic cluster model (1.1) and investigated its global dynamics by using singular perturbation theory and multiple time scales techniques. The results supported the view that TB can be acquired from one or few contacts with an infectious individual. Generally, the probability that a susceptible individual, who does not belong to any active cluster, has a close contact with an active case is very low. Hence for those individuals who are only exposed to casual contacts the risk of infection is significantly smaller than that of individuals who are in active clusters. Nevertheless, the total number of secondary infections caused by casual contacts is greater than those produced by contacts in active clusters. This is so because the size of the subpopulation living in the active clusters is significantly smaller than the total population size. That is, it would not be surprising to find that the dynamics of tuberculosis at the population level in cities depends more on casual contacts than the close contacts.

The modified model is given by the following nonlinear system:

$$\frac{dS_1}{dt} = -(p\beta(n)+\gamma)S_1 + \frac{S_2}{N_2}nkE_2 - (1-p)\beta^* \frac{I}{N-n}S_1,$$
$$\frac{dE_1}{dt} = p\beta(n)S_1 - \gamma E_1 + \frac{E_2}{N_2}nkE_2 + (1-p)\beta^* \frac{I}{N-n}S_1,$$
$$\frac{dI}{dt} = kE_2 - \gamma I, \qquad (2.4)$$
$$\frac{dS_2}{dt} = \lambda - \mu S_2 + \gamma S_1 - \frac{S_2}{N_2}nkE_2 - (1-p)\beta^* \frac{I}{N-n}S_2,$$
$$\frac{dE_2}{dt} = \gamma E_1 - (k+\mu)E_2 - \frac{E_2}{N_2}nkE_2 + (1-p)\beta^* \frac{I}{N-n}S_2$$

where β is the transmission rate within the cluster and assumed to depend on the average cluster size n, β^* is the casual transmission rate, p denotes the average fraction of time spent by the active case within his/her generalized household and 1− p, the average fraction of time spent by this source-case outside the cluster.

The rate of infection within clusters becomes pβ (n) S_1, while the rate of infection outside is given by (1−p) $\beta^* \frac{1}{N-n}$ (S_1+S_2), where N is the total population size, and (N − n) represents the average total number of individuals outside the cluster.

Hence, (1−p) $\beta^* \frac{1}{N-n} S_i, (i = 1,2)$ gives the number of new infections per unit time in the N_1 population, that is, the incidence from S_1 to E_1 and the incidence from S_2 to E_2. There are no new cases of active TB within each epidemiologically active cluster, and consequently, the infection rate is pβ (n) S_1.

In the system of equations (2.2), when p = 1 and β(n)is a constant, the extended cluster model becomes the basic cluster model.

The basic reproductive number for the model in (2.2) is

$$R_0 = \left[\frac{p\beta(n)n}{p\beta(n)+\gamma} + (1-p)\frac{\beta^*}{\gamma}\frac{K}{K-n}\right]\left(\frac{1}{\frac{\mu}{k}+1}\right), \qquad (2.5)$$

where, $K = \frac{\lambda}{\mu}$ is the asymptotic carrying capacity of the total population. Song and colleagues (2002) discussed two special forms of $\beta(n)$ and concluded that casual infection indeed contributes to R_0 as well as close infection.

2.2.2 Treatment of latent TB.

Earlier models (prior to the 1970s) targeted the evaluation of control strategies of TB such as vaccination strategies.

However, these "optimal" strategies have not worked well toward the elimination of TB globally or even regionally. The reasons behind the lack of success of these policies are debatable. Either these strategies have not been applied by the policy-makers or they are not truly "optimal". Part of this work shows that the focus should include control measures in the latent-TB class. The reason is simple. The huge pool of latent-TB patients is a time bomb or reservoir of infection (Reichman and Tanne; 2002).

Forces or new diseases that compromise the immune system may lead to new TB outbreaks, as has occurred with HIV. Mathematical models that stress the importance of treating individuals with latent TB are introduced by Blower and Castillo-Chavez and Song in 2001. Adding an early latent class and long-term latent class into the model generates the following system:

$$\begin{aligned}
\frac{dS}{dt} &= \lambda - \beta SI - \mu S, \\
\frac{dE_1}{dt} &= \beta SI - (\mu + \omega + r_0)E_1, \\
\frac{dE_2}{dt} &= (1-p)\omega E_1 - (\kappa + \mu + r_1)E_2, \\
\frac{dI}{dt} &= p\omega E_1 + kE_2 - (\mu + d + r_2)I
\end{aligned} \tag{2.6}$$

Early latent-TB individuals progress to active TB at the rate pω and to long-term latent TB at the rate (1 − p)ω; long-term latent-TB individuals develop active TB at the rate k and treatment rates are r_0, r_1, and r_2 for early latent TB, long-term latent TB, and active TB, respectively, d is TB induced death rate and μ is the natural death rate.

The Castillo-Chavez and B. Song latent TB model shows that treatment of 25% of early latent-TB cases together with treatment of 80% of active-TB cases may result in the elimination of TB.

2.2.3 Model with Genetic Susceptibility

Murphy et al (2002) characterized the transmission process by a genetically susceptible phenotype model. The population is first divided into a neutral group (N), which denotes those without a susceptibility genotype and a susceptible group (S), which denotes those with a susceptible genotype. Each group is further subdivided into uninfected group (U_i), latent group (L_i) and infectious group (T_i) (i=N, S) by the progression of TB. In the work, they assumed that birth occurs at a constant rate (b) with a fraction (v) being genetically susceptible to infection. Transmission of *Mycobacterium tuberculosis*, which depends on the transmission rates (β_i) that are determined by broad demographic and social contexts as well as by genotype, occurs when there is close contact between an infectious and a susceptible individual. Murphy et al (2002) also defined four transmission rates (β_i) for different transmission of TB, that is, the average number of contacts per unit time resulting in successful transmission of *Mycobacterium tuberculosis* due to contact between two individuals from the neutral group (β_z) or from the susceptible group (β_w) or from both groups respectively (β_x and β_y), which represent possible interactions that may occur among the model subpopulations. The model is described as follows:

$$
\begin{aligned}
\frac{dU_N}{dt} &= b(1-v) - \beta_w U_N \frac{T_N}{P} - \beta_X U_N \frac{T_S}{P} - \mu U_N, \\
\frac{dU_S}{dt} &= bv - \beta_y U_S \frac{T_N}{P} - \beta_X U_S \frac{T_S}{P} - \mu U_S, \\
\frac{dL_N}{dt} &= (1-P_N)\beta_w U_N \frac{T_N}{P} + (1-P_N)\beta_x U_N \frac{T_S}{P} - r_N L_N - \mu L_N, \\
\frac{dL_S}{dt} &= (1-P_S)\beta_y U_S \frac{T_N}{P} + (1-P_S)\beta_x U_S \frac{T_S}{P} - r_S L_S - \mu L_S, \\
\frac{dT_N}{dt} &= P_N \beta_w U_N \frac{T_N}{P} + P_N \beta_x U_N \frac{T_S}{P} + r_N L_N - \mu_{TB} T_S, \\
\frac{dT_S}{dt} &= P_S \beta_y U_S \frac{T_N}{P} + P_S \beta_x U_S \frac{T_S}{P} + r_S L_S - \mu_{TB} T_S
\end{aligned}
\qquad (2.7)
$$

where μ is natural death rate, μ_{TB} is TB-induced death rate, r_N is progression rate. For getting the

threshold condition R_0 of the model, we use the following formula, due to Murphy (2002),

$$R_0 = W + L + XY - WL, \tag{2.8}$$

where,

$$W = (\beta_w(1-v))\left[\frac{1}{\mu_{TB}}\right]\left[P_N + \frac{r_N(1-P_N)}{r_N+\mu}\right]$$

$$X = (\beta_x(1-v))\left[\frac{1}{\mu_{TB}}\right]\left[P_N + \frac{r_N(1-P_N)}{r_N+\mu}\right]$$

$$Y = (\beta_y v)\left(\frac{1}{\mu_{TB}}\right)\left(P_S + \frac{r_s(1-P_S)}{r_s+\mu}\right)$$

$$L = (\beta_z v)\left(\frac{1}{\mu_{TB}}\right)\left(P_s + \frac{r_s(1-P_s)}{r_s+\mu}\right)$$

where, W and L are the basic reproduction numbers for the genetically neutral subpopulation and the genetically susceptible subpopulation respectively, and X and Y account for the contact (interaction) between members of different subpopulations. Numerical experiments showed that $R_0 = 1$ (the bifurcation point), and is thus called the basic reproductive number (R_0) for a heterogeneous population.

To account for treatment, Murphy et al (2003) added treatment into the model and defined the fraction of the population receiving effective chemoprophylaxis, as the rate of effective per capita therapy. Hence, it's formulated with the following expressions

R_0=W+L+XY-WL

Where

$$W = \frac{\beta_w(1-v)(P_N\mu + (1-lt_N)r_N)}{\mu at_N + \mu_{TB}(\mu + (1-lt_N)r_N)},$$

$$X = \frac{\beta_x(1-v)(P_N\mu + (1-lt_N)r_N)}{\mu at_N + \mu_{TB}(\mu + (1-lt_N)r_N)},$$

$$L = \frac{\beta_z v(P_S\mu + (1-lt_S)r_S)}{\mu at_S + \mu_{TB}(\mu + (1-lt_S)r_S)},$$

$$Y = \frac{\beta_y v(P_S\mu + (1-lt_S)r_S)}{\mu at_S + \mu_{TB}(\mu + (1-lt_S)r_S)}.$$

It is clear that when the therapy level $(at_i, i = N, S)$ increases, the denominator of R_0 becomes larger, and thus the value of R_0 is smaller. As a result the disease will be eradicated.

