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# Modelling the impact of TB superinfection on the dynamics of HIV-TB coinfection



by  
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## Declaration

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and has not previously, in its entirety or in part, been submitted at any university for a degree.

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## Abstract

In this thesis, a mathematical model describing the interaction between HIV and TB in the presence of TB superinfection is presented. The model takes into account two strains of *Mycobacterium tuberculosis* (MTB), where one strain is drug-sensitive and the other is resistant to at least one of the first-line anti-tuberculosis drugs. The impact of TB superinfection on the incidence and prevalence of TB in HIV-negative and HIV-TB coinfecting individuals is evaluated. Various control measures such as condom use, antiretroviral therapy, isoniazid preventive therapy and increased TB detection are studied using this model. Numerical results show that TB superinfection increases the prevalence and incidence of TB and its impact is more in HIV-negative than HIV-TB coinfecting individuals. The results also show that TB superinfection promotes strain coexistence and increases the associated HIV mortality. Increased condom use was found to have a high positive impact towards the control of the two epidemics. Antiretroviral therapy decreases the TB notification rate and its impact on HIV prevalence increases with the coverage and efficacy. Isoniazid preventive therapy has a clear effect on the TB prevalence. Finally, increased TB detection was found to have a less impact on the TB incidence in HIV-TB coinfecting individuals.

## Opsomming

In hierdie verhandeling word 'n wiskundige model vir die interaksie tussen MIV en TB, in 'n situasie met TB superinfeksie voorgelê. Die model neem twee variante van TB in ag. Een van die variante is sensitief vir MTB behandeling, terwyl die ander weerstandig is vir ten minste een van die eerste-linie TB behandelings. Die impak van TB superinfeksie op die insidensie and prevalensie van TB in MIV negatiewe en MIV-TB ko-geïnfekteerde individu word ondersoek. Verskeie beheer maatreels soos kondoom gebruik, anti-retrovirale behandeling (vir MIV) en isonazid voorkomende behandeling en verhoogde TB deteksie (vir TB) word ondersoek. Numeriese resultate wys TB superinfeksie verhoog die prevalensie en insidensie van TB en dat dit 'n groter bydrae maak by MIV negatief as by MIV-TB ko-geïnfekteerde individu. Die resultate wys verder TB superinfeksie promofeer variant ko-habitasie en verhoog MIV verwante mortaliteit. Verhoogde kondoom gebruik is gevind om 'n positiewe bydrae te maak tot die beheer van beide epidemies. Anti-retrovirale terapie verlaag die TB aanmeldings koers en die impak van ART verhoog saam met 'n verhoging in die dekking en effektiwiteit daarvan. Voorkomende behandeling het 'n beduidende impak op TB prevalensie. Ons vind dat TB deteksie 'n beperkte impak maak op TB insidensie by MIV-TB ko-geïnfekteerde individu.

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# Chapter 1

## Introduction

### 1.1 Epidemiology of tuberculosis infection

Tuberculosis (TB) is an airborne disease that is caused by the bacteria *Mycobacterium tuberculosis* (MTB) which normally attacks the lungs (pulmonary tuberculosis). In an uncommon situation, MTB also attacks the other parts of the body such as the nervous system, bones, joints, lymph nodes, skin and the digestive system (extrapulmonary tuberculosis). It is only active pulmonary tuberculosis that is infectious. Coughing up blood, loss of weight, breathlessness, fever and fatigue are some of the symptoms that can be witnessed in an individual infected with tuberculosis. Tuberculosis is one of the leading causes of mortality, second to human immunodeficiency virus (HIV) [21].

An uninfected individual gets MTB from another individual who is actively infected with pulmonary tuberculosis through contact, especially when an infected individual coughs, sneezes, laughs, spits or talks. Once an individual gets MTB one can progress to active disease within the first five years or can remain latently infected with TB throughout his/her life time. This is referred to as primary infection. Only 5-10% of the individuals can progress to active disease through primary infection. If an individual progress to active disease within the first five years, then this is called fast progression. Latently infected individuals can live with the bacteria for years and some can even die without developing active tuberculosis. Individuals with the latent infection are non-infectious and do not show any symptoms of tuberculosis since they will not be clinically ill [54]. Susceptibility to MTB

infection varies from one individual to the other. Those that are at a high risk of getting tuberculosis include: people with HIV, people in close contact with tuberculosis patients, people who are malnourished, health care workers, prisoners, alcoholics, intravenous drug users and the homeless [19].

Individuals latently infected with tuberculosis can only progress to active disease in two ways.

- Through reactivation of the latent infection, initially obtained from the primary infection [14, 54]. This is known as endogenous reactivation.
- Through reinfection where by an individual acquires a new infection from another individual who is actively infected with pulmonary tuberculosis [14, 54]. This is known as exogenous reinfection.

These two situations are categorised as post-primary infections. Also categorised under post-primary infection is superinfection. A detailed discussion on superinfection is given in subsection 1.1.3.

It is known that a third of the world's population is infected with *Mycobacterium tuberculosis* [33, 39]. New cases of active TB (about 9 million) arise every year in the world with the highest percentage contribution being from the developing countries (mostly Asia and sub-Saharan Africa). About 1.6 million people died of TB in the world in 2005 and out of these 195,000 (12%) were HIV-infected patients [20].

The recent report released by WHO, indicates that there were 9.2 million new TB cases in 2006, including 700,000 (8%) cases among people living with HIV and 500,000 (5.4%) cases of multidrug resistant TB. 1.7 million people died of TB and out of these 200,000 (11.8%) were HIV-positive. Asia and sub-Saharan Africa were the most hit regions having 83% of the new tuberculosis infections in 2006 [38].

The HIV burden has greatly increased the prevalence and infection of tuberculosis in sub-Saharan Africa where the HIV epidemic is high [54]. The emergence of drug-resistant and multidrug-resistant strains have also contributed significantly to the TB epidemic. From 2000 to 2007, on average 56.3% of the TB cases reported were resistant to least one anti-tuberculosis drug and 22.3% were multidrug-resistant [53].

### 1.1.1 Tuberculosis control

The vaccine bacille Calmette-Guérin (BCG) is used in most countries. Young children are vaccinated with BCG to impart some degree of protection against tuberculosis. However, this protection is thought to be declining over time due to interactions between the vaccine and environmental mycobacteria mostly in tropical regions [14, 31].

Control of tuberculosis involves treating active disease, stopping secondary infections and preventing primary infections. In recognition to these facts, the World Health Organisation (WHO) instituted a strategy called directly observed treatment, short-course (DOTS), which is based on early diagnosis and directly observed treatment of active cases [45]. Currently, latent infections are treated with isoniazid (INH) which is administered for six to twelve months. Alternatively, rifampicin could as well be used instead of isoniazid for four months. Active tuberculosis is treated by a combination of isoniazid, rifampicin for six months and then supplemented by pyrazinamide and ethambutol for two months to reduce the possibility of emergence of drug-resistance. If the patient is co-operative and is able to take regularly and finish the regimen, then the first combination is enough to cure tuberculosis. However, if mono-resistance to rifampicin is detected, then the patient should continue with isoniazid, pyrazinamide or ethambutol for 18 months. On the other hand, the patient should continue with rifampicin, pyrazinamide or ethambutol for 12 months if mono-resistance to isoniazid is detected [21].

The initiation of isoniazid preventive therapy (IPT) for treating latent tuberculosis remains unclear. In poor countries where the prevalence of active tuberculosis is high and the resources for ruling it out are limited, initiating IPT still remains a big problem. Development of drug-resistance is another concern that limits the implementation of IPT [17].

### 1.1.2 Multidrug-resistant and extensively drug-resistant tuberculosis

Multidrug-resistant tuberculosis (MDR TB) is defined as one that is resistant to at least isoniazid and rifampicin, the two best first-line anti-tuberculosis drugs. Extensively drug-

resistant tuberculosis (XDR TB) is one that is resistant to isoniazid, rifampicin, any fluoroquinolone and at least 1 of 3 injectable second-line drugs capreomycin, kanamycin, amikacin [9, 19, 44]. These two types of tuberculosis are common in individuals who;

- do not complete or take regularly their medicine as prescribed by physicians,
- get a relapse either after treatment or self-cure,
- come into contact with individuals that have drug-resistant tuberculosis [9, 19].

Drug resistance to tuberculosis can also arise due to poorly managed care and control of the disease, poor prescribing practices and low drug quality. In a survey that was done by Centers for Disease Control and Prevention (CDC) and World health Organisation (WHO) to assess the worldwide frequency and distribution of MDR and XDR TB from 2000 to 2004, they reported that 20% of the TB cases were resistant to at least one of the first-line anti-tuberculosis drugs and 2% resistant to second-line drugs [18]. People with HIV are at a high risk of getting XDR-TB and MDR-TB. In 2006, over 200 cases of MDR-TB were identified in the province of KwaZulu Natal in South Africa [35, 44]. MDR TB treatment requires the use of second-line drugs that are less effective, more toxic and expensive than first-line anti-tuberculosis drugs [18].

### 1.1.3 Tuberculosis superinfection

Superinfection refers to the multiple infection of a host with different strains of the same parasite. These infections can take place at the same time or at a later point in time. [7, 41, 26, 39]. Martcheva *et al.* [28] defined superinfection as the concurrent or subsequent multiple infection of a host with the same parasite, may it be with identical or different strains. In this thesis, we take superinfection in the same way it was considered in [7, 26, 39]. In some cases superinfection results in strain replacement whereby the more fit strain replaces the less fit strain, and in other cases an individual can remain infected with two strains (mixed infection). It has been postulated that superinfection shortens the latency period of some bacterial diseases such as hepatitis A, speeds up the progression of HIV to AIDS and plays a big role in activating the passive carriers of tuberculosis [26, 28].



Evidence for superinfection in tuberculosis has already been reported [16, 29, 42]. Multiple infections with different strains of *M. tuberculosis* may occur in areas where the prevalence of active TB is high. This could possibly mean that superinfection is most likely to be common in crowded areas. There are suggestions that superinfection may affect the diagnosis of drug-resistance most especially if a patient is infected with both drug-sensitive and drug-resistant strains [29, 52]. This may be of much concern to physicians and clinicians since it impacts control programmes and management of tuberculosis in general.

Because individuals who are infected with resistant strains stay longer in the infectious state due to either improper regimen, late identification of the resistance phenotype, or lower efficacy of treatment [30, 39], superinfection may lead to increased mortality. If the treatment efficacy of an individual infected with only one resistant strain is low, then the treatment efficacy for an individual infected with both resistant and sensitive strains could be much lower.

## 1.2 Epidemiology of HIV infection

HIV is a human immunodeficiency virus that causes acquired immunodeficiency syndrome (AIDS) and which has claimed the lives of many people in the world. The different modes of HIV transmission include horizontal transmission (from one adult to another adult through heterosexual or homosexual contact), vertical transmission (from an infected mother to her unborn child) and transmission from one individual to another through either blood transfusion or needle-sharing. Out of the three modes of HIV transmission, heterosexual is the major mode of transmission contributing about 90% of the HIV infections in Africa [56]. HIV infection is associated with a progressive decrease of the CD4<sup>+</sup> T cell count and an increase in viral load. There are four stages of HIV infection which are based on the patients CD4<sup>+</sup> T cell count and these include: primary HIV infection, clinically asymptomatic stage, symptomatic HIV infection and progression from HIV to AIDS. Progression to AIDS is associated with an increased likelihood of opportunistic infections and other clinical events associated with HIV, including wasting and death [37]. It normally takes an average of 10-15 years for an infected individual to progress to the AIDS stage in developed countries and might be less in developing countries.

By the end of 2007, it was estimated that 33.3 million people were living with HIV and out of these 30.8 million were adults, 15.4 million were women and 2.5 million were children under 15 years. Also 2.5 million people were newly infected with HIV and 2.1 million AIDS death occurred in the same year. 76% of these deaths were in sub-Saharan Africa [50].

### 1.2.1 HIV control

The most plausible HIV control measures involve prevention of the infection. These preventive strategies include condom use, abstinence, faithfulness and male circumcision. Condom use and male circumcision were shown to have a big impact on HIV with male circumcision alone reducing HIV transmission rate by 37% [5, 56]. Treatment of HIV consists of a combination of antiretroviral therapies (ARV). These therapies are based on three or more anti-HIV medications that typically combine a protease inhibitor (PI), or a non-nucleoside reverse transcriptase inhibitor (nnRTI), with at least two nucleoside reverse transcriptase inhibitors (nRTI). These drugs block the replication of the virus and thus increases the survival time of HIV-infected individuals, but do not lead to viral eradication within individuals and hence do not cure [1, 23]. The effects of ART on HIV largely depends on the stage of infection at which treatment is initiated, levels of coverage, the scale and stage of HIV epidemic that the community is experiencing. ART has been shown to have a big impact on HIV if the coverage is high [23, 34, 36].

## 1.3 Coinfection of HIV and TB

Coinfection refers to the simultaneous infection of a single host by two or more virus or bacteria particles. So, an individual coinfection with TB and HIV carries both the MTB bacteria and the HIV virus. The number of MTB infections is believed to have increased in the last decade due to the coinfection of HIV and TB. These infections are thought to be due to the development of tuberculosis among TB infected individuals that are infected with HIV. On the other hand, treatment of tuberculosis has been hindered by the emergence of HIV [15, 35, 43, 48]. Once an individual gets infected with HIV, the immune system weakens due to the infection and thus susceptibility to opportunistic infections such as tuberculosis increases [43]. Tuberculosis is the most common opportunistic infection in

patients starting antiretroviral treatment (ART) worldwide [17, 35]. An individual who is infected with HIV is at a high risk of latent MTB reactivation and can rapidly progress to active TB soon after infection or reinfection with TB [15, 48]. Individuals infected with MTB only have a life time risk of developing active TB that ranges between 10% to 20%, but individuals coinfecting with MTB and HIV have an annual risk of developing active TB of 10% or more [15, 48]. Most individuals coinfecting with MTB and HIV die due to tuberculosis and yet tuberculosis is curable. The most worrying thing is that patients with tuberculosis who are HIV-positive are susceptible to dying from other opportunistic infections during their treatment period [15].

Little research has been done to understand the epidemiology of tuberculosis in children, yet tuberculosis is a common cause of acute pneumonia in HIV-infected children. The BCG vaccination which is widely used in most countries is associated with high mortality in children who are on HIV treatment [17].

## 1.4 Motivation and overview

Tuberculosis and HIV are the major causes of mortality in the world. Tuberculosis is one of the most common opportunistic infection in people with HIV, and HIV is also known to have increased the burden of tuberculosis mostly in sub-Saharan Africa. A number of mathematical models have been developed to describe the dynamics of one-strain tuberculosis [2, 31, 32], two-strain tuberculosis [7, 39, 47, 55] and multi-drug resistant tuberculosis [49]. Models looking at the joint epidemics of TB and HIV [13, 15, 34, 36, 43, 48] have also been presented. The question which has not been tackled so far is the effect of superinfection on the incidence and prevalence of TB in individuals with and/or without HIV. Evidence for mixed-infections (a situation where an individual is infected with more than one strain) in tuberculosis and TB-HIV infected individuals has already been reported [16, 29]. We are thus concerned about knowing the effects of superinfection on the prevalence and incidence of tuberculosis.

Having given a general introduction and motivation of this work, the rest of this thesis is structured as follows.

In chapter 2, we give a review of mathematical models that have been developed to either describe the dynamics of TB or HIV infection or HIV-TB coinfection.

In chapter 3, a simple mathematical model that describes the dynamics of tuberculosis in the presence of two strains (drug-sensitive and drug-resistant strains) is developed. The model incorporates in the aspect of superinfection. Mathematical analysis and simulations of the model are given.

In chapter 4, we give an extension of the model described in chapter 3 to include HIV. The mathematical analysis of the HIV-only model is given and simulations of the HIV-TB coinfection model are given. A study on TB and HIV control measures is also done.

In chapter 5, we give a detailed conclusion on our findings.

# Chapter 2

## Literature review

Many researchers have developed and analysed mathematical models that endeavour to explain the dynamics of TB infection and HIV-TB coinfection. These models vary in terms of the number and variables representing compartments and the parameters used. A few of these models have been fitted with data collected from epidemiological studies. The data is however scarce and sometimes unavailable. We present a literature review of some of the compartmental models that have been developed to explain the dynamics of either TB or HIV infection or HIV-TB coinfection. We take note of the assumptions made, the number of compartments used, the states of HIV and TB considered, the way the parameters were estimated, the model analysis and interpretation and the data used (if the model is fitted to data). We classify the models in different categories. We begin by considering models with a single strain of TB. This is followed by models with two strains of TB. We also revisit models on HIV infection dynamics before we conclude by looking at the HIV-TB coinfection models.

### 2.1 Models on one strain of TB

In this section we give an overview of the models developed to describe the dynamics of tuberculosis by looking at only one strain of MTB. This strain could either be a drug-sensitive or drug-resistant or multi-drug resistant strain.

Ssematimba *et al.* [2], developed a model to investigate the effect of population density on

the dynamics of tuberculosis in Uganda. The model used the TB transmission dynamics earlier described in [4]. They established restrictions on the size of the area occupied by individuals that would be needed in order to evaluate TB. They assumed homogeneous mixing in the population, that is, uninfected individuals have equal chances of getting tuberculosis once they come into contact with an infectious individual. Their model consists of four compartments; susceptible, latently infected, infectious and recovered or treated individuals. They assumed that immigrants and new borns are uninfected with tuberculosis. They did not consider exogenous reinfection. Mathematical analysis of the model was done. Simulations were run and numerical results comparing the size of the area, recruitment rate and the different epidemiological classes were obtained. Parameter values were estimated from the literature. Their model suggested that overcrowding and unsanitary conditions play a major role in explaining the observed trends of tuberculosis in Uganda and the world in general.

Gomes *et al.* [31], developed a mathematical model to evaluate the impact of vaccination on human tuberculosis. The model consists of four compartments; susceptible, latent, infectious and recovered or cured. They assumed individuals get infected with *M. tuberculosis* at a rate that is proportional to the density of infectious individuals. They introduced bacille Calmette-Guérin (BCG) vaccination which was assumed to reduce the risk of *M. tuberculosis* infection. They obtained a reinfection threshold, above which reinfection dominates the transmission dynamics of tuberculosis. Their model was also used to evaluate the efficacy of vaccination on the partial protection induced by the immune response against reinfection. Parameter values were estimated from the literature. Simulations were run for 400 years. The model suggested that vaccination does not improve on the protection against reinfection.

In 2000, Dye and Williams [8], used a system of ten ordinary differential equations derived from ten compartments to study the criteria for the treatment of multi-drug resistant tuberculosis (MDR-TB) in adults over 15 years of age. The model contained eight states of tuberculosis which include: susceptible, latent (slow breakdown to disease), latent (fast breakdown to disease), infectious, non-infectious, treatment failure, self-cure and cure (by treatment). Parameter values were estimated from the literature. Simulations were run and numerical results based on the detection and cure rates obtained. In order to prevent MDR-TB, they estimated that approximately 70% of infectious MDR-TB cases need to

be detected and treated with a cure rate of 80% each year. They further suggested that second-line drugs could be essential in increasing the cure rates of MDR-TB, although these drugs are few, costly and sometimes toxic.

## 2.2 Models on two strains of TB

This section gives an overview of the models in the literature which describe the transmission dynamics of tuberculosis involving two-strains.

Rodrigues *et al.* [39], developed a TB transmission model which is an extension of the one proposed by Gomes *et al.* [31]. The model included two strains with different sensitivities to antibiotics (that is, one strain is drug-sensitive and the other is drug-resistant). The model consists of five compartments looking at the host population divided into different categories that is, susceptible, latently infected with a drug-sensitive strain, latently infected with a drug-resistant strain, actively infected with a drug-sensitive strain and actively infected with a drug-resistant strain. They assumed that resistant strains can emerge when individuals are infected with a resistant strain or as a result of treatment failure with the former and the latter being termed primary resistance and acquired resistance respectively. They also assumed that when an individual is infected with both resistant and sensitive strains, then one will progress to tuberculosis of the resistant strain only. They considered the same reactivation rate for both sensitive and resistant strains. They further assumed that the period of infectiousness of a resistant TB case is on average two months longer than that of a sensitive case. Stability and numerical analysis of the model were done. An extension to mixed infections that considered progression to active TB of either drug-sensitive or drug-resistant strain after superinfection was also given. They concluded that primary resistance plays a significant role as far as infection with resistant strains is concerned.

Castillo-Chavez *et al.* [7], developed two models to describe the transmission of TB. The first model (one-strain TB model) consists of four compartments ie. susceptible, latent (infected but not infectious), infectious and treated individuals. The second model (two-strain TB model) is an extension of the first model. Two compartments ie latent and infectious representing the developmental stages of the resistant strain were added. They ignored

the treatment of the resistant strain by stating that its hard to be treated. They did not consider fast progression after primary infection and exogenous reinfection of latent individuals. They also assumed that superinfection is only by resistant strains. Mathematical and numerical analysis of the two models were done. They concluded that mixing plays a key role in tuberculosis transmission.

Cohen and Murray [49], developed a model to describe the transmission dynamics of multidrug-resistant (MDR) tuberculosis by giving special attention to the heterogeneity of fitness of MDR strains and competition during an epidemic. The model consists of nineteen ordinary differential equations. They assumed that MTB infection rate varies according to the prevalence of people with active tuberculosis. They considered three different strains of tuberculosis; drug-sensitive TB, unfit MDR-TB and fit MDR-TB. They also considered seven states of TB; susceptible, latent infection with slow progression, latent infection with fast progression, undetected infectious TB, detected infectious TB, infectious TB failed therapy and cured TB. Their parameter values were estimated from the literature. They used their model to evaluate the implementation of directly observed treatment, short-course (DOTS) treatment for both drug-sensitive and MDR-TB. Simulations were run to evaluate the impact of DOTS 30 years after its initiation. Their model suggested that fit MDR strains outcompete both the drug-sensitive and unfit MDR-TB even in the presence of a well-functioning control programme.

## 2.3 Models for HIV

This section gives a review of the HIV infection models that have been formulated. We give attention to the types of HIV transmission considered, control measures taken into account and the way the parameters were estimated.

Kgosimore and Lungu [27] developed a model that describes the dynamics of HIV infection of both juveniles who were assumed to be infected through vertical transmission and HIV/AIDS-infected adults. The model caters for treatment of both groups of people, first in the absence of vertical transmission and then in the presence of vertical transmission. The model consists of four sub-populations, susceptible, untreated infected, treated infected and AIDS. People in the AIDS class were assumed to be sexually inactive and thus



their sexual activity and infectivity was considered negligible. The reproduction numbers of the model in the absence and presence of vertical transmission were calculated. They obtained a critical threshold parameter ( $R_v^*$ ), below which treated juveniles can reach adulthood without causing an epidemic. Numerical simulations of the model were presented, illustrating the results of five countries in sub-Saharan Africa which included Botswana, Senegal, Swaziland, Uganda and Zambia. The model suggested that a significant proportion of infected juveniles on treatment can reach adulthood without causing an epidemic.