2.3 Dynamics of Co-infections with M. tuberculosis and HIV

The focus of this study was to explore the hypothesis that the presence of infection with M. tuberculosis in the body worsens the clinical picture for HIV; and, that the presence of HIV can activate the M. tuberculosis infection. A simple mathematical model was developed to describe the interaction of the immune system's key players, T cells and macrophages, with the pathogens HIV and M. tuberculosis. The study, by Kirschner (1997), is the first dynamic model to examine HIV together with an opportunistic infection, namely Mycobacterium tuberculosis, the bacteria that cause TB. He defined four populations: $T(t)$ represents the armed CD4+ and CD8+ T cell population at time t in days; $M(t)$ represents the macrophage population; $V(t)$ represents the HIV population and $T_b(t)$ represents the M. tuberculosis population. Assuming that the populations are large enough in size to be modeled deterministically, he represented the dynamics by the following ordinary differential equations:

$$\frac{dT(t)}{dt} = S_T(t) - \mu_T(t) + r_T T(t)\left[\frac{(V(t)+T_b(t))}{C+V(t)+T_b(t)}\right] - k_1 V(t)T(t) \tag{2.9}$$

= source/death/immune response growth/infection & loss

$$\frac{dM(t)}{dt} = \mu_M[M_0 - M(t)] - k_2 M(t)V(t) + r_M^2 M(t)T_b(t)$$

= source/death/infection & loss/stimulation/recruitment (3.0)

$$\frac{dV(t)}{dt} = V(t)[N_1 k_1 T(t) + N_2 g_v M(t)] - V(t)[k_3 T(t) + k_4 M(t)] - \mu_v V(t) \tag{3.1}$$

= source (T and M)/ immune response/death

$$\frac{dT_b(t)}{dt} = r_{Tb} T_b(t)(K - T_b(t)) - \mu_{Tb} T_b(t) - T_b(t)[k_5 T(t) + k_6 M(t)] \tag{3.2}$$

= logistic growth/death/immune response

The model is explained as follows. Equation (2.9) represents the change in the $CD4^+$ and $CD8^+$ T cell populations over time. The first term is the source term of new T cells. This is modelled, not as a parameter, but as a function of time, and it is documented that the precursors to these T cells are affected by the presence of HIV (Kirschner et al., 1998). Thus, $S_T(t)$ is a decreasing function of time. This is followed by a natural loss term, because T cells have a finite life span. Next is growth of T cells, presented in this form to represent expansion by the presence of antigen. Since T cells do not grow without bound, they chose a saturating growth term of Michaelis-Menten type, where r_T is the maximal growth-response rate. The final term is a loss of T cells from the uninfected class, due to infection by HIV.

Equation (3.0) represents the change in the macrophage population over time. The reasons for including the macrophage population are many. Macrophages survive once infected with HIV, and slowly bud new virus particles (Orenstein et al., 1997). They, therefore, play a role as a viral source referred to as a reservoir. Also infected macrophages can infect CD4+ T cells through presentation of antigen (Lewis and McGee, 1992). Finally, as mentioned above, macrophages play a major role in TB pathogenesis. The first term of Equation (3.0) represents the birth-death process for macrophages. The next term represents the loss of uninfected macrophages due to infection by HIV. The final term is a recruitment of new macrophages to the infection site, governed by the presence of pathogen.

Equation (3.1) represents the change in the HIV population over time. The first two terms represent source terms for the virus population. This follows from (2.9) and (3.0) when the T cells and macrophages, respectively, begin to produce new viruses after becoming infected with HIV. Macrophage infection, however, is not well understood, and the author allowed for the possibility of a different production rate of virus (g_v) than infection (k_2). They assumed that once a cell becomes infected with HIV, the cell produces on the average Ni (N1 for T cells and N2 for macrophages) new viral particles (Perelson, 1989; Perelson et al., 1993).

The following two terms of (3.1) are immune clearance terms CD8+ T cells and macrophages clear or kill virus and infected cells. The final term of (3.1) is natural death clearance terms for HIV, as viruses have a finite life span.

Equation (3.2) represents the change in the M. tuberculosis population over time. The first term is a logistic growth term, which represents bacterial growth. This is followed by a natural death term and immune clearance/ killing terms, with rate constants k_5 and k_6, respectively.

The study concluded that co-infection may indeed play a dramatic role in disease.

2.4 Modelling tuberculosis in areas of high HIV prevalence

Hughes et al (2006) developed a discrete event simulation model of tuberculosis (TB) and HIV disease, parameterized to describe the dual epidemics in Harare, Zimbabwe.

The TB model is a discrete event simulation model which allows the population to belong to six epidemiological classes, dependent on TB status. Movements through the pathways of the model are determined by an individual's attributes (age, gender, HIV status)

The schematic for the model is given in figure 2.1 below.

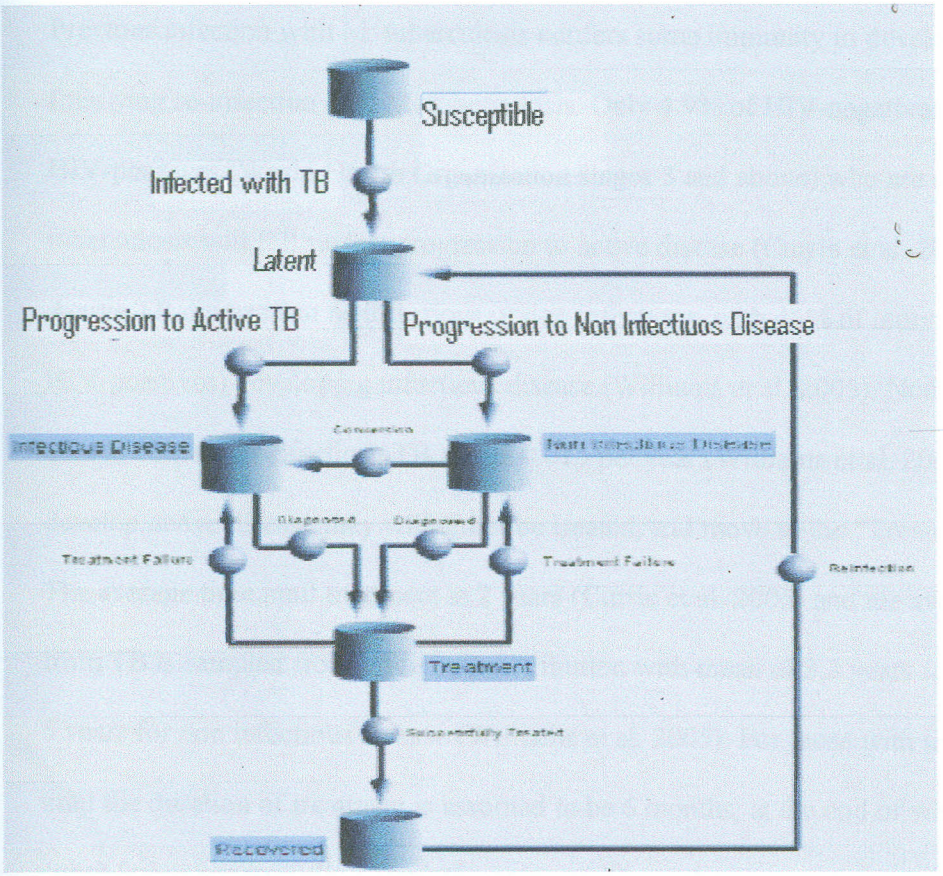


Figure 2.1: Schematic of the discrete event simulation tuberculosis (TB) model. (Hughes et al, 2006)

Death can occur from any state, and death rates are higher for individuals with active disease. The authors assumed that the TB disease progression parameters for HIV-positive individuals only change when the individuals enter late-stage HIV, defined to be World Health Organization stages 3 and above, approximately 6 years after infection (Morgan et al. 2002, World Health Organization 1990). Susceptible individuals are not infected with M. tuberculosis. When they become infected, they enter the latent infection class. Individuals will then follow one of two routes: develop active disease within 5 years, termed fast progression to active disease; or retain a latent M. tuberculosis infection, progressing to active disease at a rate of 0.001 per year for HIV negatives (Vynnycky and Fine 1997) and 0.1 per year for late-stage HIV positives (Williams et al. 2005). Approximately 14% of HIV-negatives will exhibit fast progression (Vynnycky and Fine 1997) and 67% of individuals in late-stage HIV (Edlin et al. 1992).

Previous infection with M. tuberculosis confers some immunity to developing active disease following re-infection with M. tuberculosis. Only 4.9% of HIV-negatives and 50% of late-stage HIV-positives (World Health Organization stages 3 and above) who are re-infected with M. tuberculosis will follow fast progression to active disease (Currie et al. 2005).

Active TB disease can be infectious or non infectious, with 46% of individuals (30% of late-stage HIV-positives) developing infectious disease (Williams et al. 2005). Non infectious individuals are able to convert to infectious TB at rate 0.015 per year (Williams et al. 2005). When individuals develop active disease they will either be treated, and move to the "Treated" class, or they will die. The average time until treatment is 2 years (Currie et al. 2005) and the average time until death from TB is sampled from a Weibull distribution with mean of 3.3 years for infectious disease and 5 years for non infectious disease (Williams et al. 2005). For those with infectious disease, the time until the duration of treatment is assumed to be 6 months, at the end of which the individual will either fail or successfully complete treatment. Those that successfully complete the treatment course become "recovered" and those that fail will return to active disease. When persons have recovered they are again susceptible to re-infection from an infectious person, although they have an increased immunity compared with the "susceptible" population.

2.5 Effects of isoniazid preventive therapy for latent tuberculosis infection in HIV–tuberculosis co-infected populations.

Cohen, T et al (2006), developed a mathematical model of TB/HIV co-epidemics to examine the impact of community-wide implementation of isoniazid preventive therapy (IPT) for TB–HIV co-infected individuals on the dynamics of drug-sensitive and -resistant TB epidemics. To assess the impact of community-wide IPT on the dynamics of drug-resistant TB, Cohen, T et al (2006), constructed a simple deterministic model of TB transmission based on a structure previously developed for the evaluation of control policies. The TB infection process was linked to a dynamic

model of HIV transmission, and the model thus included interacting subpopulations of HIV-infected and non-infected individuals. See Appendix 6 for the model structure.

The model consists of two parallel models (one for HIV-infected and one for HIV-uninfected). Individuals move from one sub-model to the other when they are infected with HIV. Green compartments represent infection disease with a drug-sensitive *M. tuberculosis* strain. Each of the compartments summarizes a number of distinct infection disease states; Orange boxes represent states of latent infection with *M. tuberculosis*. Light blue boxes represent states of TB disease. Solid black arrows represent infection and progression with TB. Finely dotted black arrows represent re-infection events. Medium dashed black arrows represent self-cure from TB disease. Coarse dashed black arrows represent breakdown of chemotherapeutic cures. Finely dotted red arrows represent acquired drug resistance. Solid red arrows represent isoniazid preventive therapy (IPT).

The latent infection compartments include individuals who can progress to TB disease either slowly or rapidly or who can be re-infected with another strain of circulating *M. tuberculosis*. The TB disease compartments include those who have active (infectious) disease and extra pulmonary (noninfectious) disease. Individuals with TB disease may self-cure (contain their infection and return to latency) or, if they have active disease and are detected and treated, they may recover from disease. Those who are treated for drug-sensitive TB may acquire drug resistance.

Individuals in all compartments (with the exception of those with TB disease) may be re- infected by circulating strains of *M. tuberculosis* (dotted arrows). IPT works by clearing drug-sensitive organisms from latently infected individuals (red arrows).

S: susceptible to TB infection

L: latently infected with drug-sensitive TB, slowly progressive

E: latently infected with drug-sensitive TB, rapidly progressive

Lr: latently infected with unfit drug-resistant TB, slowly progressive

Er: latently infected with unfit drug-resistant TB, rapidly progressive

Lr2: latently infected with fit drug-resistant TB, slowly progressive

Er2: latently infected with fit drug-resistant TB, rapidly progressive

Ld: latently infected with both sensitive and unfit drug-resistant strains, slowly progressive

Ld2: latently infected with both sensitive and fit drug-resistant strains, slowly progressive

Ld3: latently infected with both unfit and fit drug-resistant strains, slowly progressive

U: extra pulmonary drug-sensitive TB (noninfectious)

I: undetected, infectious drug-sensitive TB (will not be treated)

D: detected, infectious drug-sensitive TB (may be treated)

Ur: extra pulmonary unfit drug-resistant TB (noninfectious)

Ir: undetected, infectious unfit drug-resistant TB (will not be treated)

Dr: detected, infectious unfit drug-resistant TB (may be treated)

Ur2: extra pulmonary fit drug-resistant TB (noninfectious)

Ir2: undetected, infectious fit drug-resistant TB (will not be treated)

Dr2: detected, infectious fit drug-resistant TB (may be treated)

R: chemotherapeutic cure from drug-sensitive TB

Rr: chemotherapeutic cure from unfit drug-resistant TB

Rr2: chemotherapeutic cure from fit drug-resistant TB

States with an *h* prefix are HIV-infected states. These states are as described above with one additional state:

hP: individuals who are in this state had HIV and a drug-sensitive latent TB infection and were given IPT.

Note that individual arrows representing HIV infection are not depicted for the sake of clarity. Individuals in any non-HIV infection state may become infected and will move to the corresponding h_i state.

They found that isoniazid preventive therapy (IPT) for HIV–TB co-infected individuals reduces the reactivation of latent *Mycobacterium tuberculosis* infections and is being evaluated as a potential community-wide strategy for improving TB control. They concluded that community-wide IPT in areas of emerging HIV and drug-resistant TB should be coupled with diagnostic and treatment policies designed to identify and effectively treat the increasing proportion of patients with TB/HIV. According to the same paper the rate of rapid to slow progression is 0.2

2.6 The Cursed Duet: Dynamics of HIV-TB Co-infection in South Africa

Diego C.P et al (2007), used an epidemiological model to explore the co-infection transmission dynamics of HIV/AIDS and tuberculosis in South Africa, specifically in adults aged 15 to 49. In the model, the population is divided into seven epidemiological classes: Susceptible (*S*), Latent TB (*L*), Infectious TB (*I*), HIV-positive (*H*), HIV-positive with latent TB (H_L), HIV-positive individuals with infectious TB (H_I) and HIV-positive individuals with other opportunistic infections different from TB (A). In the model H_L and H_I represent the HIV-TB co-

infection. The compartment model is shown in (Figure 2.3). They stated that an individual who is HIV-positive and is actively infected with TB is an indicator of AIDS; and they therefore denoted the AIDS class induced by TB as H_1. They also considered other opportunistic infections associated with HIV in the *A* class. They assumed successful treatment for TB.

The susceptible class (S) is composed of individuals aged between 15 to 49 years old, who are neither infected by HIV nor TB. In this model, TB infection is spread between infectious and susceptible individuals through airborne spread (droplets). HIV is also transmitted between infectious and susceptible individuals and no particular route of transmission is assumed (direct sexual contact, exposure to infected body fluids or tissues, etc.) Therefore, susceptible individuals can either be infected with TB by individuals in the epidemiological classes I or H_I and with HIV by individuals in H, H_L, H_I or *A*.

People infected with HIV have an increasing risk for progressive disease to AIDS, (H_I), through TB infection and reactivation of the latent TB infection (Sharma S.K, 2005). HIV also increases the risk of TB progression from re-infection externally caused (Sharma S.K, 2005). The latent class (L) is composed of individuals who have TB infection but cannot pass the disease (they are individuals who are infected but not infectious). Consequently, they can be infected with HIV by individuals from the epidemiological classes H, H_L, H_I or A. The active TB class I is composed of infectious TB individuals. They can be infected with HIV by individuals from H, H_L, H_I or A classes. The HIV class H is composed of individuals who are HIV-positive. Consequently, they can be infected with TB infection by individuals from I or

H_I classes. The H_L class are individuals who have HIV-positive and latent TB. Similarly, the H_I class is composed of individuals who have HIV-positive and active TB. Finally, the A class is composed by individuals who have HIV-positive and an opportunistic infection different from TB. The total population is $N = S + L + I + H + H_L + H_I + A$ where *S* is the total size of susceptible population, $L + I$ is the total size of TB individuals if HIV was not present in the population, $H + H_L$ is the HIV population and (H_I +A) is the total number of individuals suffering from AIDS.

Individuals enter the susceptible class at the per-capita rate b and die at the natural per-capita rate μ. Susceptible individuals infected with TB enter the latent period (L) at rate $\beta_1(\frac{I+\delta H_t}{N})$ an the HIV-positive class (H) at the rate $\beta_2\left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right)$ where β_1 and β_2 are the transmission rates per year for TB and HIV respectively, the quantity $\frac{I+\delta H_t}{N}$ is the probability of contacting an individual infected with TB out of the total populatio and $\left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right)$ is the risk measure associated with levels of HIV in the population; parameter $\delta > 1$ indicates that an individual with HIV and active TB is more infectious to pass TB disease compared with an HIV-negative individual with active TB. The rates $1 \le \varepsilon_1 \le \varepsilon_2 \le \varepsilon_3$ indicate that it is easier to become infected with HIV-positive from an individual with HIV-positive with latent TB or from an individual with AIDS than from an individual infected just with HIV-positive. Individuals who are in the latent class can go back to the susceptible class due to successful treatment for TB at the rate γ_1, die at the rate μ, or progres to the infectious class (I) at the rate k. Latent TB individuals can also move to the HIV-positive class (H_L) at the rate $\beta_4\left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right)$ where the transmission rate for HIV is β_4. Infectious TB individuals (I) recover due to successful treatment at the rate γ_2, die from TB at the rate τ, or enter the class (H_I) at the rate $\beta_5\left(\frac{H+\varepsilon_1 H_L+\varepsilon_2 H_I+\varepsilon_3 A}{N}\right)$ where β_5 is the transmission rate for HIV. Individuals who are HIV-positive can either be infected with TB or other opportunistic infection.