Mukandavire *et al.* [56] developed a sex structured model to assess the effect of male circumcision and condom use as control measures for HIV/AIDS. The model consists of eight compartments, three for female populations and five for male populations. The female and male populations were each partitioned into three sub-populations; susceptible, infective and AIDS. The male susceptibles and infectives were further categorised into two groups representing the uncircumcised and circumcised populations. Males in the AIDS group were assumed to be sexually inactive and thus were taken to be in the same category of uncircumcised population. The model also catered for emigration except for the individuals in the AIDS class. The model's numerical simulations were done to assess the effects of male circumcision and condom use in the absence of HIV/AIDS treatment. The model suggested that male circumcision has a potential of reducing the transmission of HIV/AIDS. They concluded that more effective results can be obtained if male circumcision is combined with condom use.

Gross *et al.* [24] developed a model to describe the dynamics of HIV-1 in the presence of superinfection and viral diversity. The model population was divided into two groups, low and high risk groups based on the level of sexual activity. The model took into account two subtypes of HIV-1 which were denoted by virus 1 and 2, and a recombinant of the two viruses denote by virus 3. Susceptible individuals were assumed to be infected by any combination of viruses given by set  $I$ , where  $I = \{1, 2, 3, 13, 23, 12, 123\}$ . Infectious individuals were also assumed to transmit any of the viruses given in set  $I$ . Newly infected individuals were assumed to be susceptible to superinfection by other viral combinations for a short period of time. Simulations were run for a period of 50 years after introducing HIV-1 by limiting susceptibility to superinfection to an average of 30 days. It was found that 20% of HIV-1 infections were recombinant and 4% were multiple infections after 25 years of the epidemic. They concluded that HIV-1 superinfection restricted to early HIV-1

infection could result to high fractions of recombinant virus infections in a population.

## 2.4 Models for TB-HIV coinfection

This section gives an overview of the models developed to describe the dynamics of HIV-TB coinfection.

Bacaër *et al.* [34], looked at a simple mathematical model that describes the interaction between HIV and TB epidemics. Their model consists of six compartments with three states of TB (susceptible, latent TB and active TB) and two states of HIV (HIV-negative and HIV-positive). They considered one strain of TB in their model which was based on research carried out in a South African township. Their model was fitted to data from the township. They estimated some of the model parameters based on the collected data. The model was used to evaluate some of the control measures which included condom use, isoniazid preventive therapy, antiretroviral therapy (ART) and increased TB detection rate. The model suggested that ART has a small impact on the incidence of HIV, though it was found to reduce the TB notification rate. Increased condom use, TB detection and preventive therapy were found to have a positive effect on the joint epidemics.

Currie *et al.* [12], developed a compartmental difference equation model based on TB and HIV epidemics to compare the effectiveness of TB chemotherapy with highly active antiretroviral therapy (HAART), treatment of latent TB infection (TLTI) and reduction of HIV transmission. The model consists of three stages of HIV (HIV-negative, early stages of HIV and late stages of HIV which is after four years of infection). HIV prevalence was defined by a double logistic equation. One type of *M. tuberculosis* infection was considered with six states (susceptible, latent, infectious TB, non-infectious TB, failed treatment and receiving IPT). Their model was fitted to data from Kenya, Uganda and South Africa using a Bayesian methodology. They used the data to obtain the numerical values of some of the parameters. In addition to HAART and IPT, they also evaluated other control measures such as condom use, increased TB detection and better TB cure. Simulations were run for 20 years from the year 2000 to 2020. The model showed that finding and curing active TB and HAART are the most effective control measures for HIV and TB. TLTI and condom use are relatively ineffective over a short period of time. They concluded that active TB

treatment should be strongly emphasised.

Guwatudde *et al.* [13], developed a model to address the effect of preventive therapy (PT) on tuberculosis in HIV infected individuals in sub-Saharan Africa. The model consists of eleven compartments; five for HIV negative individuals, five for HIV positive individuals and one for HIV positives who are latently infected with tuberculosis that are on PT. They considered five states of tuberculosis; vaccinated, susceptible, latently infected, active infectious TB and active non-infectious TB. BCG vaccination was considered to reduce on the risk of getting infected with TB. They ignored exogenous reinfection of TB. They assumed that individuals get infected with HIV at a constant rate. Their parameters were estimated from the literature. Simulations were run for a period of 20 years. They concluded that the impact of PT on TB in the population is likely to be small.

Cohen *et al.* [48], developed a mathematical model to evaluate the impact of isoniazid preventive therapy (IPT) on TB-HIV coinfecting individuals in sub-Saharan Africa. The model consists of forty-five ordinary differential equations. It took into account two states of HIV infection (HIV-negative and HIV-positive), and twenty-two states of TB infection. Four stages of TB were considered (susceptible, latent, active and recovered), three types of *M. tuberculosis* infection were considered (drug-sensitive, fit drug-resistant and unfit drug-resistant TB). They assumed that some of the individuals with a latent infection progress rapidly and others slowly to active TB. They also considered three types of active TB, extra-pulmonary, detected pulmonary and undetected pulmonary TB. Apart from TB treatment, the model also catered for the treatment of individuals who are HIV-positive. It was assumed that an individual can be latently infected with a maximum of two strains. If superinfection with a third strain occurs, then the incoming strain replaces one of the previous strains in a manner that is proportional to the relative fitness of the pre-existing strains. Parameter values were estimated from the literature. Simulations were run for 30 years after the introduction of treatment (IPT). They concluded that the use of IPT to prevent the progression of latent *M. tuberculosis* in HIV-TB coinfecting individuals could reduce the burden of TB disease and infection for a number of years but could also increase the emergence of drug-resistant TB.

## 2.5 Link between the review and this thesis

We intend to extend the model presented in [34] by adding another strain of TB which is resistant to at least one of the first-line anti-tuberculosis drugs and include the possibility of TB superinfection. We endeavour to evaluate the contribution of TB superinfection on the prevalence and incidence of tuberculosis in HIV-negative and HIV-TB coinfecting individuals.

In relation to the interventions discussed in [12, 13, 34, 48, 56], we intend to study the effectiveness of condom use, antiretroviral therapy (ART), isoniazid preventive therapy (IPT) and increased TB detection on the control of TB and HIV in the presence of TB superinfection.

The assumption taken in [7] that superinfection is only by resistant strains is not realistic. In our case, we assume that an individual can be superinfected with either a resistant or a sensitive strain. We also assume that an individual can not be actively infected with two strains and progression to active disease after superinfection is independent of the strain type.

Finally, we intend to keep the MTB and HIV infection rates varying depending on the prevalence of individuals with active TB and HIV respectively. Making these two constant as it was done in [13] may not be appropriate for sub-Saharan Africa where the burden of TB and HIV is already high.

## 2.6 Conclusion

An understanding of the pathogenesis and epidemiology of TB and HIV, and the interaction between the two is essential in the development of mathematical models that can predict the dynamics of the two epidemics. In this chapter we have reviewed some of the mathematical models used to describe the transmission dynamics of TB and HIV. But the model assumptions, the number of parameters and equations used differ, and a few of them have been validated by experimental data. We acknowledge the limitations of data for parameter estimations. This has an impact of limiting the use of the mathematical

models to real life scenarios. We now consider a two-strain TB model with superinfection in the next chapter.

# Chapter 3

## The two-strain tuberculosis model with superinfection

### 3.1 Introduction

In this chapter, we develop a simple model that describes the dynamics of the transmission of tuberculosis in the presence of two strains. Our model is close to the one presented in [39], but in our case, we add an extra compartment for those latently infected with two strains. This model can also be viewed as an extension of the model presented in [34] in the absence of HIV.

### 3.2 Model development

We denote the drug-sensitive strain by subscript 1 and the drug-resistant strain by subscript 2 and the mixed infection of both drug-resistant and drug-sensitive strains by subscript 12. The host population is divided into the following subgroups; susceptible ( $S$ ), who have never been exposed to the MTB bacteria; latent ( $E$ ), those who are infected but not infectious and infectious ( $I$ ), those who are capable of transmitting the infection. Individuals are born susceptible to infection at a constant rate  $B$ . Susceptible individuals are infected with *M. tuberculosis* of either strain 1 or strain 2 at a rate that is proportional to the prevalence of individuals with active TB of strain 1 or strain 2 respectively. A

proportion  $p$  of individuals progress directly to active TB (move to state  $I$ ) after primary infection. The remaining proportion get latently infected with TB (move to state  $E$ ). Latently infected individuals acquire some protective immunity that reduces the risk of getting another infection [31, 48]. We assume that individuals latently infected with TB do not infect others. Individuals who have latent TB, for instance, those in state  $E_1$  can either die due to natural causes or progress to active disease through exogenous reinfection or endogenous reactivation or get reinfected with a different strain of TB (strain 2) at a rate  $c$ . The process where by an individual is reinfected with a different strain of tuberculosis is termed *superinfection*. After superinfection a proportion  $\theta_2$  progress to active disease and the remaining proportion remain latently infected with two strains (move to state  $E_{12}$ ). Since we assume that primary infection induces some protection towards any other incoming infection, we take the reinfection and superinfection parameters  $\{q_1, q_2, c\} \leq p$ . Individuals in state  $E_2$  have similar infection dynamics. Individuals latently infected with two strains of tuberculosis, where one strain is drug-sensitive and the other is drug-resistant can progress to active tuberculosis of the more fit strain. Recovery from active TB by treatment or self-cure takes the individuals from state  $I$  to state  $E$ . The flows between the different states (compartments) of the model are clearly shown in Fig. 3.1. Table. 3.1 shows the model parameters and their definitions. Table. 3.2 shows some key epidemiological definitions that are important in TB dynamics.

The following observations and assumptions are also essential in the development of the model and numerical simulations.

- Individuals who are latently infected with TB are likely to be reinfected with a different strain of *M. tuberculosis*. The probability of getting another strain will always be independent of whether an individual is already infected or not. An individual who has been superinfected has a higher chance of progressing from the latent state to the active state [28]. We will thus consider parameter values of reactivation from latent TB to active TB for the state  $E_{12}$  to be higher than those for the states  $E_1$  and  $E_2$ .
- All individuals with active TB are assumed to be either in state  $I_1$  or state  $I_2$ . Individuals in state  $I_1$  are either actively infected with TB of strain 1 or actively infected with TB of strain 1 and latently infected with TB of strain 2. To clarify

this assumption, let  $I_{10}$  denote the number of people with active TB of strain 1 only and  $I_{12}$  denote the number of people with active TB of strain 1 and latently infected with TB of strain 2. We take  $I_1 = I_{10} + I_{12}$ . Similarly,  $I_2 = I_{20} + I_{21}$ , where  $I_{20}$  denotes the number of people with active TB of strain 2 only and  $I_{21}$  denotes the number of people with active TB of strain 2 and latently infected with TB of strain 1. Strain 1 is easier to treat than strain 2 and individuals infected with strain 2 take a longer period in the infectious class due to its low treatment rates [39].

- We do not differentiate between pulmonary TB and extra-pulmonary TB, smear-positive or infectious TB and smear-negative or non-infectious TB, primary resistance (resistance obtained when an individual is infected with a resistant strain) and acquired resistance (resistance obtained as a result of treatment failure). The model does not take into consideration age and sex of individuals.

The two-strain tuberculosis model with superinfection can be represented by the system of ordinary differential equations:

$$\left. \begin{aligned} \frac{dS}{dt} &= B - S(i_1 + i_2) - \mu S, \\ \frac{dE_1}{dt} &= [(1-p)S - q_1 E_1]i_1 - (a_1 + \mu + c i_2)E_1 + (1 - \tau_1)b_1 I_1, \\ \frac{dE_2}{dt} &= [(1-p)S - q_2 E_2]i_2 - (a_2 + \mu + c i_1)E_2 + (1 - \tau_2)b_2 I_2, \\ \frac{dE_{12}}{dt} &= (1 - \theta_1)c E_2 i_1 + (1 - \theta_2)c E_1 i_2 - (\omega_1 i_1 + \omega_2 i_2 + \sigma_1 + \sigma_2 + \mu)E_{12} \\ &\quad + \tau_1 b_1 I_1 + \tau_2 b_2 I_2, \\ \frac{dI_1}{dt} &= (pS + q_1 E_1 + \theta_1 c E_2 + \omega_1 E_{12})i_1 + a_1 E_1 + \sigma_1 E_{12} - (b_1 + m)I_1, \\ \frac{dI_2}{dt} &= (pS + q_2 E_2 + \theta_2 c E_1 + \omega_2 E_{12})i_2 + a_2 E_2 + \sigma_2 E_{12} - (b_2 + m)I_2, \end{aligned} \right\} \quad (3.1)$$

where  $i_1 = (k_1 I_1)/P$  and  $i_2 = (k_2 I_2)/P$ .  $P$  is the total population which can be obtained from

$$P = S + E_1 + E_2 + E_{12} + I_1 + I_2.$$

The rate of change of the population is given by the differential equation

$$\frac{dP}{dt} = B - \mu P - \delta(I_1 + I_2), \quad (3.2)$$



TABLE. 3.1. Definitions of the parameters used in the model.

$B$	Birth rate;
$\mu$	Mortality rate for individuals without active TB;
$m$	Mortality rate for individuals who have active TB. Note that $m > \mu$ ;
$k_1, k_2$	MTB transmission rate;
$p$	Proportion of individuals without TB that progress to active TB after primary infection. The remaining proportion, $1 - p$ acquire latent TB;
$c$	Superinfection rate;
$\tau_1, \tau_2$	Proportion of individuals that move to state $E_{12}$ after recovery;
$\theta_1, \theta_2$	Proportion of individuals that progress to active TB of the incoming strain after superinfection. The remaining proportion remain latently infected with two strains;
$\sigma_1, \sigma_2$	Rate at which individuals latently infected with two strains of TB progress to active TB of either strain 1 or 2 through reactivation;
$q_1, q_2$	Rate at which individuals latently infected with one strain of TB progress to active TB through reinfection;
$\omega_1, \omega_2$	Rate at which individuals latently infected with two strains of TB progress to active disease through reinfection;
$a_1, a_2$	Rate at which individuals latently infected with one strain of TB progress to active TB through reactivation;
$\beta_1, \beta_2$	Rate at which individuals with active TB recover without treatment;
$\gamma_1, \gamma_2$	Rate at which individuals with active TB are detected;
$\varepsilon_1, \varepsilon_2$	Proportion of individuals who have active TB that are detected and successfully treated;
$b_1, b_2$	Recovery rate from active TB. Note that $b_1 = \beta_1 + \gamma_1\varepsilon_1$ and $b_2 = \beta_2 + \gamma_2\varepsilon_2$ .

which is derived from adding all the equations in system (3.1), where  $\delta = m - \mu$ .

All the variables and parameters in the model (3.1) are considered to be positive and the model lies in the feasible region (that is, where the model makes biological sense)

$$W = \left\{ (S, E_1, E_2, E_{12}, I_1, I_2) \in \mathbb{R}_+^6 : P \leq \frac{B}{\mu} \right\}$$

which can be shown to be positively invariant with respect to system (3.1).

### Positivity and boundedness of solutions

It is necessary to prove that all the variables  $S, E_1, E_2, E_{12}, I_1$  and  $I_2$  of model 3.1 are non-negative all the time since the model describes human population.

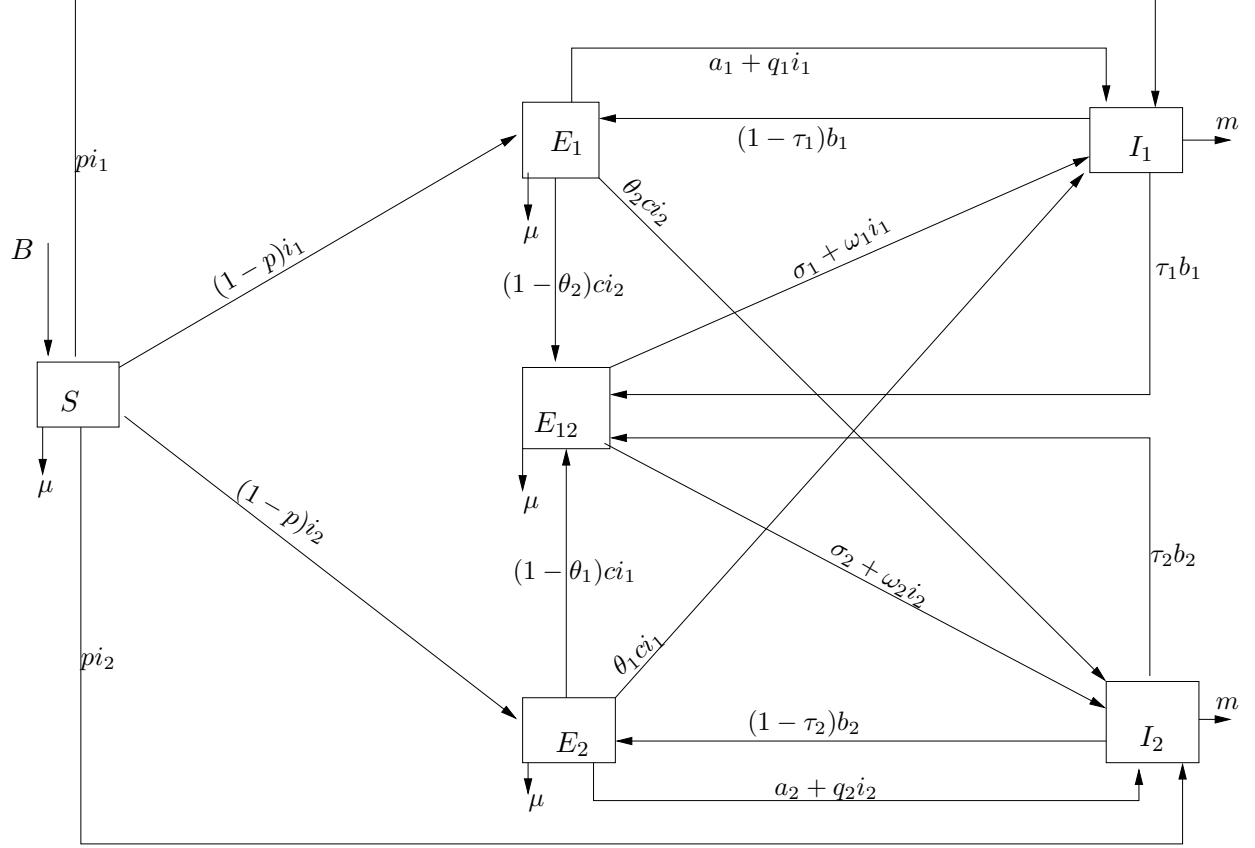


FIG. 3.1. The schematic representation of the two-strain TB model with superinfection.

**Theorem 3.2.1** *Let  $S(0) \geq 0$ ,  $E_1(0) \geq 0$ ,  $E_2(0) \geq 0$ ,  $E_{12}(0) \geq 0$ ,  $I_1(0) \geq 0$  and  $I_2(0) \geq 0$ . The solutions  $S$ ,  $E_1$ ,  $E_2$ ,  $E_{12}$ ,  $I_1$  and  $I_2$  of system (3.1) are positive for all  $t \geq 0$ . For the model system (3.1), the region  $W$  is positively invariant and all solutions starting in  $\mathbb{R}_+^6$  approach, enter, or stay in  $W$ .*

**Proof:** It is easy to prove that the solutions of system (3.1) are positive for  $t \geq 0$  with initial conditions in  $\mathbb{R}_+^6$  if not we assume for a contradiction that there exists a first time  $t_s$ :  $S(t_s) = 0$ ,  $S'(t_s) < 0$  and  $S(t) > 0$ ,  $E_1(t) > 0$ ,  $E_2(t) > 0$ ,  $E_{12}(t) > 0$ ,  $I_1(t) > 0$ ,  $I_2(t) > 0$  for  $0 < t < t_s$  or there exists a  $t_u$ :  $E_1(t_u) = 0$ ,  $E_1'(t_u) < 0$  and  $S(t) > 0$ ,  $E_1(t) > 0$ ,  $E_2(t) > 0$ ,  $E_{12}(t) > 0$ ,  $I_1(t) > 0$ ,  $I_2(t) > 0$  for  $0 < t < t_u$  or there exists a  $t_v$ :  $E_2(t_v) = 0$ ,  $E_2'(t_v) < 0$  and  $S(t) > 0$ ,  $E_1(t) > 0$ ,  $E_2(t) > 0$ ,  $E_{12}(t) > 0$ ,  $I_1(t) > 0$ ,  $I_2(t) > 0$  for  $0 < t < t_v$  or there exists a  $t_x$ :  $E_{12}(t_x) = 0$ ,  $E_{12}'(t_x) < 0$  and  $S(t) > 0$ ,  $E_1(t) > 0$ ,  $E_2(t) > 0$ ,  $E_{12}(t) > 0$ ,  $I_1(t) > 0$ ,  $I_2(t) > 0$  for  $0 < t < t_x$  or there exists a  $t_y$ :  $I_1(t_y) = 0$ ,  $I_1'(t_y) < 0$  and  $S(t) > 0$ ,

$E_1(t) > 0$ ,  $E_2(t) > 0$ ,  $E_{12}(t) > 0$ ,  $I_1(t) > 0$ ,  $I_2(t) > 0$  for  $0 < t < t_y$  or there exists a  $t_z$ :  $I_2(t_z) = 0$ ,  $I_2'(t_z) < 0$  and  $S(t) > 0$ ,  $E_1(t) > 0$ ,  $E_2(t) > 0$ ,  $E_{12}(t) > 0$ ,  $I_1(t) > 0$ ,  $I_2(t) > 0$  for  $0 < t < t_z$ .

Putting all the above assumptions into consideration, we obtain

$$\begin{aligned} S'(t_s) &= B > 0, \\ E_1'(t_u) &= (1-p)S(t_u)i_1(t_u) + (1-\tau_1)b_1I_1(t_u) > 0, \\ E_2'(t_v) &= (1-p)S(t_v)i_2(t_v) + (1-\tau_2)b_2I_2(t_v) > 0, \\ E_{12}'(t_x) &= (1-\theta_1)cE_2(t_x)i_1(t_x) + (1-\theta_2)cE_1(t_x) + \tau_1b_1I_1(t_x) + \tau_2b_2I_2(t_x) > 0, \\ I_1'(t_y) &= a_1E_1(t_y) + \sigma_1E_{12}(t_y) > 0, \\ I_2'(t_z) &= a_2E_2(t_z) + \sigma_2E_{12}(t_z) > 0, \end{aligned}$$

which gives a contradiction in all the six cases meaning that  $S$ ,  $E_1$ ,  $E_2$ ,  $E_{12}$ ,  $I_1$  and  $I_2$  remain positive for  $t \geq 0$ . Since  $P(t) \geq I_1(t)$  and  $P(t) \geq I_2(t)$ , then

$$B - (\mu + \delta)P(t) \leq P'(t) \leq B - \mu P(t).$$

Thus,  $P(t)$  is bounded which implies that any solution of model 3.1 with initial conditions in  $W$  stays there for  $t \geq 0$ .  $\square$

In the absence of the disease (that is,  $\delta = 0$ ), then equation (3.2) reduces to

$$\frac{dP}{dt} + \mu P = B. \quad (3.3)$$

Solving equation (3.3), we have

$$\begin{aligned} e^{\mu t} \frac{dP}{dt} + \mu e^{\mu t} P &= B e^{\mu t}, \\ \frac{d}{dt}(e^{\mu t} P) &= B e^{\mu t}, \end{aligned}$$

where  $e^{\mu t}$  is the integrating factor. Integrating both sides and rearranging, we have the general solution to equation (3.2) as

$$P(t) = \frac{B}{\mu} + \xi e^{-\mu t}, \quad (3.4)$$

where  $\xi$  is a constant of integration.