If they are infected with TB, they enter the HIV-positive and latent TB class (H_L) at the rate $\beta_3(\frac{I+\delta H_t}{N})$ where β_3 is the transmission rate. Otherwise, they progress to the AIDS class (A) at the rate ω. Individuals in this class die from both diseases, HIV and any other opportunistic infection, at rate σ. HIV-positive with latent TB individuals go back to the HIV-

positive class (H_L) due to successful treatment for TB at the rate γ_3 or progress to AIDS or HIV-TB co-infection class (H_I) at the rate λ. Individuals infected with HIV-positive and active TB die from HIV and TB at the rate α.

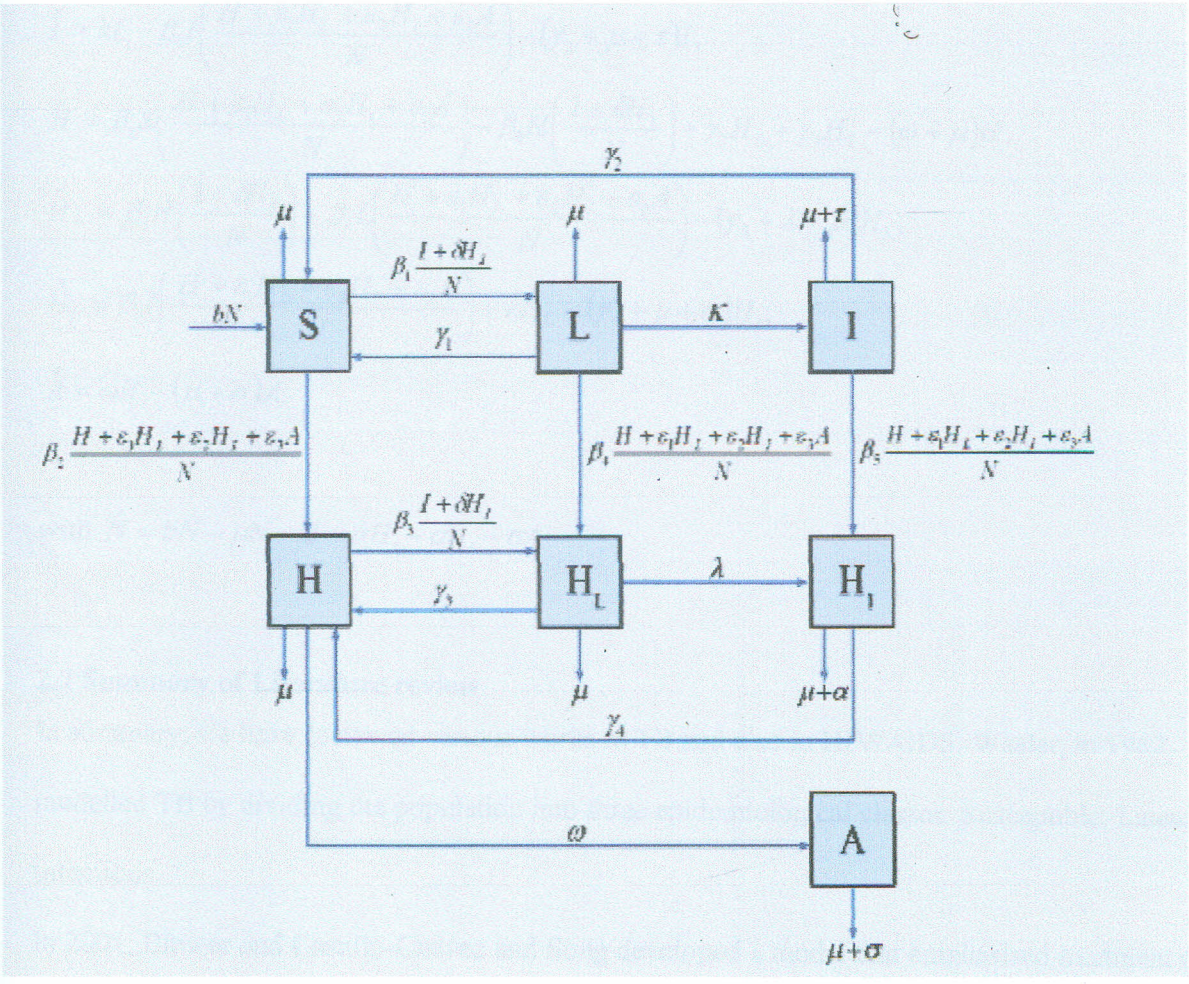


Figure 2.3: Schematic representation of the flow between the different epidemiological classes.

The model that describes the dynamics of the HIV-TB co-infection is given by the following system of nonlinear differential equations: (Diego C.P et al, 2007)

$$\dot{S} = bN - \beta_1 S\left(\frac{1+\delta H_t}{N}\right) - \beta_2 S\left(\frac{H+\varepsilon_1 H_L + \varepsilon_2 H_I + \varepsilon_3 A}{N}\right) - \mu S + \gamma_1 L + \gamma_2 I,$$

$$\dot{L} = \beta_1 S\left(\frac{1+\delta H_t}{N}\right) - \beta_4 L\left(\frac{H+\varepsilon_1 H_L + \varepsilon_2 H_I + \varepsilon_3 A}{N}\right) - (\gamma_1 + k + \mu)L,$$

$$\dot{I} = kL - \beta_5 I\left(\frac{H+\varepsilon_1 H_L + \varepsilon_2 H_t + \varepsilon_3 A}{N}\right) - (\gamma_2 + \mu + \tau)I,$$

$$\dot{H} = \beta_2 S\left(\frac{H+\varepsilon_1 H_L + \varepsilon_2 H_t + \varepsilon_3 A}{N}\right) - \beta_3 H\left(\frac{I+\delta H_t}{N}\right) + \gamma_3 H_L + \gamma_4 H_I - (\omega + \mu)H,$$

$$\dot{H}_L = \beta_3 H\left(\frac{1+\delta H_t}{N}\right) + \beta_4 L\left(\frac{H+\varepsilon_1 H_L + \varepsilon_2 H_I + \varepsilon_3 A}{N}\right) - (\gamma_3 + \lambda + \mu)H_L,$$

$$\dot{H}_I = \beta_5 I\left(\frac{H+\varepsilon_1 H_L + \varepsilon_2 H_I + \varepsilon_3 A}{N}\right) + \lambda H_L - (\gamma_4 + \mu + \alpha)H_t,$$

$$\dot{A} = \omega H - (\mu + \sigma)A,$$

with $\dot{N} = bN - \mu N - \tau I - \alpha H_t - \sigma H_t - \sigma A$

2.7 Summary of Literature review

In summary, we have reviewed various works in TB and also in HIV/AIDS. Waaler, in 1962, modelled TB by dividing the population into three epidemiological classes: Susceptible, Latent and infectious.

In 2001, Blower and Castillo-Chavez and Song developed a model that emphasised treatment of latent TB. The model had an early latent TB and a long – term latent TB.

Aparicio and his colleagues in 2002 developed a basic generalised household (cluster model) for TB transmission focusing on close and casual contacts within and outside social networks.

Song and others in 2002 extended the basic cluster model by including the average time spent by an active case within and outside his/her generalised household.

Murphy on his part characterised the transmission of TB by a genetically susceptible phenotype model.

The study, by Kirschner (1997), is the first dynamic model to examine HIV together with an opportunistic infection, namely Mycobacterium tuberculosis, the bacteria that cause TB.

The focus of this study was to explore the hypothesis that the presence of infection with M. tuberculosis in the body worsens the clinical picture for HIV; and, that the presence of HIV can activate the M. tuberculosis infection. A simple mathematical model was developed to describe the interaction of the immune system's key players, T cells and macrophages, with the pathogens HIV and M. tuberculosis.

Hughes et al, 2006 developed a discrete event simulation model of tuberculosis (TB) and HIV disease, parameterized to describe the dual epidemics in Harare, Zimbabwe.

The TB model is a discrete event simulation model which allows the population to belong to six epidemiological classes, dependent on TB status.

Cohen, T et al, 2006, developed a mathematical model of TB/HIV co-epidemics to examine the impact of community-wide implementation of isoniazid preventive therapy (IPT) for TB–HIV co-infected individuals on the dynamics of drug-sensitive and -resistant TB epidemics. To assess the impact of community-wide IPT on the dynamics of drug-resistant TB, Cohen, T et al (2006), constructed a simple deterministic model of TB transmission based on a structure previously developed for the evaluation of control policies.

Lastly, Diego C.P et al (2007) used an epidemiological model to explore the co-infection transmission dynamics of HIV/AIDS and tuberculosis in South Africa, specifically in adults aged 15 to 49.

In the model, the population is divided into seven epidemiological classes: Susceptible (S), Latent TB (L), Infectious TB (I), HIV-positive (H), HIV-positive with latent TB (H_L), HIV-positive individuals with infectious TB (H_I) and HIV-positive individuals with other opportunistic infections different from TB (A).