Let  $P(0) = P_0$ , then

$$\begin{aligned}\xi &= P_0 - \frac{B}{\mu}, \\ \Rightarrow P(t) &= P_0 e^{-\mu t} + \frac{B}{\mu}(1 - e^{-\mu t}).\end{aligned}$$

From the above solution, it is clear that  $P(t) \rightarrow \frac{B}{\mu}$  as  $t \rightarrow \infty$ . Thus system (3.1) will always have the disease-free equilibrium  $(\frac{B}{\mu}, 0, 0, 0, 0)$ .

TABLE. 3.2. Similarity between the medical vocabulary and the two-strain TB model with superinfection. Adopted from [34].

Total population	$P = S + E_1 + E_2 + E_{12} + I_1 + I_2$
TB notification rate	$(\gamma_1 I_1 + \gamma_2 I_2)/P$
MTB prevalence	$(E_1 + E_2 + E_{12} + I_1 + I_2)/P$
TB prevalence	$(I_1 + I_2)/P$
MTB infection rate	$k(I_1 + I_2)/P$
TB cases	$T = a_1 E_1 + a_2 E_2 + \sigma_1 E_{12} + \sigma_2 E_{12} + \{(pS + q_1 E_1 + \theta_1 c E_2 + \omega_1 E_{12})k_1 I_1 + (pS + q_2 E_2 + \theta_2 c E_1 + \omega_2 E_{12})k_2 I_2\}/P$
TB incidence rate	$T/P$
“Styblo’s ratio”	$1,000 \times (\text{TB incidence rate})/(\text{MTB infection rate})$
Reactivation	$(a_1 E_1 + a_2 E_2 + \sigma_1 E_{12} + \sigma_2 E_{12})/T$
Reinfection	$\{(q_1 E_1 + \omega_1 E_{12})k_1 I_1 + (q_2 E_2 + \omega_2 E_{12})k_2 I_2\}/T/P$
Superinfection	$(\theta_1 c E_2 k_1 I_1 + \theta_2 c E_1 k_2 I_2)/T/P$
Primary disease	$pS(k_1 I_1 + k_2 I_2)/T/P$

### 3.3 Mathematical analysis

Before carrying out the mathematical analysis of the whole model it is enlightening to consider its submodels. We are able to gain insights into the dynamics of the whole model by considering smaller models. We consider firstly, the TB model with one strain, by setting  $E_2 = E_{12} = I_2 = 0$ . Secondly, we consider the TB model with two strains in the absence of superinfection by setting  $E_{12} = 0$ . Thirdly, we consider the whole model. Qualitative analysis of some models are not tractable and we resort to numerical simulations to obtain insights into the dynamics of the model.

### 3.3.1 Analysis of the one-strain TB model

In a case where there is one strain of tuberculosis and no superinfection, system (3.1) reduces to,

$$\left. \begin{aligned} \frac{dS}{dt} &= B - S \frac{k_1 I_1}{N} - \mu S, \\ \frac{dE_1}{dt} &= [(1-p)S - q_1 E_1] \frac{k_1 I_1}{N} - (a_1 + \mu) E_1 + b_1 I_1, \\ \frac{dI_1}{dt} &= (pS + q_1 E_1) \frac{k_1 I_1}{N} + a_1 E_1 - (b_1 + m) I_1, \end{aligned} \right\} \quad (3.5)$$

where  $N$  is the total population, given by  $N = S + E_1 + I_1$ . The model has a disease-free equilibrium point  $X_0 = (S^0, E_1^0, I_1^0) = (\frac{B}{\mu}, 0, 0)$ .

The dynamics of the one-strain TB model will be considered in

$$W_0 = \left\{ (S, E_1, I_1) \in \mathbb{R}_+^3 : N \leq \frac{B}{\mu} \right\}$$

which can be shown to be positively invariant with respect to system (3.5).

The equations given in system (3.5) are similar to the ones considered by Bacaër *et al.* [34] for TB without HIV. In addition to other results, our analysis gives the global stability of the disease-free equilibrium and the local stability of the endemic equilibrium. These two results were not presented in [34].

#### The basic reproduction number

The basic reproduction number is defined as the average number of secondary infectious cases that an infectious individual would generate during his/her infectious period in a population that is wholly susceptible [7, 39, 51]. It is usually denoted by  $R_0$ . If  $R_0 < 1$ , then on average, an infected individual produces less than one new infected individual over the course of one's infectious period, and thus the infection will not persist. On the other hand, if  $R_0 > 1$ , then on average an infected individual produces more than one new infected individuals over the course of one's infectious period and thus the disease will persist in the population. For the case of a single infected compartment,  $R_0$  is simply the product of the infection rate and the mean duration of the infection, but for more complicated models with several infected compartments this simple definition is not enough. A more general

basic reproduction number can be defined as the number of new infections produced by an infectious individual in a susceptible population at a disease-free equilibrium [51].

Using the method presented in [51], we can write system (3.5) as

$$\begin{aligned}\frac{dX}{dt} &= f(X) \\ &= \mathcal{F}(X) - \mathcal{V}(X) \\ &= \mathcal{F}(X) - (\mathcal{V}^-(X) - \mathcal{V}^+(X)),\end{aligned}$$

where  $X = (S, E_1, I_1)$ ,  $\mathcal{F}$  is the rate of appearance of new infections in each compartment,  $\mathcal{V}^+$  is the rate of transfer into each compartment by all other means and  $\mathcal{V}^-$  is the rate of transfer out of each compartment. Progression from  $E$  to  $I$  is not considered as a new infection. Hence,

$$\mathcal{F} = \begin{pmatrix} (1-p)S\frac{k_1 I_1}{N} \\ pS\frac{k_1 I_1}{N} \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} q_1 E_1 \frac{k_1 I_1}{N} + (a_1 + \mu)E_1 - b_1 I_1 \\ -q_1 E_1 \frac{k_1 I_1}{N} - a_1 E_1 + (b_1 + m)I_1 \end{pmatrix}.$$

The derivatives  $D\mathcal{F}(X_0)$  and  $D\mathcal{V}(X_0)$  are partitioned according to **Lemma 1** in [51] so that

$$D\mathcal{F}(X_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix} \text{ and } D\mathcal{V}(X_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where  $F$  and  $V$  are the matrices given by the derivatives of  $\mathcal{F}$  and  $\mathcal{V}$  with respect to the infected classes evaluated at the disease-free equilibrium point  $X_0$  and given by

$$F = \begin{pmatrix} 0 & (1-p)k_1 \\ 0 & pk_1 \end{pmatrix} \text{ and } V = \begin{pmatrix} a_1 + \mu & -b_1 \\ -a_1 & b_1 + m \end{pmatrix}.$$

The basic reproduction number is defined as the spectral radius of the next generation matrix,  $FV^{-1}$ . It is given by

$$R_1^{TB} = \frac{k_1(a_1 + p\mu)}{a_1 m + m\mu + \mu b_1}, \quad (3.6)$$

which is the same as the one obtained by Bacaër *et al.* [34].

**NOTE:** The above reproduction number was obtained by considering the sensitive strain only. Similarly, the analysis of the resistant strain leads to the reproduction number given by

$$R_2^{TB} = \frac{k_2(a_2 + p\mu)}{a_2m + m\mu + \mu b_2}. \quad (3.7)$$

### Local stability of disease-free equilibrium $X_0$

We need to show that if  $\mathcal{F}$  is set to zero, then all the eigenvalues of  $Df(X_0)$  have negative real part for the disease-free equilibrium point  $X_0$  to be locally stable. This is in accordance with A(5) of Theorem 2 in [51]. The Jacobian of  $f$  at  $X_0$  with  $\mathcal{F}$  set to zero is,

$$J_0 = \begin{pmatrix} -\mu & 0 & -k_1 \\ 0 & -(a_1 + \mu) & b_1 \\ 0 & a_1 & -(b_1 + m) \end{pmatrix}.$$

The eigenvalues of the Jacobian are:  $-\mu$ ,  $-r_1 \pm \sqrt{r_1^2 - 4r_0}$ , where

$$\begin{aligned} r_1 &= \mu + b_1 + a_1 + m, \\ r_0 &= m\mu + b_1\mu + a_1m. \end{aligned}$$

Since  $r_1$  and  $r_0$  are positive, then all eigenvalues have negative real part and thus the results can be summarised in the Theorem given below.

**Theorem 3.3.1** *The disease-free equilibrium point  $X_0$  is locally asymptotically stable if  $R_1^{TB} < 1$  and unstable if  $R_1^{TB} > 1$ .*

### Global stability of disease-free equilibrium $X_0$

**Theorem 3.3.2** *The disease-free equilibrium  $X_0 = (\frac{B}{\mu}, 0, 0)$  of system (3.5) is globally asymptotically stable in  $W_0$  if  $R_1^{TB} \leq 1$  and unstable if  $R_1^{TB} > 1$ .*

**Proof.** Consider the Lyapunov function

$$L = a_1E_1 + (a_1 + \mu)I_1.$$

Its derivative with time along the solutions of system (3.5) is

$$\begin{aligned}
L' &= a_1 E_1' + (a_1 + \mu) I_1', \\
&= a_1 \left[ ((1-p)S - q_1 E_1) \frac{k_1 I_1}{N} - (a_1 + \mu) E_1 + b_1 I_1 \right] + (a_1 + \mu) \left[ (pS + q_1 E_1) \frac{k_1 I_1}{N} \right. \\
&\quad \left. + a_1 E_1 - (b_1 + m) I_1 \right], \\
&= \frac{k_1 a_1 S I_1}{N} + \frac{p k_1 \mu S I_1}{N} + \frac{q_1 k_1 \mu E_1 I_1}{N} - [m(a_1 + \mu) + \mu b_1] I_1, \\
&= \frac{S I_1 k_1 (a_1 + p\mu)}{N} - [m(a_1 + \mu) + \mu b_1] I_1 + \frac{q_1 k_1 \mu E_1 I_1}{N} \\
&= \frac{S I_1 (m(a_1 + \mu) + \mu b_1)}{N} \left[ \frac{k_1 (a_1 + p\mu)}{(m(a_1 + \mu) + \mu b_1)} - 1 \right] + \frac{q_1 k_1 \mu E_1 I_1}{N}, \\
&\leq \frac{(m(a_1 + \mu) + \mu b_1) S I_1}{N} \left[ \frac{k_1 (a_1 + p\mu)}{(m(a_1 + \mu) + \mu b_1)} - 1 \right].
\end{aligned}$$

Since  $N \geq S$ , then we can write that

$$\begin{aligned}
L' &\leq (m(a_1 + \mu) + \mu b_1) \left[ \frac{k_1 (a_1 + p\mu)}{(m(a_1 + \mu) + \mu b_1)} - 1 \right] I_1, \\
&= (m(a_1 + \mu) + \mu b_1) [R_1^{TB} - 1] I_1,
\end{aligned}$$

from which  $L' \leq 0$  if  $R_1^{TB} \leq 1$  and  $L' = 0$  if  $R_1^{TB} = 1$ . It is also clear that  $L' = 0$  implies that  $I_1 = 0$ , which means that the disease-free equilibrium point is globally asymptotically stable and thus the proof follows.  $\square$

### The endemic steady states of the one-strain TB model

Let the endemic steady states be given by  $X^* = (S^*, E_1^*, I_1^*)$ , with  $S^* > 0$ ,  $E_1^* > 0$ , and  $I_1^* > 0$ . By equating system (3.5) to zero and using the following notation

$$\left. \begin{aligned}
N^* &= S^* + E_1^* + I_1^*, s^* = S^*/N^*, e_1^* = E_1^*/N^*, i_1^* = I_1^*/N^*, b = B/N^*, \\
s^* + e_1^* + i_1^* &= 1,
\end{aligned} \right\} \quad (3.8)$$

we obtain

$$b - s^* k_1 i_1^* - \mu s^* = 0, \quad (3.9)$$

$$((1-p)s^* - q_1 e_1^*) k_1 i_1^* - (a_1 + \mu) e_1^* + b_1 i_1^* = 0, \quad (3.10)$$

$$(ps^* + q_1 e_1^*) k_1 i_1^* + a_1 e_1^* - (b_1 + m) i_1^* = 0. \quad (3.11)$$



From equation (3.9), we can see that

$$s^* = \frac{b}{k_1 i_1^* + \mu} \Leftrightarrow S^* = \frac{B}{k_1 i_1^* + \mu}. \quad (3.12)$$

Adding equations (3.10) and (3.11) gives

$$s^* k_1 i_1^* - \mu e_1^* - m i_1^* = 0. \quad (3.13)$$

Substituting for  $s^* = 1 - e_1^* - i_1^*$  in equation (3.13), we have

$$\begin{aligned} (1 - e_1^* - i_1^*) k_1 i_1^* - \mu e_1^* - m i_1^* &= 0, \\ k_1 i_1^* - k_1 e_1^* i_1^* - k_1 i_1^{*2} - \mu e_1^* - m i_1^* &= 0, \end{aligned}$$

which gives

$$e_1^* = \frac{k_1 i_1^* - m i_1^* - k_1 i_1^{*2}}{k_1 i_1 + \mu}. \quad (3.14)$$

Substituting for  $e_1^*$  in equation (3.11) and using the fact that  $s^* = 1 - e_1^* - i_1^*$ , we obtain

$$i_1^* \{(k_1 - m - k_1 i_1^*)(q_1 k_1 i_1^* + a_1 - p k_1 i_1^*) + (k_1 i_1^* + \mu)(p k_1 - p k_1 i_1^* - b_1 - m)\} = 0.$$

This implies that  $i_1^* = 0$ , or

$$((k_1 - m) - k_1 i_1^*)((q_1 k_1 - p k_1) i_1^* + a_1) + (k_1 i_1^* + \mu)((p k_1 - b_1 - m) + p k_1 i_1^*) = 0. \quad (3.15)$$

The case  $i_1^* = 0$  corresponds to the disease-free equilibrium  $X_0$ . Simplifying equation (3.15), we obtain the polynomial

$$C(i_1^*) = i_1^{*2} + C_1 i_1^* + C_0 = 0, \quad (3.16)$$

where  $C_1 = \frac{(m q_1 - m p - q_1 k_1 + a_1 + b_1 + m + p \mu)}{q_1 k_1}$  and  $C_0 = \frac{m a_1 + b_1 \mu + m \mu - k_1 (a_1 + p \mu)}{q_1 k_1^2}$ .

The simplification of  $C_0$  gives  $C_0 = \frac{m a_1 + b_1 \mu + m \mu}{q_1 k_1^2} (1 - R_1^{TB})$ , where  $R_1^{TB} = \frac{k_1 (a_1 + p \mu)}{m a_1 + b_1 \mu + m \mu}$ .

After finding  $i_1^*$ , we can also compute  $e_1^*$  using equation (3.14),  $S^*$  using equation (3.12) and the other steady states from

$$s^* = 1 - e_1^* - i_1^*, N^* = S^*/s^*, E_1^* = e_1^*N^*, I_1^* = i_1^*N^*. \quad (3.17)$$

It is clear that if  $R_1^{TB} > 1$ , then  $C_0 < 0$  and if  $R_1^{TB} < 1$ , then  $C_0 > 0$ . Equation (3.16) has a solution given by

$$i_1^* = \frac{-C_1 \pm \sqrt{C_1^2 - 4C_0}}{2} \quad (3.18)$$

Note that:

- (i). If  $C_1 > 0$  and  $C_0 < 0$ , then equation (3.18) has one positive solution.
- (ii). If  $C_1 > 0$  and  $C_0 > 0$ , then equation (3.18) has two negative solutions.
- (iii). If  $C_1 < 0$  and  $C_0 < 0$ , then equation (3.18) has one positive solution.
- (iv). If  $C_1 < 0$  and  $C_0 > 0$ , then equation (3.18) has two positive solutions.

We thus have the following Theorem on the existence of the endemic steady states.

**Theorem 3.3.3** *The endemic steady state  $X^*$  exists and*

- (i) *for any  $C_1$  and  $R_1^{TB} > 1$ , then system (3.5) has one endemic equilibrium point;*
- (ii) *if  $C_1 < 0$  and  $R_1^{TB} < 1$ , then system (3.5) has two endemic equilibria.*

### Local stability of endemic equilibrium

We will use the center manifold theory which is described in [6] (Theorem 4.1) and [36] (Theorem 3.6). The theory is used to determine the local stability of a nonhyperbolic equilibrium and the type of bifurcation that occurs. We present it here for the purpose of easier referencing.

**Theorem 3.3.4** *Consider the following general system of ordinary differential equations with a parameter  $\phi$*

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R} \quad \text{and} \quad f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}), \quad (3.19)$$

*where 0 is an equilibrium point of the system (that is,  $f(0, \phi) \equiv 0$  for all  $\phi$ ) and assume*

*A1 :  $A = D_x f(0, 0) = \left(\frac{\partial f_i}{\partial x_i}(0, 0)\right)$  is the linearization matrix of the system (3.5) around the equilibrium 0 with  $\phi$  evaluated at 0. Zero is a simple eigenvalue of  $A$  and other eigenvalues of  $A$  have negative real parts;*

*A2 : Matrix  $A$  has a right eigenvector  $w$  and a left eigenvector  $v$  (each corresponding to the zero eigenvalue).*

Let  $f_r$  be the  $r$ th component of  $f$  and

$$a = \sum_{r,i,j=1}^n v_r w_i w_j \frac{\partial^2 f_r}{\partial x_i \partial x_j}(0, 0),$$

$$b = \sum_{r,i=1}^n v_r w_i \frac{\partial^2 f_r}{\partial x_i \partial \phi}(0, 0).$$

The local dynamics of the system around 0 is totally determined by the signs of  $a$  and  $b$ .

- i :  $a > 0, b > 0$ . When  $\phi < 0$  with  $|\phi| \ll 1$ , 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when  $0 < \phi \ll 1$ , 0 is unstable and there exists a negative, locally asymptotically stable equilibrium;*
- ii :  $a < 0, b < 0$ . When  $\phi < 0$  with  $|\phi| \ll 1$ , 0 is unstable; when  $0 < \phi \ll 1$ , 0 is locally asymptotically stable equilibrium, and there exists a positive unstable equilibrium;*
- iii :  $a > 0, b < 0$ . When  $\phi < 0$  with  $|\phi| \ll 1$ , 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when  $|\phi| \ll 1$ , 0 is stable, and a positive unstable equilibrium appears;*
- iv :  $a < 0, b > 0$ . When  $\phi$  changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Particularly, if  $a > 0$  and  $b > 0$ , then a backward bifurcation occurs at  $\phi = 0$ .

To apply this method, it is necessary to make a change of variables. Let  $S = x_1, E_1 = x_2, I_1 = x_3$  and  $N = x_1 + x_2 + x_3$ . After this change of variables, our  $X$  and  $\frac{dX}{dt}$  becomes  $X = (x_1, x_2, x_3)$  and  $\frac{dX}{dt} = f = (f_1, f_2, f_3)$  respectively. The disease-free equilibrium remains unchanged and is given by  $X_0 = \left(\frac{B}{\mu}, 0, 0\right)$ . System (3.5) can now be re-written as

$$\left. \begin{aligned} \frac{dx_1}{dt} &= f_1 = B - \frac{k_1 x_1 x_3}{x_1 + x_2 + x_3} - \mu x_1, \\ \frac{dx_2}{dt} &= f_2 = \frac{(1-p)k_1 x_1 x_3}{x_1 + x_2 + x_3} - \frac{q_1 k_1 x_2 x_3}{x_1 + x_2 + x_3} - (a_1 + \mu)x_2 + b_1 x_3, \\ \frac{dx_3}{dt} &= f_3 = \frac{pk_1 x_1 x_3}{x_1 + x_2 + x_3} + \frac{q_1 k_1 x_2 x_3}{x_1 + x_2 + x_3} + a_1 x_2 - (b_1 + m)x_3. \end{aligned} \right\} \quad (3.20)$$

The Jacobian of system (3.20) at  $X_0$  is given by

$$J(X_0) = \begin{pmatrix} -\mu & 0 & -k_1 \\ 0 & -(a_1 + \mu) & (1-p)k_1 + b_1 \\ 0 & a_1 & pk_1 - (b_1 + m) \end{pmatrix}.$$

We can also determine  $R_1^{TB}$  by evaluating the eigenvalues of  $J(X_0)$ . We note that it is equivalent to the one given in equation (3.6). Consider the case when  $R_1^{TB} = 1$  and assume that  $k_1$  is the bifurcation parameter. Solving equation (3.6) for  $k_1$  when  $R_1^{TB} = 1$ , gives

$$k_1 = k_1^* = \frac{a_1 m + m\mu + \mu b_1}{a_1 + p\mu}. \quad (3.21)$$

Note that: If  $k_1 < k_1^*$ , then  $R_1^{TB} < 1$  and if  $k_1 > k_1^*$ , then  $R_1^{TB} > 1$ .

The Jacobian of (3.20) at  $k_1 = k_1^*$ , denoted by  $J_{k_1^*}$  has the following eigenvalues.

$$\left( 0, -\mu, \frac{mpa_1 - p\mu^2 - ma_1 - \mu a_1 - p\mu a_1 - a_1^2 - a_1 b_1}{p\mu + a_1} \right).$$

The right eigenvector (associated with the zero eigenvalue) of this Jacobian is given by  $w = [w_1, w_2, w_3]^T$ , where

$$\begin{aligned} w_1 &= -\frac{m\mu + ma_1 + \mu b_1}{\mu(p\mu + a_1)}, \\ w_2 &= \frac{m(1-p) + b_1}{p\mu + a_1}, \\ w_3 &= 1. \end{aligned}$$

$J_{k_1^*}$  also has a left eigenvector (associated with the zero eigenvalue) given by  $v = [v_1, v_2, v_3]^T$ , where

$$\begin{aligned} v_1 &= 0, \\ v_2 &= \frac{a_1}{\mu + a_1}, \\ v_3 &= 1. \end{aligned}$$

To compute  $a$ , we need to look for all the non-zero partial derivatives of  $f$  at the disease-free equilibrium (as in Theorem 3.3.4). Since  $v_1 = 0$ , then the partial derivatives of  $f_1$  are not necessary since they will cancel out after substitution. The non-zero partial derivatives of  $f_2$  and  $f_3$  of system (3.20) are given by

$$\begin{aligned}\frac{\partial^2 f_2}{\partial x_2 \partial x_3} &= \frac{-k_1^* \mu (1-p+q_1)}{B}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = \frac{-k_1^* \mu (1-p+q_1)}{B}, \quad \frac{\partial^2 f_2}{\partial x_3^2} = \frac{-2k_1^* \mu (1-p)}{B}, \\ \frac{\partial^2 f_3}{\partial x_2 \partial x_3} &= \frac{k_1^* \mu (q_1-p)}{B}, \quad \frac{\partial^2 f_3}{\partial x_3 \partial x_2} = \frac{k_1^* \mu (q_1-p)}{B}, \quad \frac{\partial^2 f_3}{\partial x_3^2} = \frac{-2k_1^* p \mu}{B}.\end{aligned}$$

Using the above expressions and making substitutions for  $a$ , we obtain

$$\begin{aligned}a &= v_2 w_2 w_3 \frac{\partial^2 f_2}{\partial x_2 \partial x_3} + v_2 w_3 w_2 \frac{\partial^2 f_2}{\partial x_3 \partial x_2} + v_2 w_3^2 \frac{\partial^2 f_2}{\partial x_3^2} + v_3 w_2 w_3 \frac{\partial^2 f_3}{\partial x_2 \partial x_3} + v_3 w_3 w_2 \frac{\partial^2 f_3}{\partial x_3 \partial x_2} + v_3 w_3^2 \frac{\partial^2 f_3}{\partial x_3^2}, \\ &= -\frac{2k_1^* \mu a_1 (m(1-p)+b_1)(1-p+q_1)}{B(\mu+a_1)(p\mu+a_1)} - \frac{2k_1^* \mu a_1 (1-p)}{B(\mu+a_1)} - \frac{2k_1^* \mu (m(1-p)+b_1)(p-q_1)}{B(p\mu+a_1)} - \frac{2k_1^* p \mu}{B}, \\ &= \frac{-2k_1^* \mu}{B} \left\{ \frac{a_1 (m(1-p)+b_1)(1-p+q_1)}{(\mu+a_1)(p\mu+a_1)} + \frac{a_1 (1-p)}{(\mu+a_1)} + \frac{(m(1-p)+b_1)(p-q_1)}{(p\mu+a_1)} + p \right\},\end{aligned}$$

from which  $a < 0$  since  $q_1 \leq p$ .

For the computation of  $b$ , we also need to look for the non-zero partial derivatives of  $f$  at the disease-free equilibrium (as in Theorem 3.3.4). We are also neglecting the partial derivatives of  $f_1$  since  $v_1 = 0$ . Thus, the other non-zero partial derivatives are given by

$$\frac{\partial^2 f_2}{\partial x_3 \partial k_1^*} = (1-p), \quad \frac{\partial^2 f_3}{\partial x_3 \partial k_1^*} = p.$$

It follows from the above expressions that

$$\begin{aligned}b &= v_2 w_3 \frac{\partial^2 f_2}{\partial x_3 \partial k_1^*} + v_3 w_3 \frac{\partial^2 f_3}{\partial x_3 \partial k_1^*}, \\ &= \frac{a_1}{(\mu+a_1)} \frac{(m(1-p)+b_1)}{(p\mu+a_1)} (1-p) + \frac{(m(1-p)+b_1)}{(p\mu+a_1)} p, \\ &= \frac{(m(1-p)+b_1)(p\mu+a_1)}{(\mu+a_1)(p\mu+a_1)}, \\ &= \frac{(m(1-p)+b_1)}{(\mu+a_1)} > 0.\end{aligned}$$

Thus, the results obtained from the above analysis can be summarised in the Theorem below.

**Theorem 3.3.5** *The unique endemic equilibrium of the one-strain TB model represented by system (3.5) is locally asymptotically stable for  $R_1^{TB} > 1$ , with  $R_1^{TB}$  close to 1.*

Feng *et al.* [54] had a model which is almost similar to this one with one extra compartment for treatment. In their model, a backward bifurcation occurred when the values of exogenous reinfection were high. It can also be noticed that for high values of  $q_1$  (exogenous reinfection), then the value of  $a$  would be greater than zero and according to Theorem 3.3.4 a backward bifurcation would occur since  $b > 0$  giving a similar result to the one obtained by Feng *et al.* [54]. Sharomi *et al.* [36] noted that models of TB dynamics with exogenous reinfection are known to exhibit the phenomenon of backward bifurcation. They did the same analysis in their HIV-TB model after analysing the TB-only sub-model and detected a backward bifurcation by taking the reinfection parameter to be 3 per year which is generally high. Since it is believed that after primary infection there is a protection induced towards any other incoming infection [31], then we should expect  $q_1 \leq p$  as it was done in [34, 39].

### 3.3.2 Analysis of the two-strain TB model without superinfection

We now consider a two-strain TB model in the absence of superinfection. In this case  $E_{12} = 0$ , and system (3.1) reduces to,

$$\left. \begin{aligned} \frac{dS}{dt} &= B - S \frac{(k_1 I_1 + k_2 I_2)}{Q} - \mu S, \\ \frac{dE_1}{dt} &= [(1-p)S - q_1 E_1] \frac{k_1 I_1}{Q} - (a_1 + \mu) E_1 + b_1 I_1, \\ \frac{dE_2}{dt} &= [(1-p)S - q_2 E_2] \frac{k_2 I_2}{Q} - (a_2 + \mu) E_2 + b_2 I_2, \\ \frac{dI_1}{dt} &= (pS + q_1 E_1) \frac{k_1 I_1}{Q} + a_1 E_1 - (b_1 + m) I_1, \\ \frac{dI_2}{dt} &= (pS + q_2 E_2) \frac{k_2 I_2}{Q} + a_2 E_2 - (b_2 + m) I_2, \end{aligned} \right\} \quad (3.22)$$

where  $Q$  is the total population, given by  $Q = S + E_1 + E_2 + I_1 + I_2$ .

The dynamics of the two-strain TB model will be considered in

$$W_1 = \left\{ (S, E_1, E_2, I_1, I_2) \in \mathbb{R}_+^5 : Q \leq \frac{B}{\mu} \right\}$$

which can be shown to be positively invariant with respect to system (3.22).

System (3.22) is comparable to the model considered by Rodrigues *et al.* [39] without treatment failure and superinfection by resistant strains.

### The basic reproduction number

Again using the method in subsection (3.3.1) with  $\frac{dX}{dt} = f(X)$ , where  $X$  is now given by  $(S, E_1, E_2, I_1, I_2)$  and the disease-free equilibrium  $X_1 = (\frac{B}{\mu}, 0, 0, 0, 0)$ , we obtain the following new expressions for  $\mathcal{F}$ ,  $\mathcal{V}$ ,  $F$  and  $V$ .

$$\mathcal{F} = \begin{pmatrix} (1-p)S\frac{k_1I_1}{Q} \\ (1-p)S\frac{k_2I_2}{Q} \\ pS\frac{k_1I_1}{Q} \\ pS\frac{k_2I_2}{Q} \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} q_1E_1\frac{k_1I_1}{Q} + (a_1 + \mu)E_1 - b_1I_1 \\ q_2E_2\frac{k_2I_2}{Q} + (a_2 + \mu)E_2 - b_2I_2 \\ -q_1E_1\frac{k_1I_1}{Q} - a_1E_1 + (b_1 + m)I_1 \\ -q_2E_2\frac{k_2I_2}{Q} - a_2E_2 + (b_2 + m)I_2 \end{pmatrix},$$

$$F = \begin{pmatrix} 0 & 0 & (1-p)k_1 & 0 \\ 0 & 0 & 0 & (1-p)k_2 \\ 0 & 0 & pk_1 & 0 \\ 0 & 0 & 0 & pk_2 \end{pmatrix} \text{ and } V = \begin{pmatrix} a_1 + \mu & 0 & -b_1 & 0 \\ 0 & a_2 + \mu & 0 & -b_2 \\ -a_1 & 0 & b_1 + m & 0 \\ 0 & -a_2 & 0 & b_2 + m \end{pmatrix}.$$

The basic reproduction number,  $R_0^{TB}$  of the two-strain TB model is also defined as the spectral radius of the next generation matrix  $FV^{-1}$  and is given by  $R_0^{TB} = \max(R_1^{TB}, R_2^{TB})$ , where

$$R_1^{TB} = \frac{k_1(a_1 + \mu p)}{(m + b_1)\mu + a_1 m} \quad (3.23)$$

and

$$R_2^{TB} = \frac{k_2(a_2 + \mu p)}{(m + b_2)\mu + a_2 m}. \quad (3.24)$$

This basic reproduction number compares well with the one obtained by Rodrigues *et al.* [39] if treatment failure is not put into consideration.

### Local stability of disease-free equilibrium $X_1$

The Jacobian of  $f$  at  $X_1$  with  $\mathcal{F}$  set to zero is

$$J_1 = \begin{pmatrix} -\mu & 0 & 0 & -k_1 & -k_2 \\ 0 & -(a_1 + \mu) & 0 & b_1 & 0 \\ 0 & 0 & -(a_2 + \mu) & 0 & b_2 \\ 0 & a_1 & 0 & -(b_1 + m) & 0 \\ 0 & 0 & a_2 & 0 & -(b_2 + m) \end{pmatrix}.$$

The eigenvalues of the Jacobian are:  $-\mu$ ,  $-y_1 \pm \sqrt{y_1^2 - 4y_0}$ ,  $-z_1 \pm \sqrt{z_1^2 - 4z_0}$ , where

$$\begin{aligned} y_1 &= \mu + m + b_1 + a_1, \\ y_0 &= \mu m + b_1 \mu + a_1 m, \\ z_1 &= \mu + m + b_2 + a_2, \\ z_0 &= \mu m + b_2 \mu + a_2 m. \end{aligned}$$

Since  $y_1, y_0, z_1, z_0$  are positive, then all eigenvalues have real negative part and the results can be summarised in the Theorem below.

**Theorem 3.3.6** *If  $R_0^{TB} < 1$ , the disease-free equilibrium point  $X_1$  is locally asymptotically stable and unstable if  $R_0^{TB} > 1$ .*

The computation of the endemic equilibrium of system (3.22) leads to a polynomial of degree five which is difficult to analyse analytically. We thus resort to numerical results which are given in section 3.4.

### 3.3.3 Analysis of the two-strain TB model with superinfection

After putting superinfection into consideration we obtain the new model which is schematically represented by Figure 3.1 and given by system (3.1).

As already explained in the model development in section 3.2,  $\tau_1$  and  $\tau_2$  denote the proportion of individuals who move to respectively states  $E_1$  and  $E_2$  after recovery. These proportions depend on the number of superinfected individuals that eventually progress to active disease of either strain 1 or strain 2. If  $\tau_1$  is much higher than  $\tau_2$ , it will imply that most individuals progress to active TB of strain 1 after superinfection. Conversely, if the number of individuals progressing to active disease of strain 2 after superinfection



is high, then  $\tau_2$  will be much greater than  $\tau_1$ . Our analysis will first be based on the assumption that progression to active disease in one of the strains after superinfection is much higher than the other. Later we will consider the case where individuals after superinfection progress to either strain 1 or strain 2 at an approximately equal rate. Rodrigues *et al.* [39] assumed that when an individual is infected with both drug-sensitive and drug-resistant strains, he/she progresses to active tuberculosis of the drug-resistant strain. Our assumption in the first analysis of this model does not differ from theirs, only that we are considering progression to active TB of either a drug-sensitive or a drug-resistant strain of active tuberculosis after superinfection.

In a case where most individuals progress to active TB of strain 1 after superinfection, that is  $\tau_1 \gg \tau_2$ , we can generally say that  $\tau_1 > 0$  and  $\tau_2 \simeq 0$ . Using the method in subsection (3.3.1) with  $\frac{dX}{dt} = f(X)$ , where  $X$  is now given by  $(S, E_1, E_2, E_{12}, I_1, I_2)$  and the disease-free equilibrium  $X_2 = (\frac{B}{\mu}, 0, 0, 0, 0, 0)$ , we obtain the following new expressions for  $\mathcal{F}$ ,  $\mathcal{V}$ ,  $F$  and  $V$ .

$$\mathcal{F} = \begin{pmatrix} (1-p)S\frac{k_1 I_1}{P} \\ (1-p)S\frac{k_2 I_2}{P} \\ 0 \\ pS\frac{k_1 I_1}{P} \\ pS\frac{k_2 I_2}{P} \end{pmatrix},$$

$$\mathcal{V} = \begin{pmatrix} q_1 E_1 \frac{k_1 I_1}{P} + (a_1 + \mu + c\frac{k_2 I_2}{P})E_1 - (1 - \tau_1)b_1 I_1 \\ q_2 E_2 \frac{k_2 I_2}{P} + (a_2 + \mu + \frac{k_1 I_1}{P})E_2 - b_2 I_2 \\ -(1 - \theta_1)cE_2 \frac{k_1 I_1}{P} - (1 - \theta_2)cE_1 \frac{k_2 I_2}{P} + (\omega_1 \frac{k_1 I_1}{P} + \omega_2 \frac{k_2 I_2}{P} + \sigma_1 + \sigma_2 + \mu)E_{12} - \tau_1 b_1 I_1 \\ -(q_1 E_1 + \theta_1 c E_2 + \omega_1 E_{12})\frac{k_1 I_1}{P} - a_1 E_1 - \sigma_1 E_{12} + (b_1 + m)I_1 \\ -(q_2 E_2 + \theta_2 c E_1 + \omega_2 E_{12})\frac{k_2 I_2}{P} - a_2 E_2 - \sigma_2 E_{12} + (b_2 + m)I_2 \end{pmatrix},$$

$$F = \begin{pmatrix} 0 & 0 & 0 & (1-p)k_1 & 0 \\ 0 & 0 & 0 & 0 & (1-p)k_2 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & pk_1 & 0 \\ 0 & 0 & 0 & 0 & pk_2 \end{pmatrix} \text{ and}$$

$$V = \begin{pmatrix} a_1 + \mu & 0 & 0 & -(1 - \tau_1)b_1 & 0 \\ 0 & a_2 + \mu & 0 & 0 & -b_2 \\ 0 & 0 & \sigma_1 + \sigma_2 + \mu & -\tau_1 b_1 & 0 \\ -a_1 & 0 & -\sigma_1 & b_1 + m & 0 \\ 0 & -a_2 & -\sigma_2 & 0 & b_2 + m \end{pmatrix}.$$

The basic reproduction number,  $R_{0s}^{TB}(\tau_1, 0)$  of the two-strain TB model with superinfection is also defined as the spectral radius of the next generation matrix  $FV^{-1}$  and is given by  $R_{0s}^{TB}(\tau_1, 0) = \max(R_{01}^{TB}, R_{02}^{TB})$ , where

$$R_{01}^{TB} = \frac{k_1(p\mu + a_1)(\mu + \sigma_1 + \sigma_2)}{m(\mu + a_1)(\mu + \sigma_1 + \sigma_2) + b_1[(\mu + \sigma_2)(\mu + \tau_1 a_1) + \mu\sigma_1(1 - \tau_1)]}, \quad (3.25)$$

and

$$R_{02}^{TB} = \frac{k_2(a_2 + \mu p)}{(m + b_2)\mu + a_2 m}. \quad (3.26)$$

Similarly, in a case where most individuals progress to active TB of strain 2 after superinfection, the basic reproduction number  $R_{0s}^{TB}(0, \tau_2)$  will be given by  $R_{0s}^{TB}(0, \tau_2) = \max(R_{10}^{TB}, R_{20}^{TB})$ , where

$$R_{10}^{TB} = \frac{k_1(a_1 + \mu p)}{(m + b_1)\mu + a_1 m} \quad (3.27)$$

and

$$R_{20}^{TB} = \frac{k_2(p\mu + a_2)(\mu + \sigma_1 + \sigma_2)}{m(\mu + a_2)(\mu + \sigma_1 + \sigma_2) + b_2[(\mu + \sigma_1)(\mu + \tau_2 a_2) + \mu\sigma_2(1 - \tau_2)]}. \quad (3.28)$$

Note that when  $\tau_1 = \tau_2 = 0$ , then the reproduction numbers  $R_{0s}^{TB}(\tau_1, 0)$  and  $R_{0s}^{TB}(0, \tau_2)$  reduce to  $R_1^{TB}$  and  $R_2^{TB}$  respectively.

Finally, when  $\tau_1 > 0$  and  $\tau_2 > 0$  (assuming that individuals after superinfection progress to either strain 1 or strain 2), the basic reproduction number  $R_{0s}^{TB}(\tau_1, \tau_2)$  is given by the spectral radius of the matrix  $ML^{-1}$ , where

$$M = \begin{pmatrix} 0 & 0 & 0 & (1-p)k_1 & 0 \\ 0 & 0 & 0 & 0 & (1-p)k_2 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & pk_1 & 0 \\ 0 & 0 & 0 & 0 & pk_2 \end{pmatrix} \text{ and}$$

$$L = \begin{pmatrix} a_1 + \mu & 0 & 0 & -(1 - \tau_1)b_1 & 0 \\ 0 & a_2 + \mu & 0 & 0 & -(1 - \tau_2)b_2 \\ 0 & 0 & \sigma_1 + \sigma_2 + \mu & -\tau_1 b_1 & -\tau_2 b_2 \\ -a_1 & 0 & -\sigma_1 & b_1 + m & 0 \\ 0 & -a_2 & -\sigma_2 & 0 & b_2 + m \end{pmatrix}.$$

### 3.3.4 Analysis of the basic reproduction numbers, $R_{0s}^{TB}(\tau_1, 0)$ , $R_{0s}^{TB}(0, \tau_2)$ and $R_{0s}^{TB}(\tau_1, \tau_2)$

We need to investigate whether superinfection has a positive or negative impact on the three basic reproduction numbers obtained in the previous subsection. Thus, we need to show if  $R_{0s}^{TB}(\tau_1, 0)$  and  $R_{0s}^{TB}(0, \tau_2)$  increase or decrease with any increase in  $\tau_1$  and  $\tau_2$  respectively for the first two reproduction numbers of the two-strain TB model with superinfection. Differentiating  $R_{0s}^{TB}(\tau_1, 0)$  with respect to  $\tau_1$  gives

$$\frac{\partial R_{0s}^{TB}(\tau_1, 0)}{\partial \tau_1} = \frac{k_1 b_1 (p\mu + a_1)(\mu + \sigma_1 + \sigma_2)(\mu\sigma_1 - a_1(\mu + \sigma_2))}{\{m(\mu + a_1)(\mu + \sigma_1 + \sigma_2) + b_1[(\mu + \sigma_2)(\mu + \tau_1 a_1) + \mu\sigma_1(1 - \tau_1)]\}^2},$$

from which  $\frac{\partial R_{0s}^{TB}(\tau_1, 0)}{\partial \tau_1} > 0$  if  $\mu\sigma_1 > a_1(\mu + \sigma_2)$ .

Also, differentiating  $R_{0s}^{TB}(0, \tau_2)$  with respect to  $\tau_2$  gives

$$\frac{\partial R_{0s}^{TB}(0, \tau_2)}{\partial \tau_2} = \frac{k_2 b_2 (p\mu + a_2)(\mu + \sigma_1 + \sigma_2)(\mu\sigma_2 - a_2(\mu + \sigma_1))}{\{m(\mu + a_2)(\mu + \sigma_1 + \sigma_2) + b_2[(\mu + \sigma_1)(\mu + \tau_2 a_2) + \mu\sigma_2(1 - \tau_2)]\}^2},$$

from which  $\frac{\partial R_{0s}^{TB}(0, \tau_2)}{\partial \tau_2} > 0$  if  $\mu\sigma_2 > a_2(\mu + \sigma_1)$ .

Numerical results of the three basic reproduction numbers are shown in Fig. 3.2. Fig. 3.2 (a) shows that  $R_{0s}^{TB}(\tau_1, 0)$  will always be higher than  $R_{0s}^{TB}(0, \tau_2)$  and the two basic reproduction numbers increase with any increase in  $\tau_1$  and  $\tau_2$  respectively. This implies that progression to active TB of the drug-sensitive strain after superinfection drives the TB epidemic at a slightly higher rate compared to progression to active TB of the drug-resistant strain after superinfection. This result is due to the fact that the transmission rate of sensitive strains was taken to be higher than that of resistant strains. On the other hand, if the transmission rate of resistant strains is higher than that of sensitive strains, then progression to active TB of the resistant strain after superinfection accelerates the

epidemic at a much higher rate than progression to active TB of the sensitive strain and  $R_{0s}^{TB}(0, \tau_2)$  will always be higher than  $R_{0s}^{TB}(\tau_1, 0)$ . Fig. 3.2 (b) shows that an increase in both  $\tau_1$  and  $\tau_2$  results in a higher increase in the basic reproduction number  $R_{0s}^{TB}(\tau_1, \tau_2)$ .

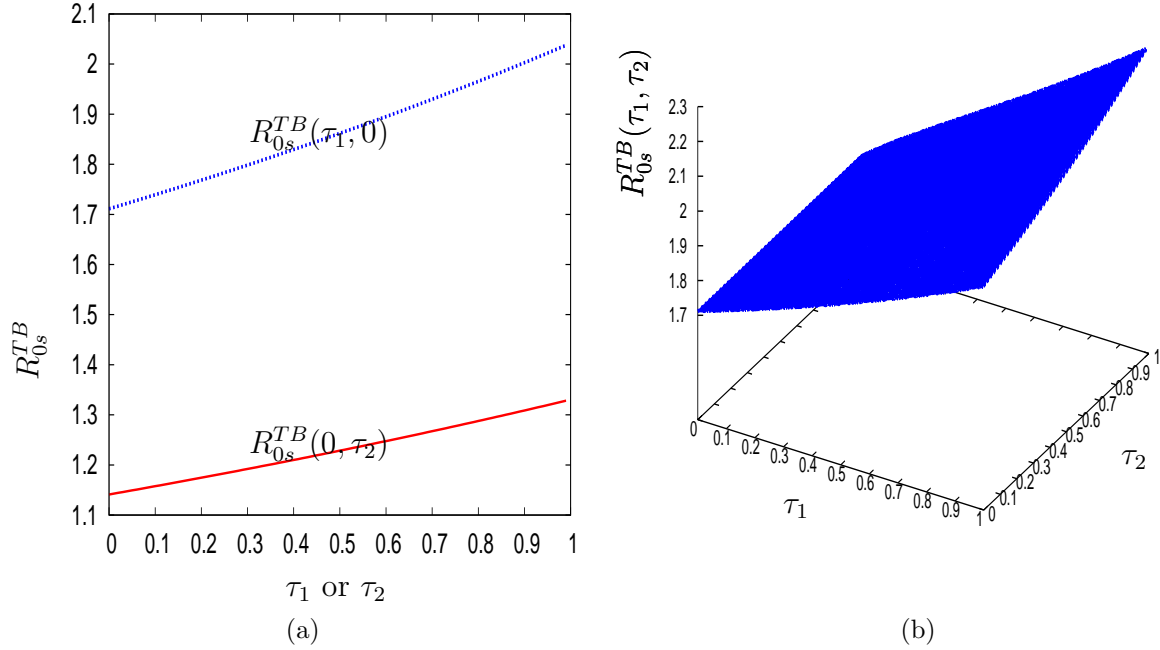


FIG. 3.2. Plots of  $R_{0s}^{TB}$  against  $\tau_1$  or  $\tau_2$  (a) and  $R_{0s}^{TB}(\tau_1, \tau_2)$  against  $\tau_1$  and  $\tau_2$  (b). Parameter values are given in Table 3.3.

## 3.4 Numerical simulations

### 3.4.1 Estimation of parameter values

In this section, we give the parameters that we used in our numerical simulations. Most of the parameters were picked from the literature as explained in the following subsections.