CHAPTER THREE
MODEL DEVELOPMENT

3.1.0 Introduction

In this section we present an overview of the Mackendrick-Von Foster equation, which we will apply in formulation of the model equations. We hence develop our models for TB in the presence of HIV as well as for TB in the absence of HIV and give an explanation of the model.

3.1.1 Population Model with Age Structure, Time dependent

This is the type of structured population model whereby the birth and death rate depend on both age and time. This occurs, when the environment changes over time. The model is often called Mackendrick-Von Foster equation. It is a first order partial differential given by

$$\frac{\partial n(a,t)}{\partial t} = -\frac{\partial n(a,t)}{\partial a} - \mu(a,t)n(a,t) \qquad a,t \geq 0 \qquad (3.1)$$

where n(a,t) is the age distribution of the population at time t and $\mu(a,t)$ is the age and time dependant natural mortality rate.

3.1.2 Model for HIV and TB

A compartmental model refers to a situation where the population is divided into different epidemiological states and the movements between the states are represented by a system of differential equations. The model will be fitted to data from available literature to estimate some parameters of these deadly diseases.

3.1.3 The Model

Blower and Castillo-Chavez in 2.2.2 above introduced a mathematical model that stresses the importance of treating individuals with latent TB where they added an early latent class and long-term latent class into the model. We borrow this to develop a model that explicitly represents two different latently infected classes: "fast progressors" denoted by E and "slow progressors" denoted by F. According to Williams et al (2006), active TB disease can be infectious or non-infectious. It

is infectious if it infects the lungs i.e. pulmonary TB and non-infectious if it infects the spine, brain and the kidney. This approach is summarized in Figure 3.1 below. In this model, newly infected individuals are assigned to one of these two compartments and experience the corresponding rate of progression. Typically individuals can move from the slow group to the fast group (if a re-infection event occurs), and vice versa if there is treatment of latent TB as suggested by Blower and his colleagues. However, an individual fully treated or naturally recovered, cannot return to the susceptible class but moves to latent slow rate class. This is due to the fact that once vaccinated with BCG, which is a component of the childhood vaccination regimen in most African countries and typically administered at birth, an individual has the bacteria in his/her system. We assume that only people with active TB can transmit the disease to others.

Table 3.2: The variables t and a represent time.

	No TB	Latent TB (fast rate)	Latent (slow rate) or Active non-infectious TB	Active TB (Infectious)
HIV-	$S_0(t)$	$E_0(t)$	$F_0(t)$	$I_0(t)$
HIV+	$S_1(t)$	$E_1(t)$	$F_1(t)$	$I_1(t)$

We let $P(t)$ denote the total population with $\phi(t)$ representing the fraction of the total population that transmit TB

$$\phi(t) = \sum_{n=0}^{1} I_n(t)/P(t) \text{ where } I_n(t) \text{ is the number of infective}$$

individuals at time t.

3.1.4 Force of Infection

Force of infection is the rate at which susceptible individuals become infected by an infectious disease. We assume that the force of infection by HIV for people aged a at time t is given by;

$$\lambda(t) = \frac{I(t)}{N(t)}\beta(t)C$$

Where $\frac{I(t)}{N(t)}$ measures the risk of getting HIV, $\beta(t)$ is the net rate of recruitment into the susceptible class and we take it to be 0.02 (Diego C.P et al, 2007) and C is the number of partners per unit time.

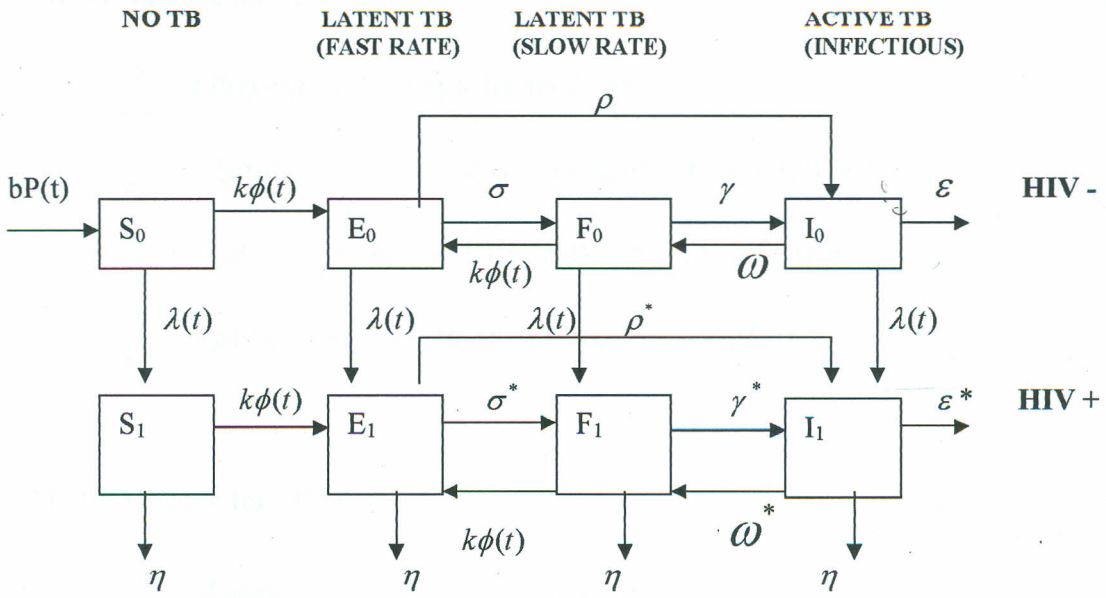


Figure 3.1: Compartmental age-structured model for HIV and TB with natural mortality μ in every compartment.

The absence of birth inflows into the S_0 compartment is due to our assumption that mother-to-child transmission of HIV is neglected. People who get infected by M.Tuberculosis move from an S-compartment to an E-compartment where they have a relatively high risk of progressing to active infectious TB (disease stage). If After a few years they haven't developed the disease, then they move to compartment F where progression to the active infectious disease is still possible but at a slow rate. But a re-infection may bring them back to the E-compartment. Successfully treated or naturally recovered people return from compartment I to the low risk compartment F. People who get infected by HIV move from a compartment with subscript 0 to the corresponding compartment with subscript 1 (HIV stage).

Where $P = S_0 + S_1 + E_0 + E_1 + F_0 + F_1 + I_0 + I_1$

Model equation for TB/HIV

$$\begin{aligned}
\frac{\partial S_0}{\partial t}+\frac{\partial S_0}{\partial a} &= bP(t)-(\mu(a)+k\phi(t)+\lambda(t,))S_0(t,a)\\
\frac{\partial E_0}{\partial t}+\frac{\partial E_0}{\partial a} &= -(\mu(a)+\rho+\sigma+\lambda(t))E_0(t,a)+k\phi(t)(S_0(t,a)+F_0(t,a))\\
\frac{\partial F_0}{\partial t}+\frac{\partial F_0}{\partial a} &= -(\mu(a)+\gamma+k\phi(t)+\lambda(t))F_0(t,a)+\sigma E_0(t,a)+\omega I_0(t,a)\\
\frac{\partial I_0}{\partial t}+\frac{\partial I_0}{\partial a} &= -(\mu(a)+\omega+\varepsilon+\lambda(t))I_0(t,a)+\rho E_0(t,a)+\gamma F_0(t,a)
\end{aligned} \tag{3.2}$$

Model equation for TB/HIV+

$$\begin{aligned}
\frac{\partial S_1}{\partial t}+\frac{\partial S_1}{\partial a} &= -(\mu(a)+k\phi(t)+\eta)S_1(t,a)+\lambda(t)S_0(t,a)\\
\frac{\partial E_1}{\partial t}+\frac{\partial E_1}{\partial a} &= -(\mu(a)+\rho^*+\sigma^*+\eta)E_1(t,a)+k\phi(t)(S_1(t,a)+F_1(t,a))+\lambda(t)E_0(t,a)\\
\frac{\partial F_1}{\partial t}+\frac{\partial F_1}{\partial a} &= -(\mu(a)+\gamma^*+k\phi(t)+\eta)F_1(t,a)+\sigma^* E_1(t,a)+\omega^* I_1(t,a)+\lambda(t)F_0(t,a)\\
\frac{\partial I_1}{\partial t}+\frac{\partial I_1}{\partial a} &= -(\mu(a)+\omega^*+\varepsilon+\eta)I_1(t,a)+\rho^* E_1(t,a)+\gamma^* F_1(t,a)+\lambda(t)I_0(t,a)
\end{aligned} \tag{3.3}$$

3.1.5 Model Equations Description

We briefly discuss an intuitive interpretation of the first-four model equations (3.2). Since they are all age-structured models, the descriptions will be similar for the other equations (3.3). The first equation implies that $S_0(t, a)$ (which represents the number of susceptible individuals, of age a, at time t) at a given point in time may change with age $\frac{\partial S_0}{\partial a}$ and likewise the number at a given age may change over time $\frac{\partial S_0}{\partial t}$, as susceptibles are recruited at the rate bP(t) and as susceptibles are lost by natural death at a rate μ(a) or as they transferred to the latent TB class, $E_0(t, a)$ at a rate $k\phi(t)$ or as they are transferred to HIV+ class at the rate $\lambda(t)$

The left-hand side of the other three equations will follow the same explanation as the first, so we will rather explain the right-hand side. The second equation means that the $E_0(t, a)$ population are lost by natural mortality of rate μ(a) or as they are transferred to the $F_0(t, a)$ and $I_0(t, a)$ classes at

the rates σ and ρ respectively and as they are transferred to E_1 at the rate $\lambda(t)$. $E_0(t, a)$ increases their population through the outflows from the $S_0(t, a)$ and $F_0(t, a)$ compartments with the equal rates as $k\phi(t)$ as shown in the model diagram. The rest of the equations will follow the same explanation.