## Demographic parameters

The natural mortality was taken to be  $\mu=0.02/\text{yr}$  as in [34, 48, 49], corresponding to a life expectancy of 50 years. Ssematimba *et al.* [2] took the life expectancy to be 45 years in their TB analysis in Uganda. This mortality was assumed to be  $0.014/\text{yr}$  in [33, 39, 55],  $0.016/\text{yr}$  in [54],  $0.0081$  in [13]. These values give a very high life expectancy and therefore will not be considered in our simulations.

## TB parameters

**Infection and mortality.** We assume that the MTB infection rate is given by the product of the active TB prevalence and the MTB transmission rate. The MTB transmission rate was taken to be  $15/\text{yr}$  as in [11] for the drug-sensitive strain and 8 per year as in [8] for the drug-resistant strain. These values are on average close to  $11.4/\text{yr}$  which was obtained in [34] after fitting their model with data from a South African township by considering one strain of TB which also lies in the range given in [11]. This value was taken to be  $13/\text{yr}$  in [7, 46] for drug-sensitive tuberculosis. This value was assumed to lie in the range 5-15 per year in [11] for drug-sensitive tuberculosis and 7.0-12.6 per year in [8] for drug-resistant tuberculosis.

The mortality for people with active TB was assumed to be  $0.25/\text{yr}$  as in [34] (citing [48]). This value was assumed to be  $0.2/\text{yr}$  in [39],  $0.3/\text{yr}$  in [8],  $0.365/\text{yr}$  in [2]. It was also taken to lie in the range 0.058-0.461 per year in [46].

**Fast progression.** We are taking the fraction of individuals who progress to active TB after primary infection to be 11% as in [34] (citing [14]). We are taking the same value for the two strains. This value was taken to be 10% in [31, 39], 5% in [13] for drug-sensitive TB, 14% in [49] (citing [8] and other reference) for multidrug-resistant TB and it was also taken to lie in the range 0.08-0.25 per year in [8] for drug-resistant TB.

**Reinfection and superinfection.** The rate at which individuals get reinfected or superinfected was considered to be the same and given by  $q_1 = q_2 = c = \omega_1 = \omega_2 = 0.25p$  as in [11] and [39] (citing [31]), where  $p$  is the probability of progressing to active TB after primary infection. Reinfection and superinfection are considered to be post primary infections

and thus can be taken to be the same. In this case the partial immunity acquired from the previous infection is 75%. Cohen and Murray [49] took this value to be 65% (citing [8] and other references) for both drug-sensitive and multidrug-resistant TB. This value was also assumed to lie in the range 50-100% in [10] (citing [11]). Feng *et al.* assumed a reinfection risk factor of 30%, taking the partial immunity acquired from the primary infection to be 70%.

**Reactivation.** The reactivation rate was taken to be 0.000113/yr in [11] (citing [14] and other references), 0.0003/yr in [34] (citing [14]), 0.005/yr in [54] (citing [46]), 0.0002/yr in [39] (citing [31]) for both drug-sensitive and drug-resistant TB, 0.000299/yr in [14] (by fitting data) for individuals older than 20 years. This value was also taken to lie in the range 0.00256-0.00527 per year in [46] as a progression to TB within 20 years, 0.0001-0.0003 per year in [8]. We are taking the reactivation rate to be 0.0003/yr as in [8, 34] for both strains. Individuals latently infected with two strains are estimated to have a relatively higher reactivation rate of 0.008/yr since they are at a greater risk of developing active disease [28].

**Detection, recovery without treatment and successful treatment.** The detection rate was taken to be 0.74/yr in [34] (citing [40]) for drug-sensitive TB, 0.5/yr in [11] for both drug-resistant and drug-sensitive TB. This value was taken to vary within the range 0.5-1.0 per year in [8] and after their numerical analysis, they concluded that the required value should be 0.7/yr in order to interrupt the transmission cycle if a cure rate of 80% is maintained for drug-resistant TB. We are taking this value to be 0.74/yr as in [34] for the drug-sensitive strain and 0.7/yr as in [8] for the drug-resistant strain.

Self-cure of active cases was taken to be 0.2/yr in [11] for both drug-resistant and drug-sensitive TB, 0.25/yr in [34] (citing [15]) for drug-sensitive TB, 0.2/yr in [49] (citing [8]) for multidrug-resistant TB. This value was also taken to lie within the range 0.15-0.25 per year in [8] for drug-resistant TB. We took this value to be 0.25/yr as in [34] for drug-sensitive TB and 0.2/yr as in [8, 11] for drug-resistant TB.

Successful treatment for detected cases was taken to be 85% for drug-sensitive TB and 73% for drug-resistant TB in [11], 80% in [34] (citing [40]) for drug-sensitive TB. The treatment efficacy for drug-resistant TB was considered to 47% in [49]. We take this value to be 80% as in [8, 34] for drug-sensitive TB and 47% as in [49] for drug-resistant TB.

With these chosen values, we get  $b_1 \simeq 0.84/\text{yr}$  and  $b_2 \simeq 0.53/\text{yr}$  as recovery rates for drug-sensitive and drug-resistant TB respectively. These recovery rates are reasonable since recovery results to an individual moving from the active TB state to the latent TB state. Notice that drug-resistant TB has a lower recovery rate since its treatment is known to be difficult. For comparison, Guwatudde *et al.* [13] assumed a cure rate of  $0.5/\text{yr}$  for drug-sensitive TB, Rodrigues *et al.* [39] assumed a treatment rate of  $2/\text{yr}$  for drug-sensitive TB and  $1.5/\text{yr}$  for drug-resistant TB, Ssematimba *et al.* [2] assumed a recovery rate of  $1.5/\text{yr}$  for drug-sensitive TB, castillo-Chavez *et al.* [7] assumed a treatment rate of  $2/\text{yr}$  for drug-sensitive TB and  $1/\text{yr}$  for drug-resistant TB.

The respective tuberculosis detection probabilities are given by

$$\frac{\gamma_1}{\gamma_1 + \beta_1 + m} \simeq 60\% \text{ and } \frac{\gamma_2}{\gamma_2 + \beta_2 + m} \simeq 61\%$$

for strain 1 and strain 2, which are almost the same. The respective average durations of the disease are also given by

$$\frac{1}{b_1 + m} \simeq 0.9 \text{ year and } \frac{1}{b_2 + m} \simeq 1.3 \text{ years}$$

for strain 1 and strain 2, giving a difference of 5 months. This implies that the period of infectiousness of a resistant TB case is on average 5 months longer than that of a sensitive TB case.

### 3.4.2 Simulations of one-strain TB model

The dynamical parameters listed in Table. 3.3 were used to produce the numerical results in each of the three categories as considered in the mathematical analysis (that is, one-strain TB model, two-strain TB model with and without superinfection). It was assumed that  $S_0 = 10,000$  [34] giving a value of  $B = 200/\text{yr}$ . The numerical results of one-strain TB model with the fixed parameters given in Table. 3.3 show that

$$R_1^{TB} \simeq 1.71, R_2^{TB} \simeq 1.28.$$

TABLE. 3.3. The parameter values for the two-strain TB model with superinfection.

Parameter definition		Value	Reference
Birth rate	B	200/yr	[34] (citing [45])
Natural mortality	$\mu$	0.02/yr	[48, 49]
TB mortality	$m$	0.25/yr	[34]
MTB transmission rate	$k_1, k_2$	15/yr, 8/yr	[11], [8]
TB infection -fast progression	$p$	11%	[34]
Reactivation	$a_1, a_2$	0.0003/yr	[8, 34]
	$\sigma_1, \sigma_2$	0.008/yr	Estimated
Reinfection	$q_1, q_2$	$0.25p$	[11, 39]
	$\omega_1, \omega_2$	$0.25p$	[11, 39]
Superinfection	$c$	$0.25p$	[11, 39]
Recovery without treatment	$\beta_1, \beta_2$	0.25/yr, 0.2/yr	[8], [8, 11]
Detection rate	$\gamma_1, \gamma_2$	0.74/yr, 0.7/yr	[34], [8]
Treatment	$\varepsilon_1, \varepsilon_2$	80%, 47%	[8, 34], [49]
Proportion of individuals that are latently infected with TB of strain 2 who progress to active TB of strain 1 after being superinfected with TB of strain 1	$\theta_1$	60%	Estimated
Proportion of individuals that are latently infected with TB of strain 1 who progress to active TB of strain 2 after being superinfected with TB of strain 2	$\theta_2$	60%	Estimated
Proportion of individuals that are actively infected with TB of strain 1 and latently infected with TB of strain 2 that enter state $E_{12}$ after treatment	$\tau_1$	50%	Estimated
Proportion of individuals that are actively infected with TB of strain 2 and latently infected with TB of strain 1 that enter state $E_{12}$ after treatment	$\tau_2$	50%	Estimated

These values are close to 1.3 that was obtained in [34]. Blower *et al.* [46] developed a model of the same dynamics and obtained a value which lies in the range 0.74-18.58 with a median of 4.47, mean of 5.26 and standard deviation of 2.82. We first simulated system (3.5) starting from the initial condition

$$S(t_0) = S^*, E_1(t_0) = E_1^*, I_1(t_0) = I_1^*,$$



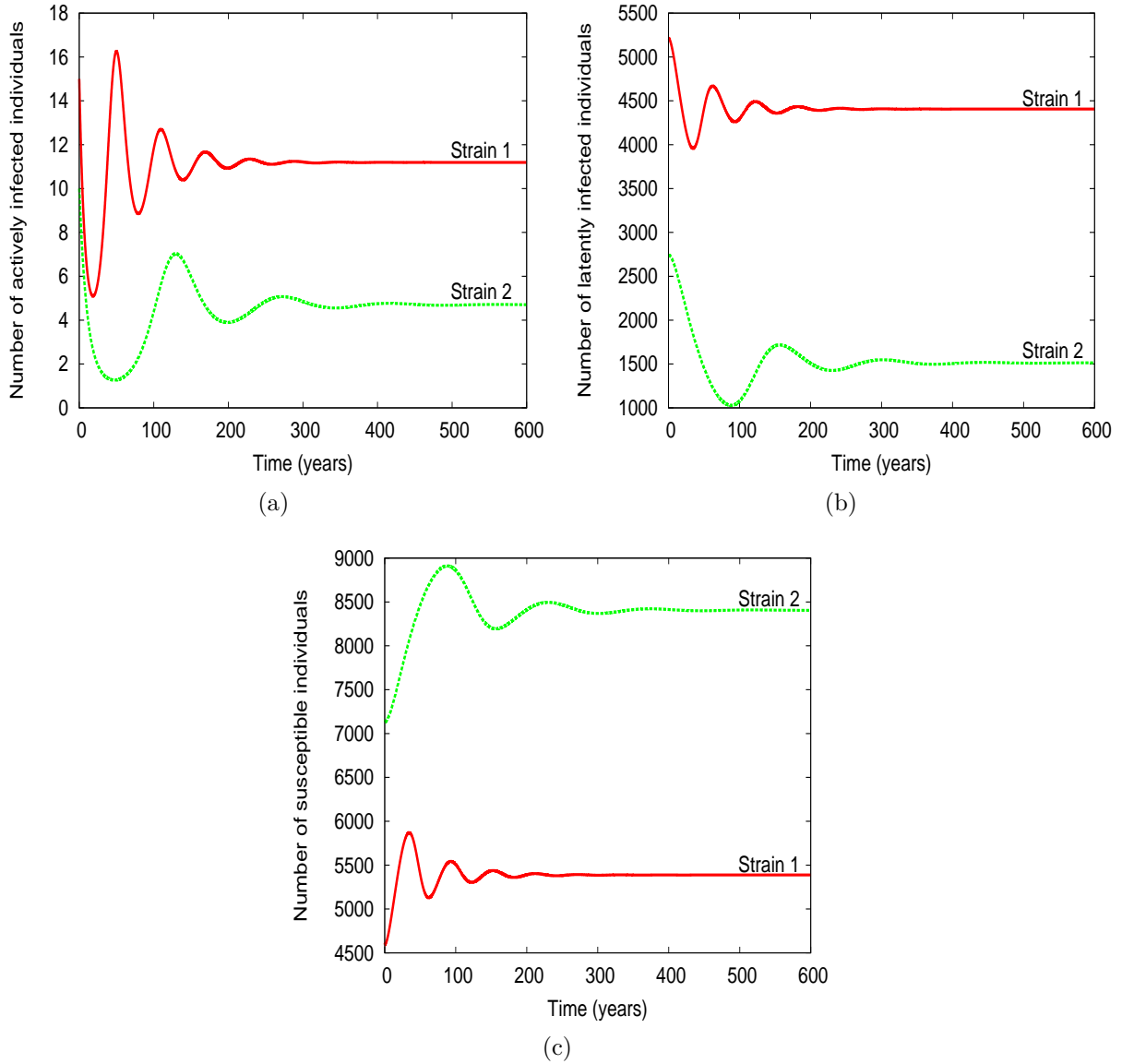


FIG. 3.3. The individual population size of each class. Actively infected (a), latently infected (b) and susceptible (c). Parameter values are given in Table 3.3.

where  $S^*, E_1^*, I_1^*$  are the endemic steady states of the one-strain TB model which can be obtained from equations (3.12) and (3.17). The simulations were run up to a point when a steady state was obtained. Fig. 3.3 shows the individual population size of the susceptible, latently infected and the infected classes. Due to the fact that strain 1 has a higher reproduction number (that is,  $R_1^{TB} > R_2^{TB}$ ), it can be noticed that the size of infected individuals of strain 1 is higher than that of strain 2. Fig. 3.4 shows the simulation

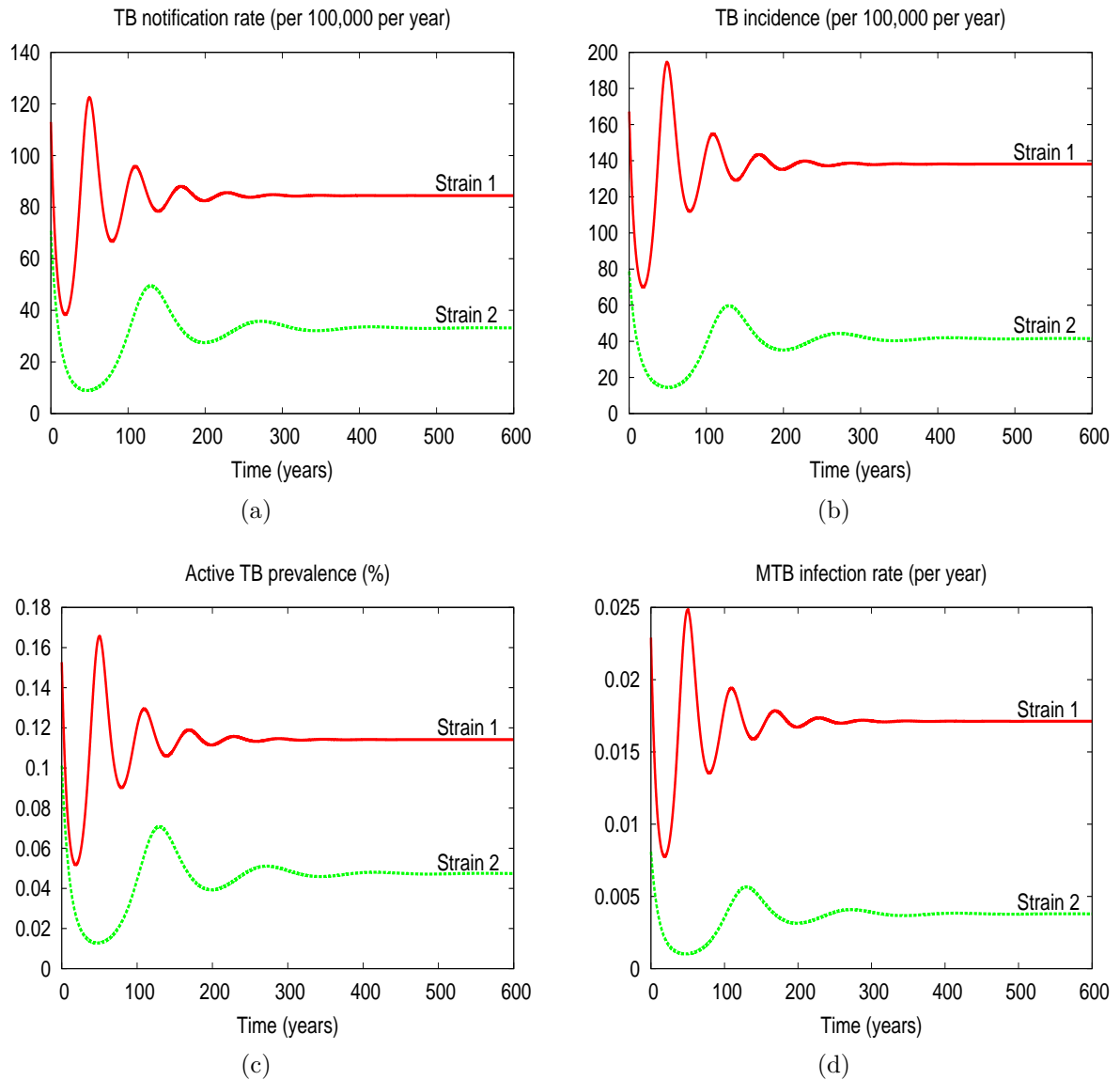


FIG. 3.4. The simulation curves for the TB notification rate (a), TB incidence rate (b), TB prevalence (c) and MTB infection rate (d) of the one-strain TB model. Parameter values are given in Table 3.3.

curves for the TB notification rate, TB incidence rate, TB prevalence and MTB infection rate against time in years. It was also observed that strain 1 has higher rates since its reproduction number is greater than that of strain 2. The steady state values of strain 1 were used as the initial conditions in the simulation of the two-strain TB model with and without superinfection. Table. 3.4 shows the characteristics of the endemic steady state of the one-strain TB model.

### 3.4.3 Simulations of two-strain TB model with and without superinfection

The numerical results of the two cases (that is, the two-strain TB model and with and without superinfection) with the fixed parameters given in Table. 3.3 and  $\tau_1 = \tau_2 = 0.5$  show that

$$R_0^{TB} \simeq 1.71, R_{0_s}^{TB}(\tau_1, 0) \simeq 1.86, R_{0_s}^{TB}(0, \tau_2) \simeq 1.23, R_{0_s}^{TB}(\tau_1, \tau_2) \simeq 1.91.$$

These values are in the same range as the ones obtained in [7] in their two-strain TB model, which are in the range 1.34-4.13.

We also present the simulation curves of the two cases (that is, the two strain TB model with and without superinfection). These two cases are represented by system (3.1) and (3.22) respectively. Our aim is to evaluate the impact of superinfection on the transmission of tuberculosis. The initial conditions for susceptible, latently infected and actively infected individuals of the drug-sensitive strain were taken to be the same as the steady state values of the one-strain TB model which are give in Table. 3.4. We introduce two individuals infected with a drug-resistant strain into a population where the the sensitive strains have reached a steady state. We assume that one individual is harbouring a latent infection and the other is actively infected. We assume that 60% of those superinfected progress to active TB of the incoming strain soon after superinfection and the other 40% remain latently infected with two strains of TB. We also assume that the proportion of individuals who move to state  $E_{12}$  from  $I_1$  and  $I_2$  after treatment are the same and equal to 50% (that is,  $\tau_1 = \tau_2 = 0.5$ ).

### 3.4.4 The impact of superinfection on tuberculosis

Fig. 3.5 shows the simulation curves for the TB notification rate (a), TB incidence (b), TB prevalence (c) and MTB infection rate (d) against time in years for the two cases considered here. The results show that superinfection has a greater impact on tuberculosis which increases with time. Comparing the results of the two-strain TB model with and without superinfection, we find that there is an increase of 12.5%, 31.3%, 43.8% and 50% in 10, 20,

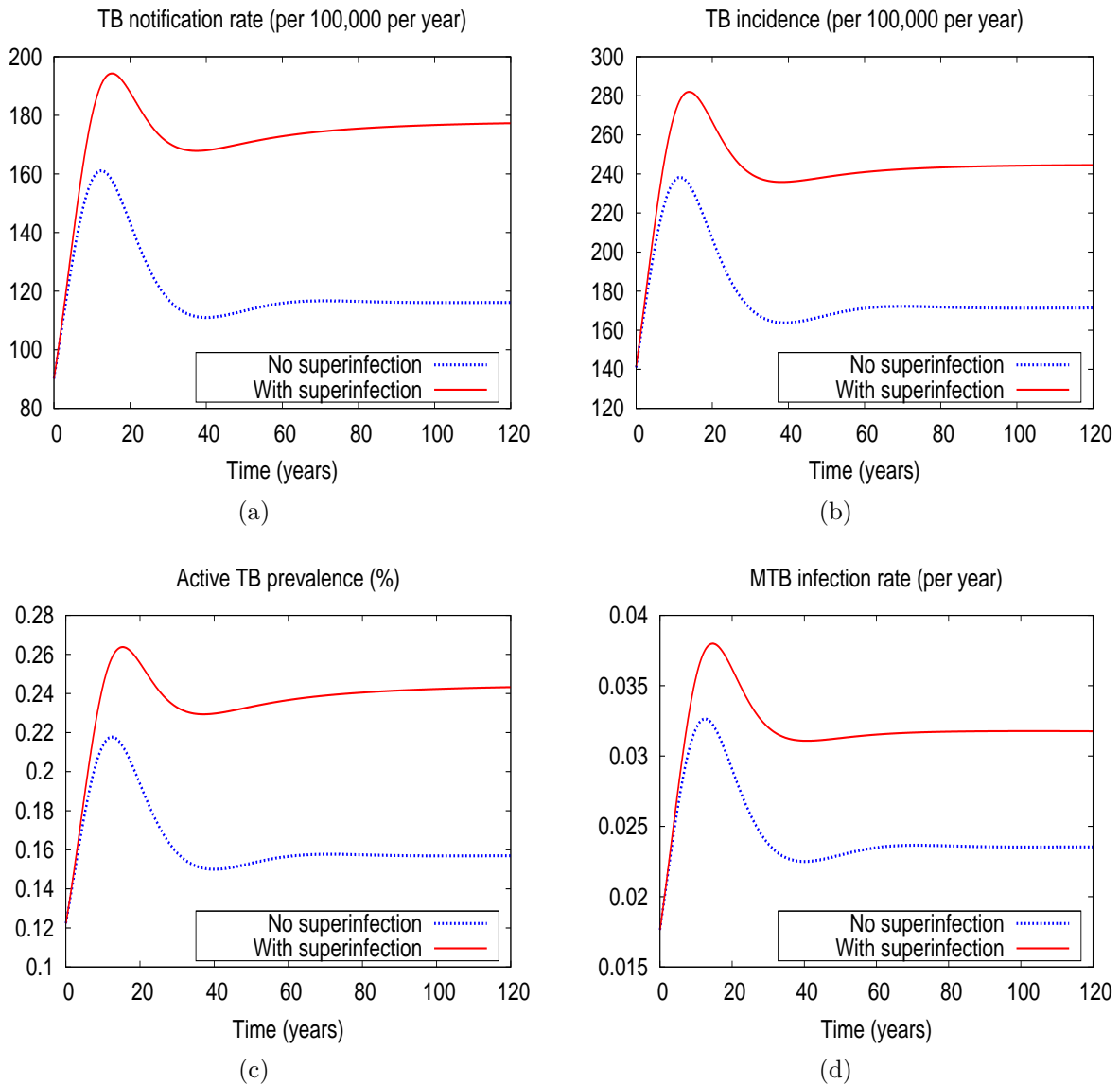


FIG. 3.5. The impact of superinfection on tuberculosis. The graph of TB notification rate (a), TB incidence rate (b), TB prevalence (c) and MTB infection rate (d) of system (3.1) and (3.22). Parameter values are given in Table 3.3.

50 and 100 years respectively in the TB prevalence. An increase of 16.5%, 31.6%, 39.2% and 42.7% in 10, 20, 50 and 100 years respectively in the TB incidence was also noted. Fig. 3.6 shows the percentage of active cases that arise due to superinfection. It was found that 0.46%, 0.94%, 2.1% and 3.0% of the active cases are due to superinfection in 10, 20, 50 and 100 years respectively. Fig. 3.7 shows the effect of strain coexistence. It was also established that resistant strains were unable to emerge in the absence of superinfection. Progression to

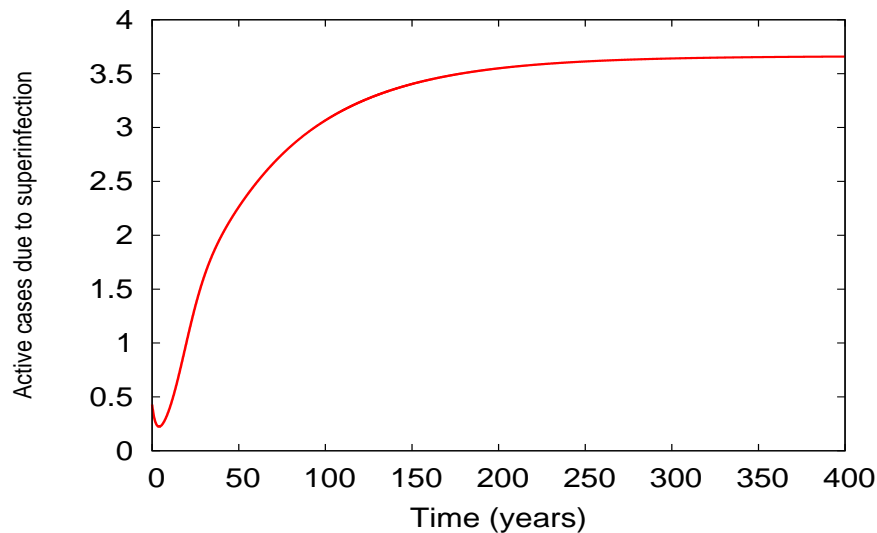


FIG. 3.6. The proportion of active cases due to superinfection. Parameter values are given in Table 3.3.

active TB of strain 2 only or either strains after superinfection leads to strain coexistence. A similar result was obtained in [39] where coexistence of strains was found to be possible after putting superinfection by resistant strains into consideration. Castillo-Chavez and

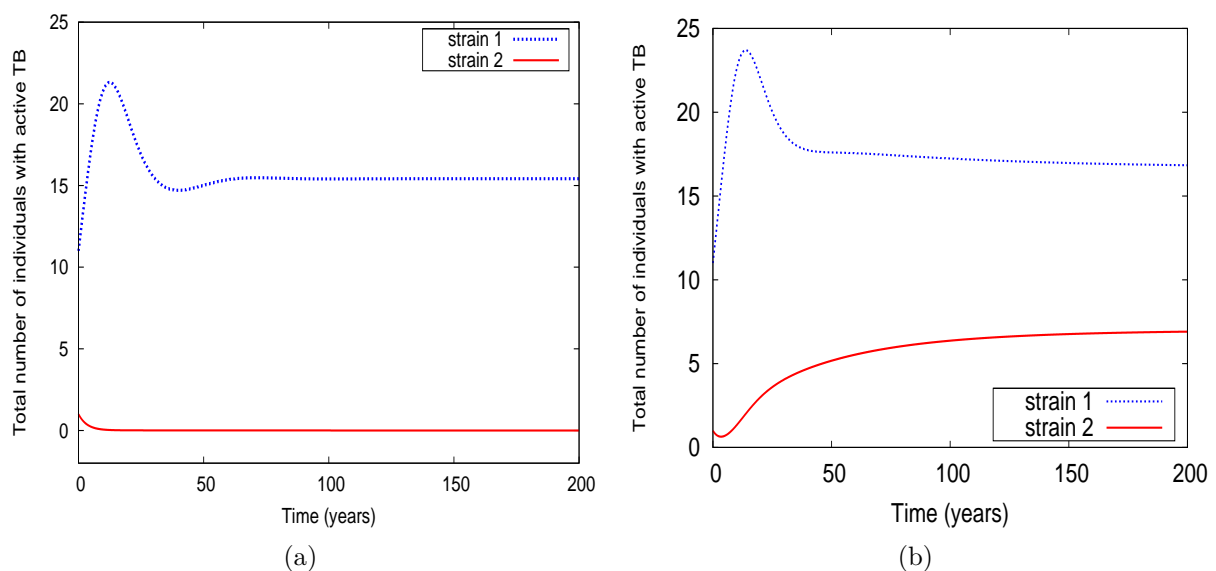


FIG. 3.7. Coexistence of strains. The effect of strain coexistence in the absence (a), and presence (b) of superinfection of the two-strain TB model. Parameter values are given in Table 3.3.

Feng [7] also found that strain coexistence was promoted by drug-resistance after adding superinfection in their model. They also found that strain coexistence was possible without superinfection if the resistant strains are due to antibiotic resistance (acquired resistance).

TABLE. 3.4. The characteristics of the endemic steady state of the one-strain TB model and two-strain TB model.

	One-strain TB model		Two-strain TB model	
	Strain 1	Strain 2	No super-infection	With super-infection
Total population $P$	9,805	9,923	9,823	9,727
Susceptible $S$	5,388	8,406	4,593	3,880
Latent TB $E_1$	4,406	-	5,214	4,539
$E_2$	-	1,512	0	1,028
$E_{12}$	-	-	-	257
Active TB $I_1$	11	-	15	17
$I_2$	-	5	0	7
TB notification rate (per 100,000/yr)	85	33	116	178
MTB prevalence	45.0%	15.3%	53.0%	60.0%
TB prevalence	0.11%	0.047%	0.16%	0.24%
MTB infection rate (per year)	0.017	0.0038	0.024	0.032
TB incidence rate (per 100,000/yr)	138	42	171	244
“Syblo’s ratio”	81	109	73	77
Reactivation	9.8%	11.0%	9.3%	24.3%
Reinfection	15.3%	3.8%	20.0%	15.2%
Superinfection	-	-	-	3.7%
Primary progression	74.9%	85.2%	70.7%	56.8%

### 3.5 TB control measures

The fight against TB has been prevention of TB reactivation by the use of isoniazid preventive therapy (IPT) and treatment of the identified (detected) active TB cases. We endeavour to study the effectiveness of the control measures and how they can change the course of tuberculosis in the presence of superinfection. We are also interested in the extent to which the control measures should be applied if we are to eliminate the epidemic. We apply the control measures on the two-strain TB model with superinfection only which is given by system (3.1).

### 3.5.1 Isoniazid preventive therapy (IPT)

Isoniazid preventive therapy is a widely used control measure for preventing individuals with latent TB from progressing to active TB. This control measure reduces the reactivation rate of both strains if applied. In our model, the reactivation rate is taken to be the same for both strains. Applying this control measure will decrease the reactivation rate of both strains at the same rate. Fig. 3.8 shows the effect of a sudden decrease in the reactivation rate of both strains. The results show that decreasing the reactivation rate of all individuals latently infected with TB by 50% and 75% leads a 29.2% and 50% reduction in the TB prevalence respectively in 10 years. Continuing with the intervention leads to a 34.8% and 56.2% reduction in the TB prevalence if the reactivation rate is decreased by 50% and 75% respectively in 20 years.

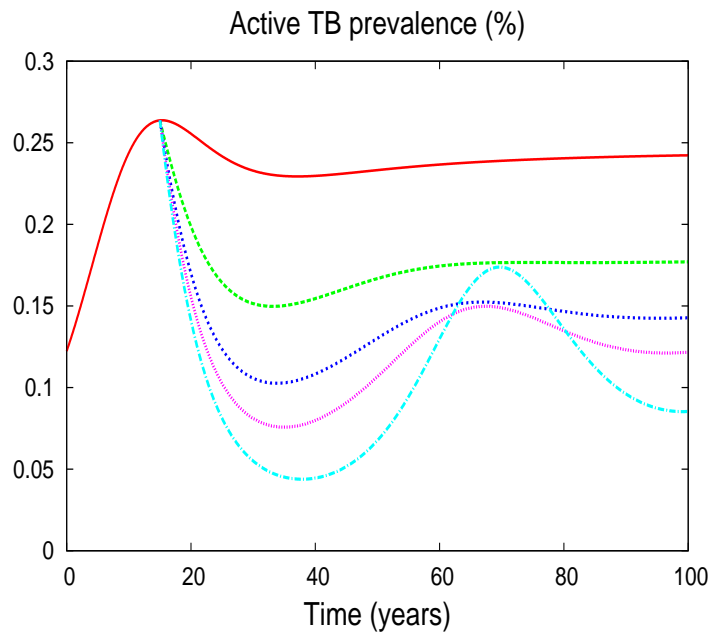


FIG. 3.8. Isoniazid preventive therapy. Assumption: treatment starting 15 years after the introduction of drug-resistant TB. The graph of TB prevalence against time. The parameter  $a_1$  is replaced by  $a_1, a_1/2, a_1/4, a_1/8, 0$ , the parameter  $a_2$  by  $a_2, a_2/2, a_2/4, a_2/8, 0$ , the parameter  $\sigma_1$  by  $\sigma_1, \sigma_1/2, \sigma_1/4, \sigma_1/8, 0$  and the parameter  $\sigma_2$  by  $\sigma_2, \sigma_2/2, \sigma_2/4, \sigma_2/8, 0$  from top to bottom. Parameter values are given in Table 3.3.

### 3.5.2 Increased TB detection

The recovery rates  $b_1$  and  $b_2$  for strain 1 and strain 2 are given as functions of their respective detection rates  $\gamma_1$  and  $\gamma_2$  (that is,  $b_1 = \beta_1 + \gamma_1 \varepsilon_1$  and  $b_2 = \beta_2 + \gamma_2 \varepsilon_2$ ). Thus, increased TB detection increases the recovery rates  $b_1$  and  $b_2$  for strain 1 and strain 2 respectively. Fig. 3.9 shows the effect of a sudden increase in the TB detection rate. We are considering two cases. The first case looks at the sudden increase in the detection rate of resistant strains keeping that of sensitive strains constant (Fig. 3.9 (a)). The results of this case show that there is no change in the TB incidence as the detection rate of resistant strains is increased. This is due to the fact that the incidence of resistant strains is significantly lower than that of sensitive strains. The second case looks at a sudden

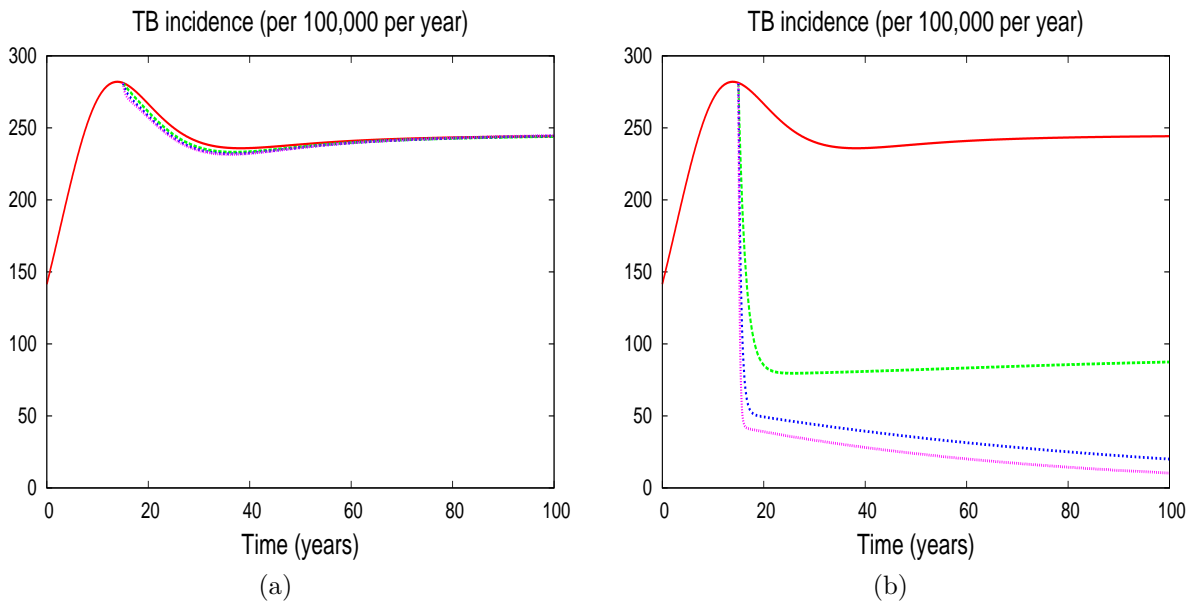


FIG. 3.9. Increased TB detection. Assumption: treatment starting 15 years after the introduction of drug-resistant TB. The graph of TB incidence against time for two cases (increased detection rate for resistant strain only (a) and both strains (b)). The detection parameter  $\gamma_2$  is replaced by  $\gamma_2, 2\gamma_2, 4\gamma_2, 8\gamma_2$  from top to bottom (a), and the parameters  $\gamma_1$  and  $\gamma_2$  by  $\gamma_1, 2\gamma_1, 4\gamma_1, 8\gamma_1$  and  $\gamma_2, 2\gamma_2, 4\gamma_2, 8\gamma_2$  respectively from top to bottom (b). Parameter values are given in Table 3.3.

increase in the detection rate of both strains (Fig. 3.9 (b)). The results show that there is a higher decrease in the TB incidence rate as the detection rate increases. Increasing the detection rate of all individuals infected with active TB by 50% and 75% leads to 68.0%



and 81.2% reduction in the TB incidence respectively in 10 years. A remarkable decrease in the TB incidence is obtained when the detection rate of both strains is increased by 75% or more. Thus, a balanced intervention for both strains is required if one is to eliminate the TB epidemic.

### 3.6 Summary

In this chapter we studied qualitatively and quantitatively a six-dimensional deterministic model for the transmission dynamics of tuberculosis by considering two strains of MTB (that is, drug-sensitive and drug-resistant strains). The model was formulated to evaluate the impact of superinfection on the tuberculosis epidemic. We first analysed the model with only one strain (one-strain TB model) and one endemic equilibrium point was obtained whenever  $R_1^{TB} > 1$ . By using the center manifold theorem, it was found that the unique endemic equilibrium point is locally asymptotically stable for  $R_1^{TB}$  near 1. It was also established that whenever  $R_1^{TB} \leq 1$ , the disease-free equilibrium point is globally asymptotically stable and unstable otherwise. These results have serious implications towards the elimination of the disease.

The basic reproduction number,  $R_0^{TB}$  of the two-strain TB model without superinfection was obtained and the disease-free equilibrium point was established to be locally asymptotically stable whenever  $R_0^{TB}$  is less than 1 and unstable otherwise. The basic reproduction numbers of the two-strain TB model with superinfection were obtained by first assuming that most individuals progress to either strain 1 only or strain 2 only after superinfection. Two reproduction numbers were obtained for each case in the first analysis. We later obtained a third reproduction number by assuming that individuals can progress to either strain after superinfection depending on the fitness of the strain. We found that the three reproduction numbers increase with an increase in the proportion of individuals that progress to active TB of any strain after superinfection. We also noted that if most individuals progress to active tuberculosis of strain 1, then the epidemic may grow faster than when most individuals progress to active TB of strain 2 after superinfection. This was due to the fact that the transmission rate of sensitive strains was taken to be higher than that of resistant strains. Considering progression to active TB of strain 2 or either

strain after superinfection was found to lead to strain coexistence.

Numerical simulations of the model were carried out to evaluate the impact of superinfection on the transmission of tuberculosis. We established that the impact of superinfection on tuberculosis is high as the TB notification rate and TB incidence increased by about 51.7% and 42.7% respectively in 100 years. It was estimated that 3.0% of active cases were due to superinfection in 100 years.

The impact of Increased TB detection and Isoniazid preventive therapy (IPT) on the epidemic was studied. We observed that increasing the detection rate of both strains could change the course of tuberculosis and hence eliminate the epidemic if high detection rates of both strains are achieved. IPT reduces the TB prevalence but its impact on TB largely depends on the rate at which latently infected individuals can be identified for treatment since they do not show symptoms.

# Chapter 4

## HIV-TB coinfection model

### 4.1 Introduction

In this chapter, we extend the model given in chapter 3 to include HIV. The model still comprises of two strains of TB (drug-sensitive and drug-resistant TB) and also incorporates in superinfection of tuberculosis. We focus on the evaluation of the impact of superinfection on both the prevalence of TB and HIV in a setting where the prevalence of HIV and TB are already known to be high, as the case in sub-Saharan Africa. We will also focus on the control measures and evaluate the effect of superinfection on these control measures. We are also interested in knowing which of the control measures is most effective in the presence of superinfection. Note that we are considering TB superinfection and not HIV superinfection. A case where both TB superinfection and HIV superinfection are considered is left for future research.

### 4.2 Model development

The model consists of twelve compartments, six for HIV-negative and the other six for HIV-positive individuals. The negative superscript refers to HIV-negative individuals and the positive superscript refers to HIV-positive individuals. All the variables and parameters written with a negative superscript have the same meaning as those used in the two-strain TB model in chapter 3. Again, the subscripts 1 and 2 refer to the sensitive and resistant

strains respectively. The transmission dynamics of TB are exactly the same as the ones discussed in the previous chapter. We assume that an individual can be infected with HIV irrespective of one's tuberculosis status. To reduce on the number of compartments we do not distinguish the routes of HIV transmission like sexual transmission, blood transfusion and mother to child transmission. We do not consider sex and age at which an individual gets the infection into consideration. We also do not consider the stages of HIV. The transmission rate for HIV is taken to be proportional to the prevalence of individuals with HIV. We take a reduced transmission rate which is given by  $g(H)$ , where

$$g(H) = de^{-\lambda H}, \quad (4.1)$$

$d$  is the maximum HIV transmission rate,  $\lambda$  is the parameter representing behaviour change (through counselling, awareness programmes and others) and  $H$  is the HIV prevalence. The term,  $e^{-\lambda H}$  is meant to reduce the transmission rate as people get to know the dangers of contracting HIV and decide to change their sexual behaviour. The reduced HIV transmission rate function,  $g(H)$  can also be interpreted in this way; when  $H$  is small, the transmission rate is high as the number of susceptible individuals will be high and as  $H$  increases, the transmission rate goes down because infectives run out of potential susceptibles. Generally,  $g(H)$  is a decreasing function of  $H$  as shown in Fig. 4.1.

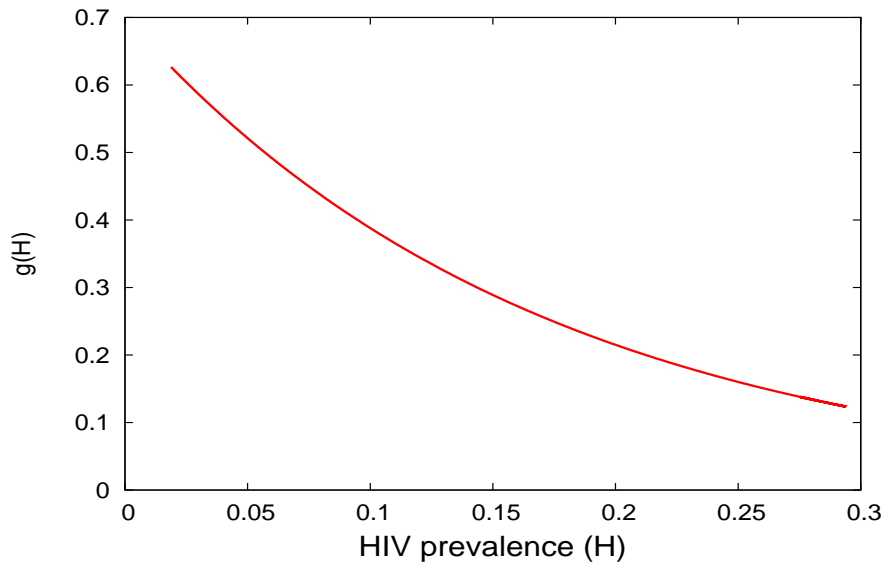


FIG. 4.1. The relationship between the reduced transmission rate,  $g(H)$  and HIV prevalence,  $H$ .

The nonlinear function  $g(H)$  has already been used by Bacaër *et al.* [34] and Williams *et al.* [5]. Fig. 4.2 gives a schematic representation of the HIV-TB coinfection model and Table. 4.1 gives the similarity between the medical vocabulary and the model.