We are neglecting here both mother-to-child transmission of HIV and the impact of HIV/TB on the number of births.

CHAPTER FOUR
PARAMETER VALUES

4.0 Introduction

In this chapter, we discuss parameter values related to TB and HIV in our model and also demographic parameters.

4.1 Parameter Values

In this section, we shall discuss parameters related to TB progression, active TB without treatment and we will finally look at parameters associated with treatment. These parameters will be derived from information obtained from available secondary data.

4.1.1 Progression from Latent to Active TB

According to Hughes and others (2006) in section 2.4 above, progression to active TB is said to be rapid if it occurs within 5 years after infection. According to the same paper, the proportion of HIV-negative people or early HIV-positive people who develop active TB within these five years is 0.14. After that, the progression is slow which 0.001/year is. In addition, the proportion of people in their late stage of HIV who develop Active TB within 5 year is 0.67, after that the progression rate is slow, 0.1/year. According to Cohen, T et al, 2006, in 2.5 above, the rate of movement from latent TB fast rate to latent TB slow rate is 0.2. We assume that this rate is the same for both HIV-infected and HIV-uninfected i.e. $\sigma = \sigma^* = 0.2$/year (Table 4.3 on page 37 below). With this information, we evaluate the following parameters ρ and ρ^* as follows. We translate this information within the model by equations;

$$\frac{\rho}{\rho+\sigma} = \frac{14}{100} \quad \ldots\ldots (4.2)$$

$$\frac{\rho^*}{\rho^*+\sigma^*} = \frac{67}{100} \quad \ldots\ldots (4.3)$$

$\gamma = 0.001$/year and $\gamma^* = 0.1$/year. From equations 4.2 and 4.3, we obtain $\rho = 0.033$/year and $\rho^* = 0.41$/year.

The reason why $\rho^* > \rho$ is due to the fact that, people who are HIV positive develop TB at a faster rate than those who are HIV-negative.

4.1.2 Active TB without Treatment

The aim of this subsection is to determine TB induced death rate for HIV positive and HIV negative individuals.

According to Corbett et al (2006), the duration of illness for untreated TB is 2.0 years if HIV-negative and 1 year if HIV-positive. The average fatality rates for HIV-negative and HIV-positive people are 43% and 78% respectively. We assume that TB can be ended by either death or self cure in the absence of treatment.

Let i be the duration of untreated TB i.e. $i = \frac{1}{r+\varepsilon}$, then the proportion of TB patients who die from TB for HIV negative individuals i.e. case fatality rate (cfr) is given by $= \frac{\varepsilon}{r+\varepsilon}$

Where r refers to the rate of self cure in for TB in HIV negative individuals, r^* is the rate of self cure in HIV positive individuals, ε is the death rate from TB in HIV negative people and ε^* represent TB death rate in HIV positive people.

This is translated within the model to obtain the following equations:

$$\frac{1}{r+\varepsilon} = 2.0 \text{ Years},$$

$$\frac{\varepsilon}{r+\varepsilon} = \frac{43}{100}$$

$$\frac{1}{r^*+\varepsilon^*} = 1 \text{Year},$$

$$\frac{\varepsilon^*}{r^*+\varepsilon^*} = \frac{78}{100}$$

Solving we obtain r = 0.29, ε = 0.22, r^* = 0.22 and ε^* = 0.78.

4.1.3 Treatment

To estimate the detection rates q and q* we consider the situation in 2005 of a township of South Africa. According to Wood et al, (2006), adult population was estimated to be 10,408. The estimate for the prevalence of HIV-negative people with undiagnosed TB was 7/762 and that of HIV-positive people with undiagnosed TB was 16/762. (See table 5.2 in appendix 6 for data).

Now let;

$\pi_0 + \pi_1$ =Number of HIV-negative people who have TB

$\pi_2 + \pi_3$ =Number of HIV-positive people who have TB

Therefore from the information given above we obtain;

$\pi_0 + \pi_1 \approx 10,408 \times 7/762 \approx 96$

- $\pi_0 + \pi_1 \approx 10,408 \times 16/762 \approx 219$

This reference also indicates that the number of TB notifications was 259 in 2005. Of these 88 (34%) were HIV-negative and 171 (66%) were HIV-positive. We finally evaluate the detection rates from the following equations as;

$q(\pi_0 + \pi_1) \approx 88$
$q^*(\pi_2 + \pi_3) \approx 171$

Hence

$q \approx 0.92$/year

And

$q^* \approx 0.78$/year.

Table 4.2: Parameter values

Natural mortality rate	μ	0.014	Diego C.P et al, 2007
Birth rate	b	0.022	Diego C.P et al, 2007
Death rate for HIV +	η	0.05	Diego C.P et al, 2007
TB transmission	k	0.22	Diego C.P et al, 2007
Duration of treatment	τ	8 months	WHO
TB and HIV-			
Fast progression rate to TB	ρ	0.033/year	Section 4.1.2
Fast to slow progression rate	σ	0.2/year	Cohen,T et al, 2006
Detection rate	q	0.92/year	Section 4.1.4
Slow progression to TB	γ	0.001/year	Hughes et al, 2006
Recovery rate if untreated	r	0.29/year	Section 4.1.3
Successful treatment	s	80%	Section 2.2.2
TB death rate	ε	0.22/year	Section 4.1.3
Total recovery rate	ω	$r(1-q)+sq$ =0.7416	Determined
TB and HIV+			
Force of infection	$\lambda(t)$	0.2	Diego C.P et al, 2007
Fast progression rate to TB	ρ^*	0.41/year	Section 4.1.2
Fast to slow progression rate	σ^*	0.2/year	Cohen,T et al, 2006
Slow progression rate to TB	γ^*	0.1/year	Hughes et al, 2006
Total recovery rate	ω^*	$r^*(1-q^*)+sq^*$ =0.6724	Determined
TB death rate	ε^*	0.78/year	Section 4.1.3
HIV positive			
Recovery rate	r^*	0.22/year	Section 4.1.3
Detection rate	q^*	0.78/year	Section 4.1.4
Successful treatment	s	80%	Section 2.2.2

4.3 Numerical solutions

To obtain numerical solutions, we made certain simplifying assumptions that the models (3.1) and (3.2) are a function not only of time (t) but also age (a) and age itself is a function of time. We hence dropped age dependence. Further, we assume that $\mu(a) = 0$ implying that the population is simply changing by the rate at which it is getting older. This now leaves us with following equations to solve using MATLAB.

$$\begin{aligned}
\frac{dS_0}{dt} &= bP(t) - (\mu + k\phi(t) + \lambda(t,))S_0(t) \\
\frac{dE_0}{dt} &= -(\mu + \rho + \sigma + \lambda(t))E_0(t) + k\phi(t)(S_0(t) + F_0(t)) \\
\frac{dF_0}{dt} &= -(\mu + \gamma + k\phi(t) + \lambda(t))F_0(t) + \sigma E_0(t) + \omega I_0(t) \\
\frac{dI_0}{dt} &= -(\mu + \omega + \varepsilon + \lambda(t))I_0(t) + \rho E_0(t) + \gamma F_0(t)
\end{aligned} \tag{4.3}$$

$$\begin{aligned}
\frac{dS_1}{dt} &= -(\mu + k\phi(t) + \eta)S_1(t) + \lambda(t)S_0(t) \\
\frac{dE_1}{dt} &= -(\mu + \rho^* + \sigma^* + \eta)E_1(t) + k\phi(t)(S_1(t) + F_1(t)) + \lambda(t)E_0(t) \\
\frac{dF_1}{dt} &= -(\mu + \gamma^* + k\phi(t) + \eta)F_1(t) + \sigma^* E_1(t) + \omega^* I_1(t) + \lambda(t)F_0(t) \\
\frac{dI_1}{dt} &= -(\mu + \omega^* + \varepsilon + \eta)I_1(t) + \rho^* E_1(t) + \gamma^* F_1(t) + \lambda(t)I_0(t)
\end{aligned} \tag{4.4}$$

We hence obtain HIV prevalence as a function of time (Fig. 4.1 in appendix 1).

TB notification rates (per year) as function of time. The rates have been on an upward trend since 2005 as depicted above (Fig 4.3 in appendix 3.)

The current level of HIV prevalence is halting the downward trend of total TB cases. This is the result of the continual rise of HIV-TB co-infection (see Figure 4.2 in appendix 2).

As of 2005 the prevalence of HIV-TB co-infection has relatively minimal contribution to the total TB prevalence compared to active TB cases. However, the current rising trend of HIV-TB co-infection will eventually be just as prevalent as active TB cases and in roughly ten years more prevalent (see Figure 4.2 in appendix 2).

Numerical simulations for the model where carried out using estimated parameter values found in literature.