The model for the transmission of HIV and TB is given by the following system of differential equations:

$$\left. \begin{aligned}
 \frac{dS^-}{dt} &= B - S^-(i_1 + i_2) - \mu^- S^- - g(H)HS^-, \\
 \frac{dE_1^-}{dt} &= [(1 - p^-)S^- - q_1^- E_1^-]i_1 - (a_1^- + \mu^- + c^- i_2)E_1^- + (1 - \tau_1^-)b_1^- I_1^- - g(H)HE_1^-, \\
 \frac{dE_2^-}{dt} &= [(1 - p^-)S^- - q_2^- E_2^-]i_2 - (a_2^- + \mu^- + c^- i_1)E_2^- + (1 - \tau_2^-)b_2^- I_2^- - g(H)HE_2^-, \\
 \frac{dE_{12}^-}{dt} &= (1 - \theta_1^-)c^- E_2^- i_1 + (1 - \theta_2^-)c^- E_1^- i_2 - (\omega_1^- i_1 + \omega_2^- i_2 + \sigma_1^- + \sigma_2^- + \mu^-)E_{12}^- \\
 &\quad + \tau_1^- b_1^- I_1^- + \tau_2^- b_2^- I_2^- - g(H)HE_{12}^-, \\
 \frac{dI_1^-}{dt} &= (p^- S^- + q_1^- E_1^- + \theta_1^- c^- E_2^- + \omega_1^- E_{12}^-)i_1 + a_1^- E_1^- + \sigma_1^- E_{12}^- - (b_1^- + m^-)I_1^- - g(H)HI_1^-, \\
 \frac{dI_2^-}{dt} &= (p^- S^- + q_2^- E_2^- + \theta_2^- c^- E_1^- + \omega_2^- E_{12}^-)i_2 + a_2^- E_2^- + \sigma_2^- E_{12}^- - (b_2^- + m^-)I_2^- - g(H)HI_2^-, \\
 \frac{dS^+}{dt} &= -S^+(i_1 + i_2) - \mu^+ S^+ + g(H)HS^-, \\
 \frac{dE_1^+}{dt} &= [(1 - p^+)S^+ - q_1^+ E_1^+]i_1 - (a_1^+ + \mu^+ + c^+ i_2)E_1^+ + (1 - \tau_1^+)b_1^+ I_1^+ + g(H)HE_1^-, \\
 \frac{dE_2^+}{dt} &= [(1 - p^+)S^+ - q_2^+ E_2^+]i_2 - (a_2^+ + \mu^+ + c^+ i_1)E_2^+ + (1 - \tau_2^+)b_2^+ I_2^+ + g(H)HE_2^-, \\
 \frac{dE_{12}^+}{dt} &= (1 - \theta_1^+)c^+ E_2^+ i_1 + (1 - \theta_2^+)c^+ E_1^+ i_2 - (\omega_1^+ i_1 + \omega_2^+ i_2 + \sigma_1^+ + \sigma_2^+ + \mu^+)E_{12}^+ \\
 &\quad + \tau_1^+ b_1^+ I_1^+ + \tau_2^+ b_2^+ I_2^+ + g(H)HE_{12}^-, \\
 \frac{dI_1^+}{dt} &= (p^+ S^+ + q_1^+ E_1^+ + \theta_1^+ c^+ E_2^+ + \omega_1^+ E_{12}^+)i_1 + a_1^+ E_1^+ + \sigma_1^+ E_{12}^+ - (b_1^+ + m^+)I_1^+ + g(H)HI_1^-, \\
 \frac{dI_2^+}{dt} &= (p^+ S^+ + q_2^+ E_2^+ + \theta_2^+ c^+ E_1^+ + \omega_2^+ E_{12}^+)i_2 + a_2^+ E_2^+ + \sigma_2^+ E_{12}^+ - (b_2^+ + m^+)I_2^+ + g(H)HI_2^-,
 \end{aligned} \right\} \quad (4.2)$$

where  $i_1 = (k_1^- I_1^- + k_1^+ I_1^+)/P_1$  and  $i_2 = (k_2^- I_2^- + k_2^+ I_2^+)/P_1$  are the MTB infection rates for strain 1 and 2 respectively.  $P_1$  is the total population which is given by

$$P_1 = S^- + E_1^- + E_2^- + E_{12}^- + I_1^- + I_2^- + S^+ + E_1^+ + E_2^+ + E_{12}^+ + I_1^+ + I_2^+$$

and  $H$  is the HIV prevalence which is also given by

$$H = (S^+ + E_1^+ + E_2^+ + E_{12}^+ + I_1^+ + I_2^+)/P_1.$$

All the parameters and variables are taken to be positive and the model lies within the feasible region

$$W_2 = \left\{ (S^-, E_1^-, E_2^-, E_{12}^-, I_1^-, I_2^-, S^+, E_1^+, E_2^+, E_{12}^+, I_1^+, I_2^+) \in \mathbb{R}_+^{12} : P_1 \leq \frac{B}{\mu} \right\}$$

which is positively invariant with respect to system (4.2).

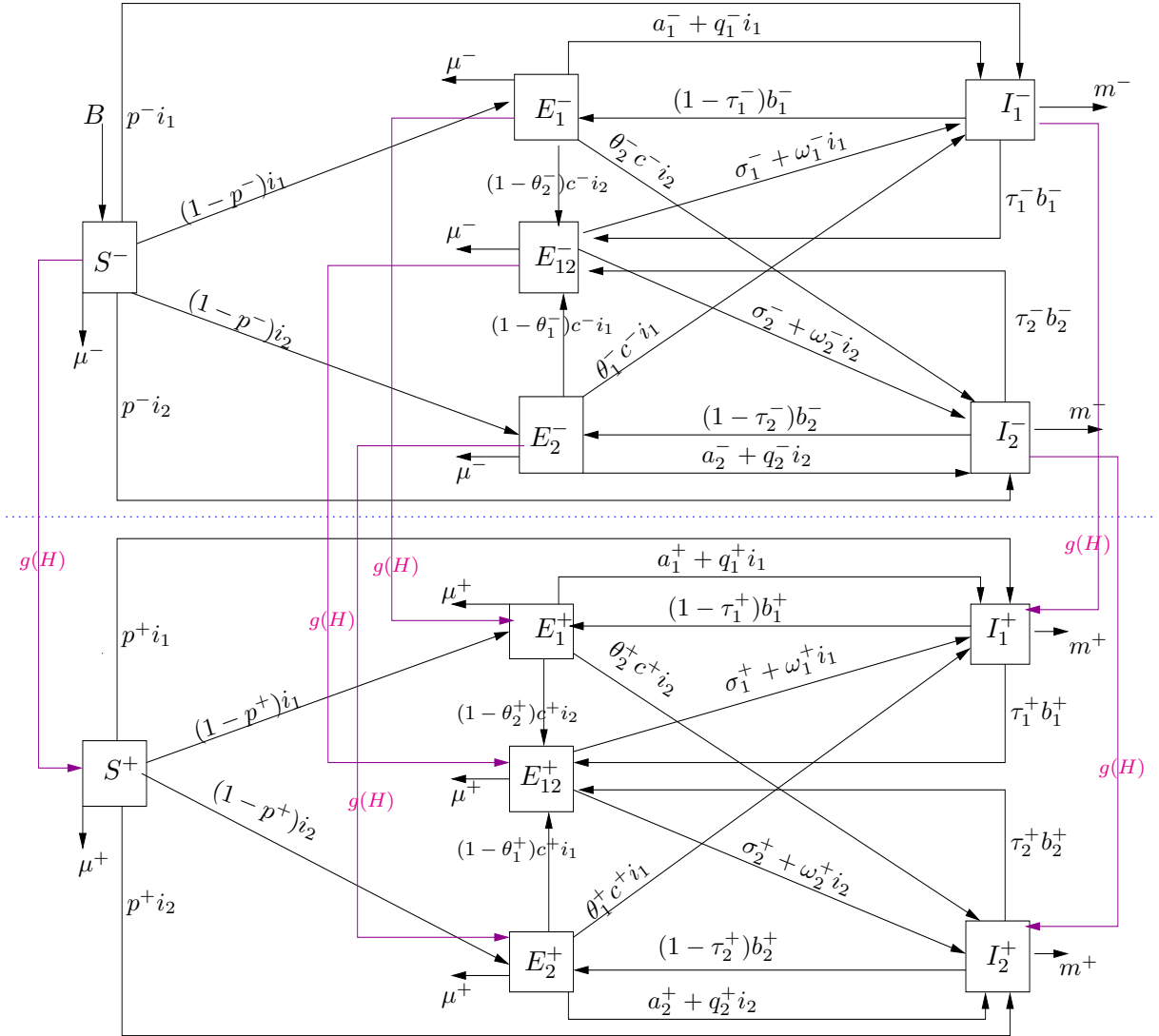


FIG. 4.2. A schematic diagram showing the overall structure and the flows between the different states of the HIV-TB coinfection model.

TABLE. 4.1. Similarity between the medical vocabulary and the HIV-TB coinfection model. Adopted from [34].

Total population	$P_1 = S^- + E_1^- + E_2^- + E_{12}^- + I_1^- + I_2^- + S^+ + E_1^+ + E_2^+ + E_{12}^+ + I_1^+ + I_2^+$
TB notification rate	$(\gamma_1^- I_1^- + \gamma_2^- I_2^- + \gamma_1^+ I_1^+ + \gamma_2^+ I_2^+)/P_1$
MTB prevalence	$(E_1^- + E_2^- + E_{12}^- + I_1^- + I_2^- + E_1^+ + E_2^+ + E_{12}^+ + I_1^+ + I_2^+)/P_1$
TB prevalence	$(I_1^- + I_2^- + I_1^+ + I_2^+)/P_1$
MTB infection rate	$\{k_1^- (I_1^- + I_2^-) + k_2^+ (I_1^+ + I_2^+)\} / P_1$
TB cases	$T = a_1^- E_1^- + a_2^- E_2^- + a_1^+ E_1^+ + a_2^+ E_2^+ + (\sigma_1^- + \sigma_2^-) E_{12}^- + (\sigma_1^+ + \sigma_2^+) E_{12}^+ + \{(p^- S^- + q_1^- E_1^- + \theta_1^- c^- E_2^- + \omega_1^- E_{12}^-)(k_1^- I_1^- + k_1^+ I_1^+) + (p^- S^- + q_2^- E_2^- + \theta_2^- c^- E_1^- + \omega_2^- E_{12}^-)(k_2^- I_2^- + k_2^+ I_2^+) + (p^+ S^+ + q_1^+ E_1^+ + \theta_1^+ c^+ E_2^+ + \omega_1^+ E_{12}^+)(k_1^- I_1^- + k_1^+ I_1^+) + (p^+ S^+ + q_2^+ E_2^+ + \theta_2^+ c^+ E_1^+ + \omega_2^+ E_{12}^+)(k_2^- I_2^- + k_2^+ I_2^+)\} / P_1$
TB incidence rate	$T/P_1$
“Styblo’s ratio”	$1,000 \times (\text{TB incidence rate}) / (\text{MTB infection rate})$
Reactivation	$\{a_1^- E_1^- + a_2^- E_2^- + a_1^+ E_1^+ + a_2^+ E_2^+ + (\sigma_1^- + \sigma_2^-) E_{12}^- + (\sigma_1^+ + \sigma_2^+) E_{12}^+\} / T$
Reinfection	$\{(q_1^- E_1^- + q_1^+ E_1^+ + \omega_1^- E_{12}^- + \omega_1^+ E_{12}^+)(k_1^- I_1^- + k_1^+ I_1^+) + (q_2^- E_2^- + q_2^+ E_2^+ + \omega_2^- E_{12}^- + \omega_2^+ E_{12}^+)(k_2^- I_2^- + k_2^+ I_2^+)\} / T / P_1$
Superinfection	$\{(\theta_1^- c^- E_2^- + \theta_1^+ c^+ E_2^+)(k_1^- I_1^- + k_1^+ I_1^+) + (\theta_2^- c^- E_1^- + \theta_2^+ c^+ E_1^+)(k_2^- I_2^- + k_2^+ I_2^+)\} / T / P_1$
Primary disease	$\{(p^- S^- + p^+ S^+)((k_1^- I_1^- + k_1^+ I_1^+) + (k_2^- I_2^- + k_2^+ I_2^+))\} / T / P_1$

### 4.3 Mathematical analysis

The mathematical analysis of the TB-only model was discussed in chapter 3 section 3.3. In this section we give the mathematical analysis of the HIV-only model. The analysis of the HIV-TB model is done using numerical simulations.

#### 4.3.1 Analysis of the HIV-only model

The model with HIV-only (obtained by setting

$$E_1^- = E_2^- = E_{12}^- = I_1^- = I_2^- = E_1^+ = E_2^+ = E_{12}^+ = I_1^+ = I_2^+ = 0$$

in system (4.2)) is given by

$$\left. \begin{aligned} \frac{dS^-}{dt} &= B - \mu^- S^- - g(H)HS^-, \\ \frac{dS^+}{dt} &= -\mu^+ S^+ + g(H)HS^-, \end{aligned} \right\} \quad (4.3)$$

where the HIV prevalence  $H$  is now given by  $H = \frac{S^+}{(S^- + S^+)}$ . The total population is also given by  $P_2 = S^- + S^+$ . The above system of equations given in (4.3) are the same as the ones considered by Bacaër *et al.* [34] for HIV only.

The disease-free equilibrium of system (4.3) is given by  $X_2 = (S_0, 0) = (\frac{B}{\mu^-}, 0)$ . Linearising the second equation of (4.3) near the disease-free equilibrium  $S^- = S_0$  and  $S^+ = 0$  gives

$$\begin{aligned} \frac{dS^+}{dt} &= -\mu^+ S^+ + g(H) \frac{S^+ S_0}{(S_0 + S^+)}, \\ &\simeq -\mu^+ S^+ + g(0) S^+, \\ &= (g(0) - \mu^+) S^+ \end{aligned}$$

From the above, its clear that the basic reproduction number for the HIV-only model is given by

$$R_0^{HIV} = \frac{g(0)}{\mu^+}.$$

This number is given by the product of the transmission coefficient  $g(0)$ , at the disease free-equilibrium and the average residence time  $\frac{1}{\mu^+}$  in the infectious class of an HIV infected individual.

Since,  $g(H) = de^{-\lambda H}$ , it implies that  $g(0) = d$ . Therefore,

$$R_0^{HIV} = \frac{d}{\mu^+}, \tag{4.4}$$

and thus we have the following result.

**Theorem 4.3.1** *If  $R_0^{HIV} < 1$ , the disease-free equilibrium point  $X_2$  is locally asymptotically stable and unstable if  $R_0^{HIV} > 1$ .*

### The endemic steady states of the HIV-only model

Let the endemic steady state be given by  $\varepsilon^* = (S^{-*}, S^{+*})$ , with  $H^* = \frac{S^{+*}}{(S^{-*} + S^{+*})}$ . We solve for the endemic equilibrium points by setting the right-hand sides of system (4.3) to



zero and the system takes the form

$$B - \mu^- S^{-*} - g(H^*)H^*S^{-*} = 0, \quad (4.5)$$

$$-\mu^+ S^{+*} + g(H^*)H^*S^{-*} = 0. \quad (4.6)$$

From  $H^* = S^{+*}/(S^{-*} + S^{+*})$ , we have

$$\begin{aligned} H^*S^{-*} + H^*S^{+*} &= S^{+*}, \\ \Rightarrow S^{-*} &= \frac{(1 - H^*)}{H^*}S^{+*}. \end{aligned}$$

Substituting for  $S^{-*}$  in equation (4.6), we have

$$\begin{aligned} -\mu^+ S^{+*} + g(H^*)H^* \frac{(1 - H^*)}{H^*} S^{+*} &= 0, \\ -S^{+*}[\mu^+ - g(H^*)(1 - H^*)] &= 0. \end{aligned}$$

This equation has solutions,  $S^{+*} = 0$  and  $\mu^+ - g(H^*)(1 - H^*) = 0$ . The case  $S^{+*} = 0$  corresponds to the disease-free equilibrium  $X_2$ .

Thus,

$$\mu^+ = g(H^*)(1 - H^*), \quad (4.7)$$

or

$$g(H^*) = \frac{\mu^+}{(1 - H^*)}. \quad (4.8)$$

Solving equation (4.5) for  $S^{-*}$ , we get

$$\begin{aligned} S^{-*} &= \frac{B}{\mu^- + g(H^*)H^*}, \\ &= \frac{B}{\mu^- + \frac{\mu^+}{(1 - H^*)}H^*}, \\ &= \frac{B(1 - H^*)}{\mu^-(1 - H^*) + \mu^+H^*}. \end{aligned}$$

Also, solving equation (4.6) for  $S^{+*}$ , we get

$$\begin{aligned} S^{+*} &= \frac{g(H^*)H^*S^{-*}}{\mu^+}, \\ &= \frac{\frac{\mu^+}{(1-H^*)} \frac{H^*B(1-H^*)}{(\mu^-(1-H^*)+\mu^+H^*)}}{\mu^+}, \\ &= \frac{BH^*}{\mu^-(1-H^*)+\mu^+H^*}. \end{aligned}$$

Thus, the endemic steady states for the HIV-only model are given by

$$S^{-*} = \frac{B(1-H^*)}{\mu^-(1-H^*)+\mu^+H^*} \quad (4.9)$$

and

$$S^{+*} = \frac{BH^*}{\mu^-(1-H^*)+\mu^+H^*}. \quad (4.10)$$

We thus have the following Theorem on the existence of the endemic steady states.

**Theorem 4.3.2** *The endemic steady state  $\varepsilon^*$  exists for  $0 \leq H^* \leq 1$ . If  $H^* = 0$ , then the endemic state collapses to the disease-free equilibrium. If  $H^* = 1$ , then  $S^{-*} = 0$ , implying that everybody is infected.*

## 4.4 Numerical Simulations

### 4.4.1 Parameter estimation

The estimation of all the TB related parameters was discussed fully in chapter 3 section 3.4.1 and we use the same parameter values for HIV-negative individuals. In this section we give a discussion of how the HIV-TB related parameters were estimated. These parameters were all estimated from the literature.

#### HIV parameters

The mortality for HIV-positive individuals was taken to be 0.1/yr which corresponds to an average survival time of ten years. Williams *et al.* [5] assumed a median survival time

of 9.8 years, Gross *et al.* [24] assumed an average survival time of 7.5 years in their HIV-1 superinfection and viral diversity model. This mortality was also taken to be 0.1/yr in [34] (citing [48]), 0.13/yr in [13] (citing [3]), 0.15/yr in [22].

The function  $g(H)$  for the HIV infection rate was used by Bacaér *et al.* [34] and fitted to data from a South African township and they obtained parameter values for  $d$  and  $\lambda$  as 0.7/yr and 5.9/yr respectively. We also use these values in our model. With these parameter values, the HIV transmission rate varies from 0.7/yr to 0.002/yr for  $H=0$  to  $H=1$  respectively. Cohen *et al.* [48] took the HIV transmission rate to be 0.4/yr.

### HIV-TB coinfection parameters

**Infection and mortality parameters.** The MTB infection rate was also taken to be the product of active TB prevalence and the transmission rate as was done in the first model in chapter 3. The MTB transmission rate was also taken to be  $\frac{2}{3}k_1$  and  $\frac{2}{3}k_2$  for strain 1 and strain 2 respectively as in [34] (citing [48]). The values of  $k_1$  and  $k_2$  are given in Table 3.3, and denoted by  $k_1^-$  and  $k_2^-$  respectively in this chapter.

The TB mortality was assumed to be 1.6/yr for HIV-positive individuals as in [34] (citing [15]). This value was taken to be 0.325/yr in [13] (citing [3] and other references), 1.0/yr in [48].

**Progression parameters.** It was assumed that 67% of HIV-positive individuals progress fast within a year to active tuberculosis after primary infection in [48]. Fast progression to active tuberculosis in HIV-positive individuals was taken to be 20% per year in [13], 30% in [34] (by fitting data from a township in South Africa). We assume that 20% of the HIV-positive individuals progress to active TB soon after primary infection as in [13].

Of those who are HIV-positive and latently infected with tuberculosis, it was assumed that 8% progress to active disease within a year through reactivation in [34] (citing [25] and other references). It was assumed that 17% progress to active disease through reactivation within a year but 30% have infectious TB in [22, 48]. The reactivation rate was also assumed to be 0.737% per year in [13] (taken as an estimate for WHO, 1994). We consider this value to be 8% per year as in [34].

Primary infection is assumed to induce some protection towards any other incoming infection [11, 34]. This protection was assumed to be 75% in [11] for both HIV-negative and HIV-positive individuals, 25% in [34] (citing [48]) for HIV-positive individuals. We take this value to be 75% as in [11]. We are thus taking the reinfection and superinfection rates to be  $0.25p^+$ , where  $p^+$  is the probability of an HIV-positive individual progressing to active TB after primary infection. Note that a protection of 25% is generally small.

**Treatment-related parameters.** The detection rate was taken to be 3.0/yr in [34] (citing [40]) for drug-sensitive TB, 0.5/yr in [12], 0.5/yr in [48] for both drug-sensitive and drug-resistant TB, 0.7/yr in [8] for drug-resistant TB. This value was taken to be 4.0 per person per year in [22] (citing [8] and other references) for both smear-positive and smear-negative tuberculosis. We take this value to be 3.0/yr as in [34] for drug-sensitive TB and 0.7/yr as in [8] for drug-resistant TB.

The rate of self-cure was taken to be 0.4/yr as in [34] (citing [15]) for both strains. This value was taken to be 0.1/yr in [48], 0.7/yr in [12].

Successful treatment of detected cases was taken to be 73% as in [48] (taken as a policy) for drug-sensitive TB and 30% as in [48] for drug-resistant tuberculosis. This value was taken to be 80% in [34] (citing [40]), 70% in [12] for drug-sensitive tuberculosis.

With these values of our choice, we get  $b_1^+ \simeq 2.8/\text{yr}$  and  $b_2^+ \simeq 1.3/\text{yr}$  as successful recovery rates for drug-sensitive and drug-resistant TB respectively. Comparing these values with what others have, we find that Guwatudde *et al.* [13] used a cure rate of 0.5/yr for drug-sensitive TB, Sharomi *et al.* [36] used a treatment rate to lie in the range 0.5-5 per year for drug-sensitive TB.

The respective tuberculosis detection probabilities are given by

$$\frac{\gamma_1^- + \gamma_2^-}{\gamma_1^- + \gamma_2^- + \beta_1^- + \beta_2^- + m^-} \simeq 67\% \text{ and } \frac{\gamma_1^+ + \gamma_2^+}{\gamma_1^+ + \gamma_2^+ + \beta_1^+ + \beta_2^+ + m^+} \simeq 61\%$$

for HIV-negative and HIV-positive individuals. In terms of strains the respective probabilities of detection for HIV-positive individuals are

$$\frac{\gamma_1^+}{\gamma_1^+ + \beta_1^+ + m^+} \simeq 60\% \text{ and } \frac{\gamma_2^+}{\gamma_2^+ + \beta_2^+ + m^+} \simeq 26\%$$

for strain 1 and strain 2. The respective average durations of the disease are also given by

$$\frac{1}{b_1^+ + m^+} \simeq 0.2 \text{ year and } \frac{1}{b_2^+ + m^+} \simeq 0.4 \text{ year}$$

for strain 1 and 2 in HIV-positive individuals, giving a difference of 2 months. This implies that in HIV-positive individuals, the period of infectiousness of a resistant TB case is on average 2 months longer than that of a sensitive TB case.

#### 4.4.2 Simulations of the HIV-only model

This subsection presents the solutions of the HIV-only model given in system (4.3). Parameter values in Table 4.2 were used. The reproduction number was determined to be

$$R_0^{HIV} \simeq 7.0.$$

We then assumed that  $H^* = 1$  and solved equations (4.5) and (4.6) to obtain the initial condition for susceptible and infected individuals. Fig. 4.3 gives the plots of the individual population size of susceptible and infected classes, and the HIV prevalence of the HIV-only model.

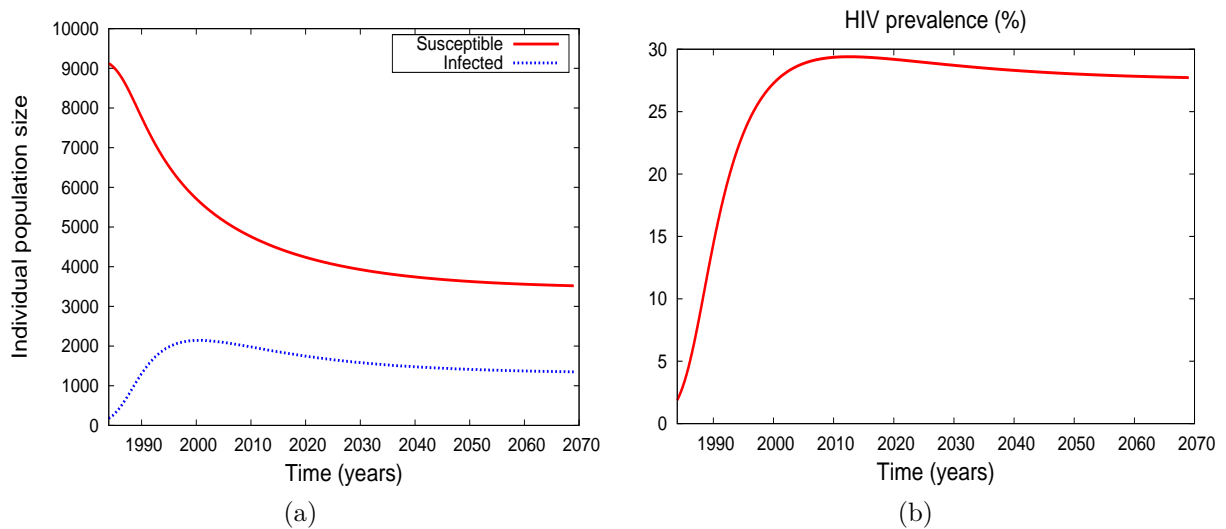


FIG. 4.3. The individual population size of susceptibles and infected (a), and the HIV prevalence (b) of the HIV-only model. Parameter values are given in Table 4.2.