The results of our numerical simulations identified that the declining trend of total tuberculosis cases will eventually shift due to HIV-TB co-infection. Figure 4.2 shows that, in 12 years, HIV-TB co-infection prevalence will be greater than active TB prevalence.

It is seen that the HIV epidemic poses a threat to the stability of TB prevalence.

The impact of the HIV/AIDS epidemic is accelerating the TB prevalence. With a higher HIV/AIDS population and increased HIV infection rates, TB prevalence persists at increasingly higher levels. It therefore follows that HIV-TB co-infection will continue to rise as a result of the HIV/AIDS epidemic.

If the HIV/AIDS population is reduced TB prevalence will experience a reduction as shown in appendix 2

CHAPTER FIVE

DISCUSSION OF RESULTS AND CONCLUSION

5.0 Introduction

In this chapter, we present the discussion of the results as well as the conclusion.

5.1 Discussion of results

We have established in section 4.2.0 that $\rho^* > \rho$. This implies that people who are HIV positive develop active TB at a faster rate than those who are HIV-negative. This means that the reactivation of latent TB as well as the progress from latent to active TB is faster in people living with HIV/AIDS than those who are HIV negative. Therefore, treatment for latent TB is essential as this will go a long way in preventing a clinical decline of HIV/AIDS patients.

In section 4.2.1, we found out that the mortality rate for tuberculosis when the patient is HIV negative is 0.22 and 0.78 when the patient is HIV positive. The rate is higher for HIV positive individuals implying that tuberculosis is the leading killer of people living with HIV/AIDS. It is therefore important to treat tuberculosis in HIV/AIDS patients in order for them to live longer lives.

We also obtained in the same section the rates of self cure for TB in HIV negative and positive individuals. $r = 0.29 > r^* = 0.22$. The rate of self cure for TB in HIV negative individuals is higher than the rate in HIV positive individuals. This is so because People living with HIV/AIDS have their immune system compromised such that they cannot effectively fight the disease.

In section 4.2.2, we obtained the detection rates for TB in HIV positive and negative population as $q^* = 0.78/year$ and $q = 0.92/year$. This implies that it is easier to detect TB in individuals who are HIV negative than it is in HIV positive individuals.

In a nutshell, our findings suggest that it is vital to keep tuberculosis in check especially in people living with HIV/AIDS because in so doing these people are likely to live longer and healthier lives.

5.2 Conclusion

In this thesis we have reviewed age-structured population models for HIV and TB interaction relying on available literature in journals. This was necessitated by lack of data in most Kenyan hospitals.

The choice to investigate these two diseases in conjunction is motivated by their close relationship.

In chapter 1, we discussed the need for epidemic modeling, statement of the problem, significance of the study and we also formulated a hypothesis of the study.

In chapter 2, we went on to review literature on TB models.

In chapter 3, we looked at TB progression as well as various stages of HIV infection. We then merged the ideas from these diseases into a more sophisticated description of the interactions of the two diseases, and how they affect each other.

The interactions between HIV and TB lead to drastic problems since the immunodeficiency caused by AIDS leads people to contract TB. To reflect this, the model presented in chapter 3 takes both diseases into account and considers all possible interactions by dividing the population into relevant categories.

In chapter 4, we reviewed different epidemiological techniques to estimate parameters in the model.

The estimation of these parameters relied on the extraction of relevant information from data available in the literature. Finally, we were able to present computed solutions of the model numerically using MATLAB.

Our findings seem consistent with reality that those with HIV develop TB at a faster rate than those who are HIV negative. This also supports our hypothesis formulated in chapter one.

Our model does have certain drawbacks. It does not take into account some important factors. For example, the random mixing assumption used in our model excludes children, which is clearly not realistic. Secondly, the absence of a recovery compartment in the model is a serious disadvantage. The addition of a recovery category would substantially improve our model. The

reduction of partial differential equations to ordinary differential equations is also a draw back that can be improved on in future. These drawbacks present an opportunity for future and further studies.

The most obvious extension of this thesis would be to incorporate the above-mentioned factors, and to include the vertical transmission of HIV/AIDS, from mother to child. Investigating local and global stability analysis for this model would also be an interesting avenue of exploration.

Appendix 1

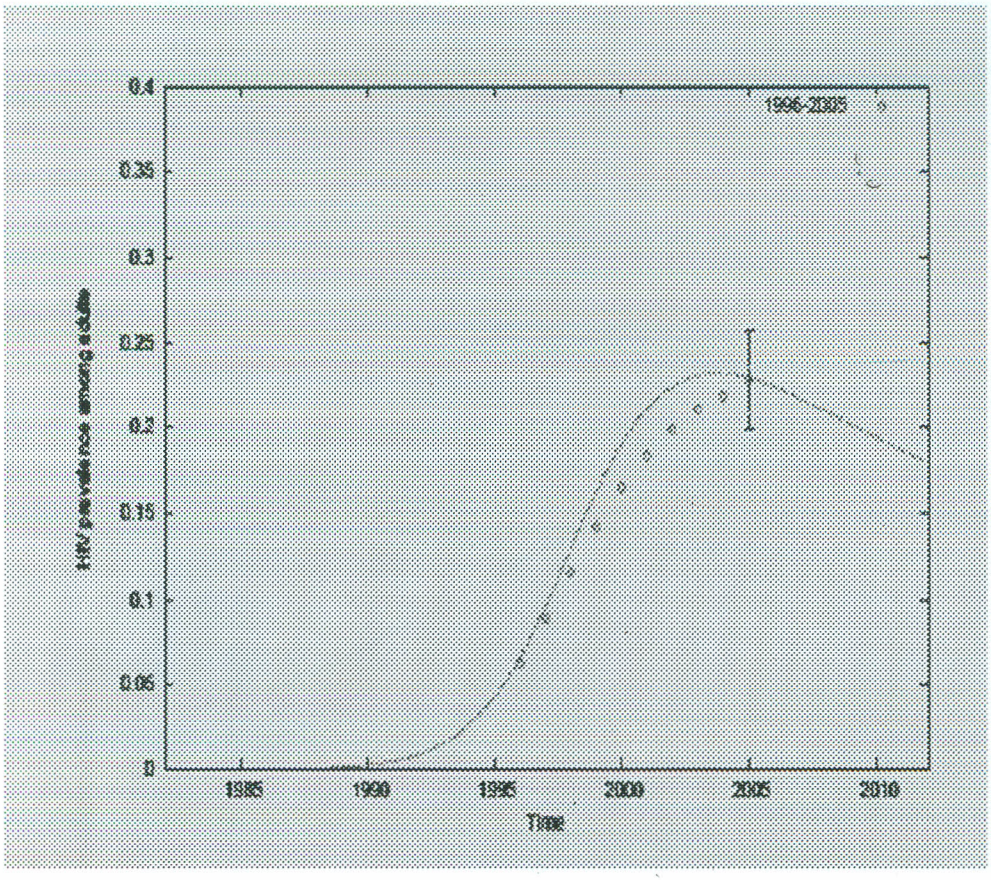


Figure 4.1: HIV prevalence as a function of time. Data from Stephen, D. Lawn et al (2006).

See appendix 5

Appendix 2

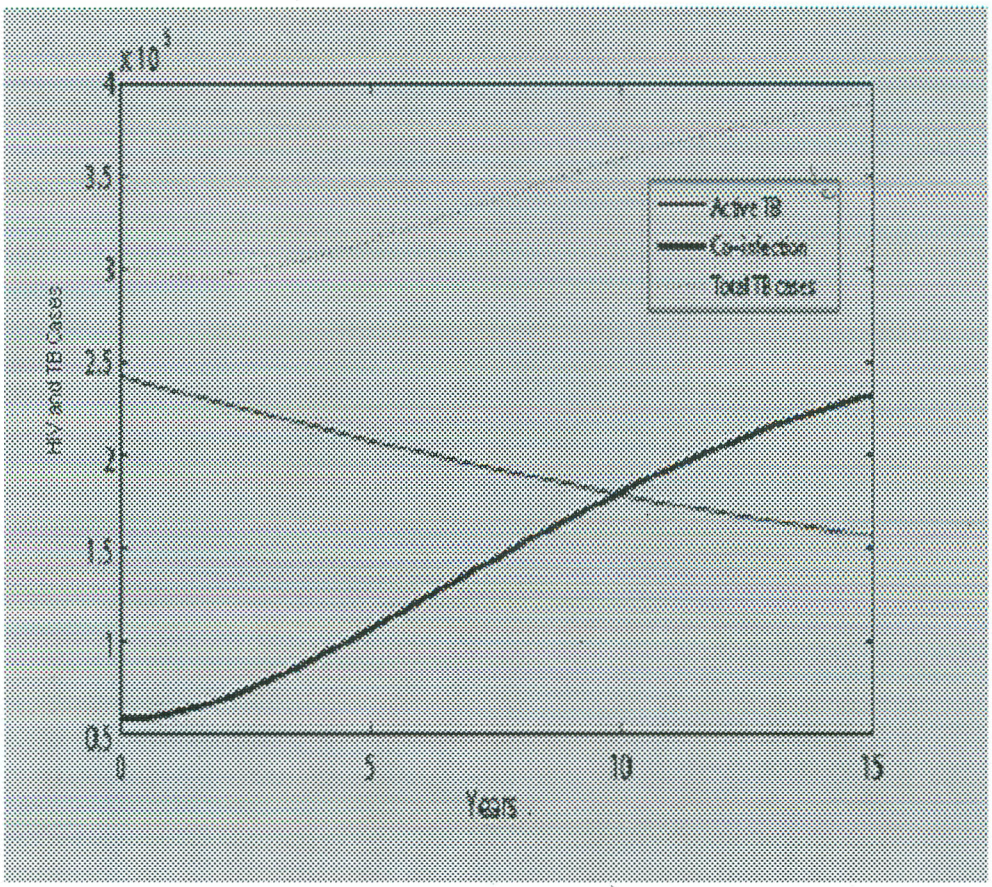


Figure 4.2: Dynamics of active TB, HIV-TB co-infection, and total TB cases over time. The current rising trend of HIV-TB co-infection will eventually be just as prevalent as active TB cases in roughly ten years and in twelve years more prevalent.

Appendix 3

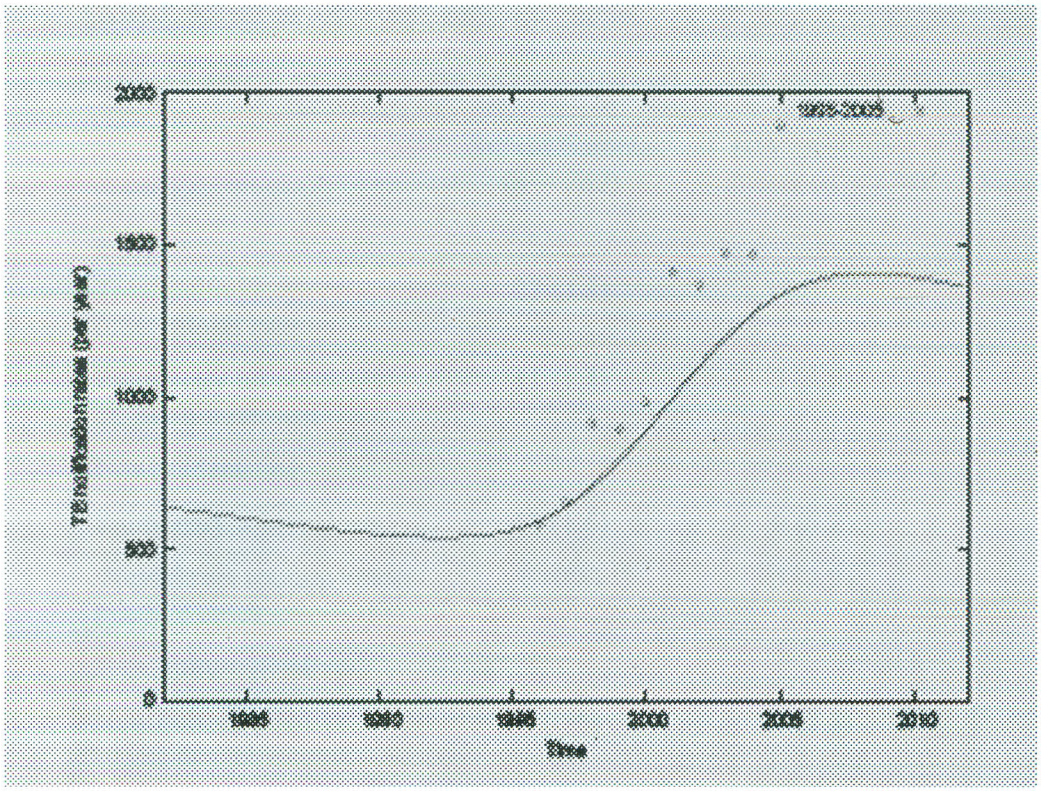


Figure 4.3: TB notification rates (per year) as function of time. The rates have been on an upward trend since 2005 as depicted above. See appendix 5 for Data.

Appendix 4

TABLE 5.2

PREVALENCE SURVEY OF 762 RANDOMLY SELECTED ADULTS

	Survey Sample (*n* = 762)	HIV-positive Subjects (*n* = 174)	HIV-negative Subjects (*n* = 588)
Total pulmonary tuberculosis cases	23 (3.3)	16 (9.2)	7 (1.2)
Pulmonary tuberculosis cases on treatment	11 (1.4)	7 (4.0)	4 (0.7)
Newly identified			
Pulmonary tuberculosis	12 (1.6)	9 (5.2)	3 (0.5)
New direct sputum smear–positive cases	6 (0.8)	5 (2.9)	1 (0.2)
New culture positive			
New culture-positive smear-negative cases	6 (0.8)	4 (2.3)	2 (0.3)

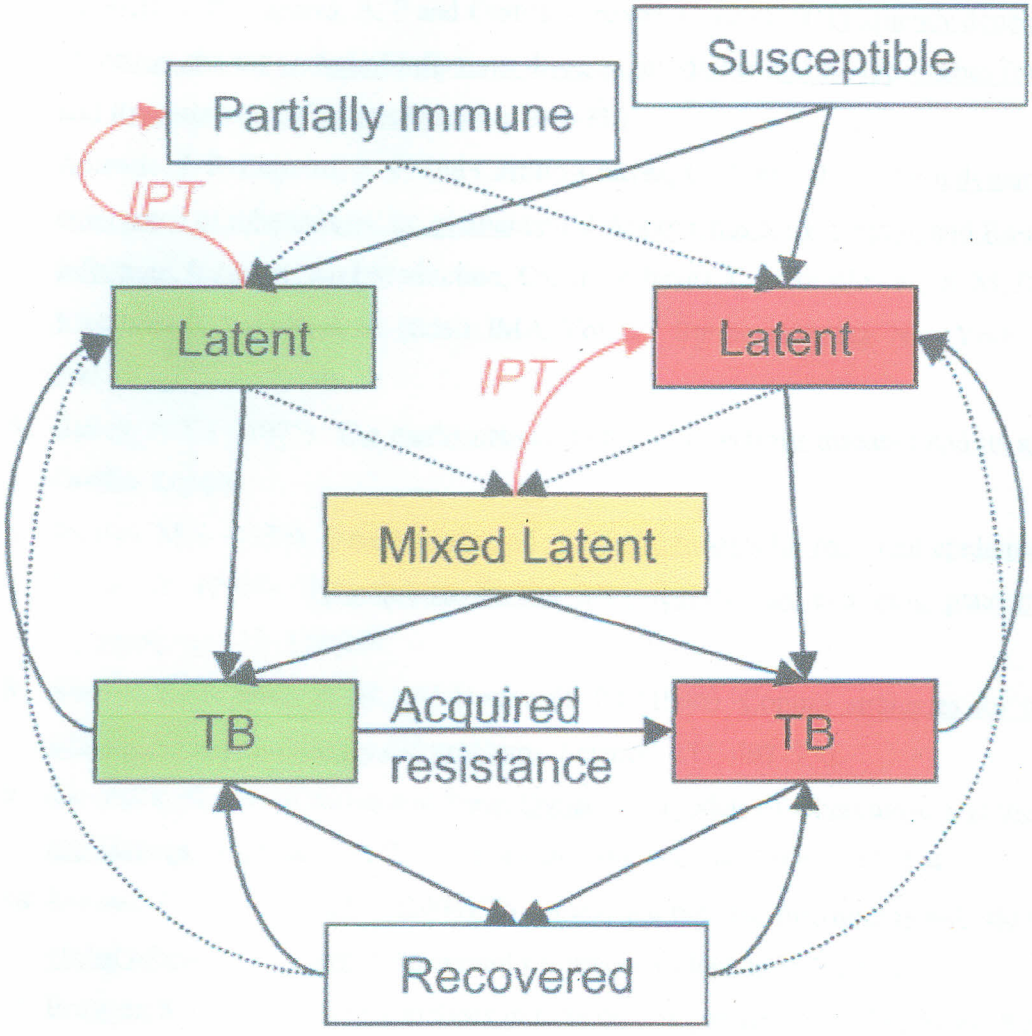
Numbers (%) of identified treated cases of tuberculosis, previously undiagnosed pulmonary tuberculosis, previously undiagnosed direct sputum smear–positive and *Mycobacterium tuberculosis* culture-positive/smear-negative cases stratified by HIV infection status.

Appendix 5

Table 5.2: Tuberculosis (TB) notification rates and the prevalence of HIV infection in a peri-urban community in the Western Cape, South Africa, 1996-2004.

Year	No. of TB notifications	Population size	TB notification rate, cases/100,000 persons	TB re-treatment rate, %	Estimated prevalence of HIV infection, %
1996	32	5518	580	3	6.3
1997	42	6429	653	21	8.9
1998	67	7339	913	7	11.6
1999	74	8250	897	20	14.2
2000	90	9161	982	17	16.5
2001	142	10,071	1410	15	18.4
2002	150	10,982	1366	18	19.9
2003	175	11,892	1472	22	21.1
2004	188	12,803	1468	24	21.9

Appendix 6



A mathematical model of TB/HIV co-epidemics to examine the impact of community-wide implementation of isoniazid preventive therapy (IPT) for TB–HIV co-infected individuals on the dynamics of drug-sensitive and -resistant TB epidemics

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