TABLE. 4.2. The parameter values for the HIV-TB coinfection.

Parameter definition		Value	Reference
HIV transmission rate	$d$	0.7/yr	[34] (fit)
Mortality	$\mu^+$	0.1/yr	[34, 48]
HIV prevention	$\lambda$	5.9	[34] (fit)
TB mortality	$m^+$	1.6/yr	[34] (citing [15])
MTB transmission rate	$k_1^+, k_2^+$	$\frac{2}{3}k_1, \frac{2}{3}k_2$	[34] (citing [48])
TB infection -fast progression	$p^+$	20%	[13]
TB reactivation	$a_1^+, a_2^+$	0.08/yr	[34] (citing [25])
	$\sigma_1^+, \sigma_2^+$	0.08/yr	[34]
TB reinfection	$q_1^+, q_2^+$	$0.25p^+$	[11, 39]
	$\omega_1^+, \omega_2^+$	$0.25p^+$	[11, 39]
TB superinfection	$c^+$	$0.25p^+$	[11, 39]
Recovery without treatment	$\beta_1^+, \beta_2^+$	0.4/yr	[34] (citing [15])
Detection rate	$\gamma_1^+, \gamma_2^+$	3.0/yr , 0.7/yr	[34] (citing [40]),[8]
Treatment	$\varepsilon_1^+, \varepsilon_2^+$	73% , 30%	[48]
A proportion of individuals that are latently infected with TB of strain 2 who progress to active TB of strain 1 after being superinfected with TB of strain 1	$\theta_1^+$	75%	Estimated
Proportion of individuals that are latently infected with TB of strain 1 who progress to active TB of strain 2 after being superinfected with TB of strain 2	$\theta_2^+$	75%	Estimated
Proportion of individuals that are actively infected with TB of strain 1 and latently infected with TB of strain 2 that enter state $E_{12}^+$ after treatment	$\tau_1^+$	50%	Estimated
Proportion of individuals that are actively infected with TB of strain 2 and latently infected with TB of strain 1 that enter state $E_{12}^+$ after treatment	$\tau_2^+$	50%	Estimated

#### 4.4.3 Simulations of the HIV-TB coinfection model

In this subsection we present the numerical results from the simulations of system (4.2). The parameter values were picked from both Table. 3.3 and Table. 4.2 for TB alone and HIV-TB coinfection respectively. The steady state values of the two-strain TB model given in Table. 3.4 were used as the initial conditions. We assume that HIV was introduced in

the population in the year 1984 with TB at a steady state by that year. We also introduce one HIV infected individual in the model who is assumed to be in the  $S^+$  class.

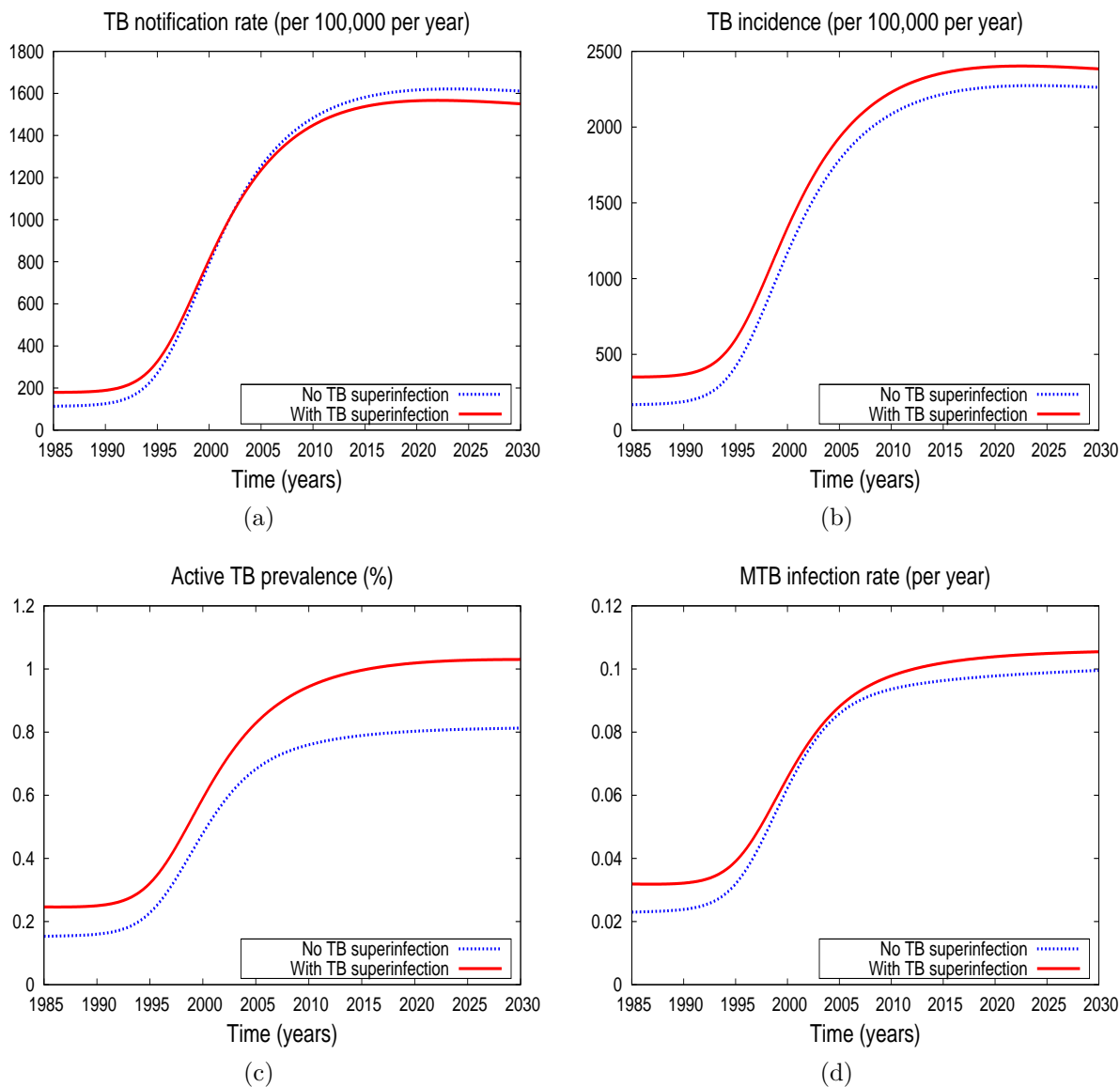


FIG. 4.4. The impact of TB superinfection on tuberculosis in HIV-TB coinfecting individuals. The graph of TB notification rate (a), TB incidence rate (b), TB prevalence (c) and MTB infection rate (d) of system (4.2). Parameter values are given in Table 4.2.

#### 4.4.4 The impact of HIV on tuberculosis

The model shows that there is a greater increase in the number of TB cases due to HIV. Fig. 4.4 shows the simulation curves of TB notification rate, TB incidence rate, TB prevalence and MTB infection rate. A greater increase in these rates is attributed to the presence of HIV. Without considering TB superinfection, the TB notification rate was observed to be 1,519 cases per 100,000 persons per year. With TB superinfection, the TB notification rate increases to 1,454 cases per 100,000 persons per year. The steady state value of the HIV prevalence was estimated to be 24.5% in the absence of TB superinfection and 23.5% in the presence of TB superinfection (Table. 4.3). A study on the trends of the TB notification rate was done in a South African Peri-Urban Community where the HIV prevalence was estimated to be as high as 22% by Lawn *et al.* [45]. Without considering TB superinfection, the TB notification rate was found to be about 1,500 cases per 100,000 persons per year.

#### 4.4.5 The impact of TB superinfection on tuberculosis in HIV infected individuals

The impact of TB superinfection on tuberculosis in HIV-TB coinfecting individuals is relatively low compared to that in HIV negative individuals. Comparing the results of the HIV-TB coinfection model with and without TB superinfection, we find that there is an increase of 55%, 8.8%, 5.3% and 4.6% in the TB incidence in 10, 20, 50 and 100 years respectively. An increase of 45%, 20%, 27% and 23% in the TB prevalence in 10, 20, 50 and 100 years respectively was also observed. The early increase in the incidence and prevalence of TB is due to the fact that the model is coming from a TB steady state where it was shown that the impact of TB superinfection on TB is very high (chapter 3). These results show that the impact of TB superinfection in HIV-TB coinfecting individuals reduces with time. The relatively low impact of TB superinfection on TB is attributed to HIV whose effect on TB is known to be high. The impact of TB superinfection in a HIV-positive population is shown in Fig. 4.4. Fig. 4.5 (a) shows the percentage of active cases that are caused by TB superinfection. There is a drop from the initial value of 3.7% obtained from the TB steady state in chapter 3 to around 2.1% in 100 years. The two strains of TB were found to coexist only in the presence of TB superinfection (Fig. 4.6). The same result was obtained in chapter 3 in the two-strain TB model without HIV. It was observed



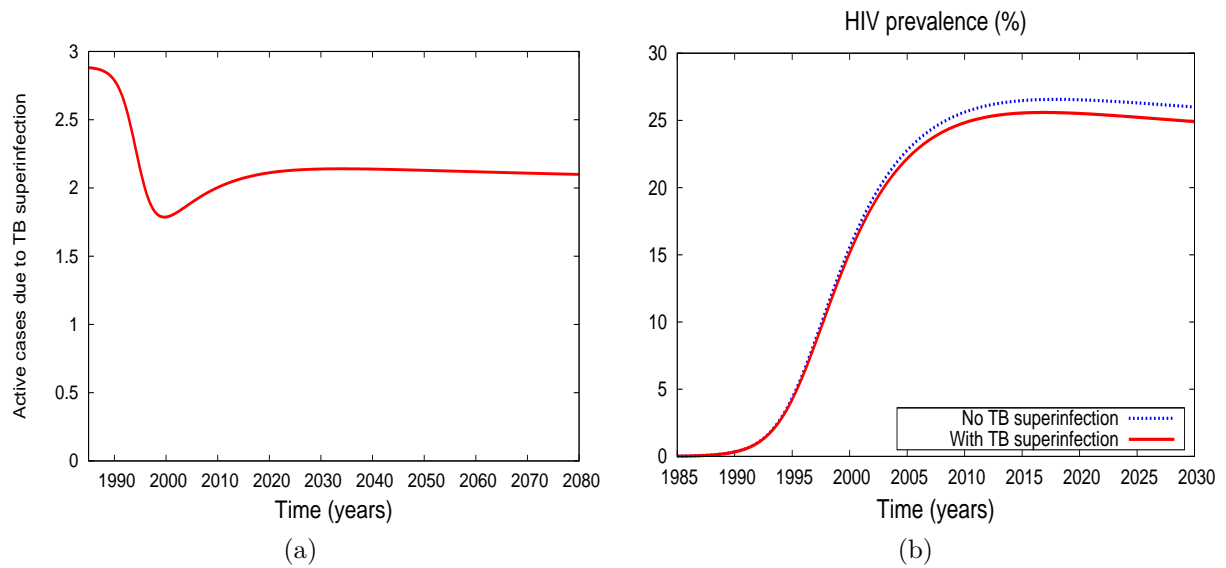


FIG. 4.5. Proportion of active cases caused by TB superinfection (a) and the HIV prevalence of the HIV-TB coinfection model. Parameter values are given in Table 4.2.

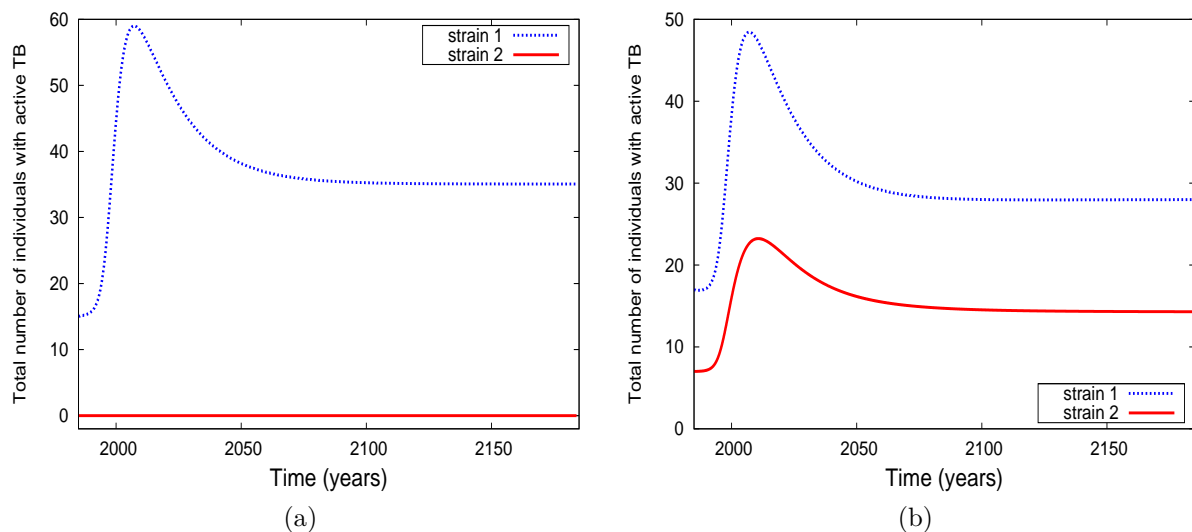


FIG. 4.6. Coexistence of strains. The effect of strain coexistence in the absence (a), and presence (b) of TB superinfection of the HIV-TB coinfection model. Parameter values are given in Table 4.2.

that TB superinfection leads to a decrease in the prevalence of HIV, though by a small percentage. Much as it is believed that tuberculosis does not cause any impact on HIV prevalence, TB superinfection affects the prevalence of HIV. This result is due to the fact that tuberculosis accelerates the progression of HIV to AIDS and increases the associated

HIV mortality. Thus, TB superinfection in HIV infected individuals causes more death leading to a decrease in the prevalence of HIV. This result is shown in Fig. 4.5 (b).

TABLE. 4.3. The characteristics of the endemic steady state of the HIV-only model and HIV-TB coinfection model.

		HIV-TB coinfection model		
		HIV-only model	No TB super-infection	With TB super-infection
Total population	$P$	4,760	4,293	4,181
Susceptible	$S^-$	3,450	1,229	1,194
	$S^+$	1,310	246	238
Latent TB	$E_1^-$	-	1,995	1,493
	$E_2^-$	-	0	384
	$E_{12}^-$	-	-	105
	$E_1^+$	-	787	511
	$E_2^+$	-	0	122
	$E_{12}^+$	-	-	92
Active TB	$I_1^-$	-	18	15
	$I_2^-$	-	0	6
	$I_1^+$	-	17	13
	$I_2^+$	-	0	9
TB notification rate (per 100,000/yr)		-	1,519	1,454
MTB prevalence		-	65.6%	65.8%
TB prevalence		-	0.82%	1.0%
HIV prevalence		27.5%	24.5%	23.5%
MTB infection rate (per year)		-	0.10%	0.11%
TB incidence rate (per 100,000/yr)		-	2,145	2,246
“Syblo’s ratio”		-	210	211
Reactivation		-	69.0%	70.4%
Reinfection		-	10.5%	7.2%
Superinfection		-	-	2.1%
Primary progression		-	20.5%	20.3%

## 4.5 HIV and TB control measures

We now evaluate possible control measures firstly by looking at the control measures on HIV in the form of condom use and antiretroviral therapy (ART). Secondly we look at the control measures for TB in the form of isoniazid preventive therapy and increased TB

detection. We start by considering condom use.

### 4.5.1 Condom use

An increase in condom use reduces the sexual contact rate and thus reducing the HIV transmission rate  $d$ . We evaluated the impact of increased condom use by lowering the value of  $d$ . Fig. 4.7 (a) shows the graph of the TB notification rate and Fig. 4.7 (b) shows the graph of the HIV prevalence obtained for different values of  $d$ . From these graphs its clear that a decrease in the value of  $d$  leads to a decrease in the TB notification rate and HIV prevalence. A decrease in the maximum transmission rate  $d$  of 50% leads to a

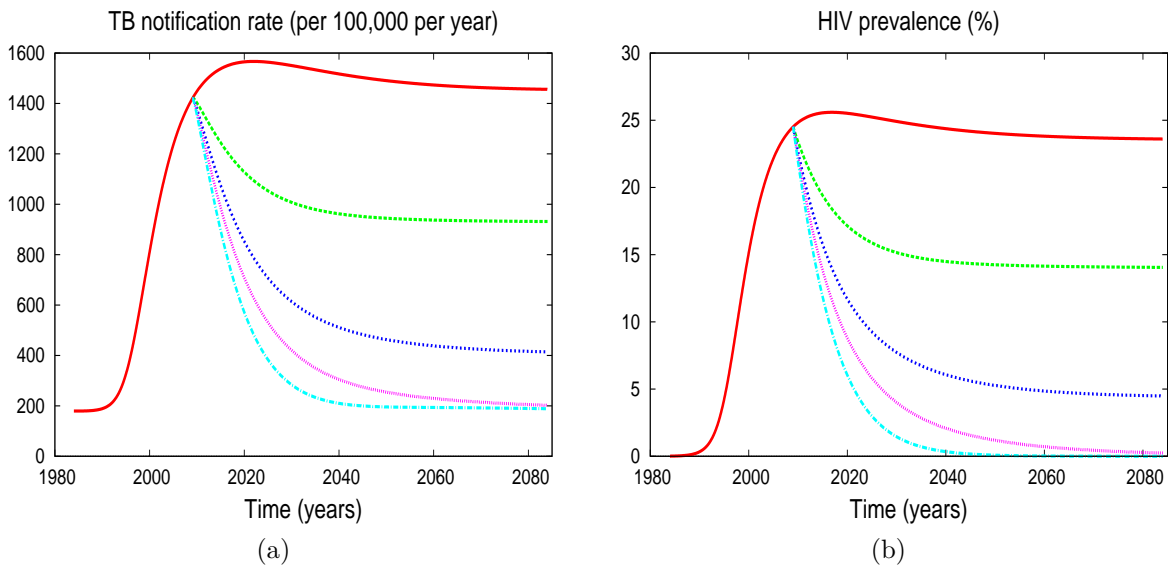


FIG. 4.7. Increasing condom use. Assumption: increase starting in 2009. Simulation curves showing the effect of increased condom use on the TB notification rate (a) and HIV prevalence (b). The parameter  $d$  is replaced by  $d, d/2, d/4, d/8, 0$  from top to bottom in both cases. Parameter values are given in Table 4.2.

16.0% and 20.8% reduction in the TB notification rate and HIV prevalence respectively in 5 years. Decreasing the value of  $d$  by 75% leads to a 25.8% and 34.1% reduction in the TB notification rate and HIV prevalence respectively in 5 years. 87.5% reduction in the value  $d$  takes the notification rate close to the original value obtained at the TB steady state in about 80 years and reduces the HIV prevalence to less than one in 45 years.

## 4.5.2 Antiretroviral therapy (ART)

Antiretroviral therapy (ART) is one of the major control measures used to lower the HIV viral load and prevent the progression of HIV to AIDS in the world today. If initiated, this control measure is believed to increase the life expectancy of HIV infected individuals by at least 20 years [34]. Since ART lowers the viral load, there is a reduction in the transmission of HIV. ART also reduces the MTB reactivation rate of individuals who are latently infected with TB. Fig. 4.8 shows the graphs of the TB notification rate and HIV

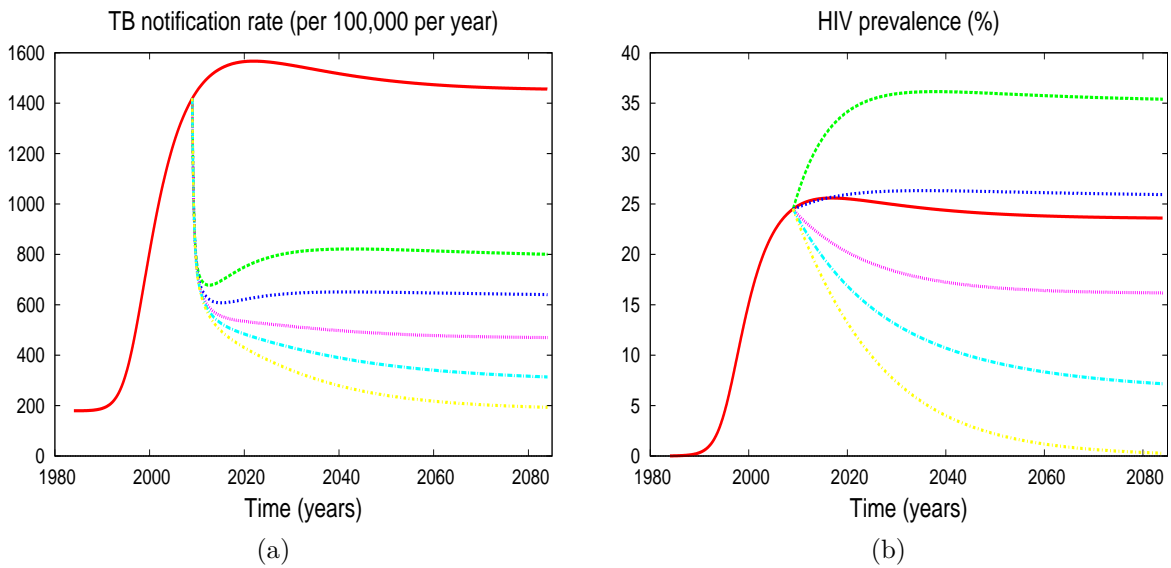


FIG. 4.8. ART. Assuming that all HIV-positive individuals are put on ART by 2009. The graph of TB notification rate (a) and HIV prevalence (b) obtained after the initiation of ART. The parameters  $\mu^+$ ,  $m^+$ ,  $a_1^+$ ,  $a_2^+$ ,  $\sigma_1^+$  and  $\sigma_2^+$  are replaced by  $\mu^+/2$ ,  $m^+/2$ ,  $a_1^+/4$ ,  $a_2^+/4$ ,  $\sigma_1^+/4$  and  $\sigma_2^+/4$  respectively. From top to bottom  $d$  is replaced by  $d$ ,  $d/2$ ,  $d/4$ ,  $d/8$ , 0. The red curve shows the case without intervention. Parameter values are given in Table 4.2.

prevalence that were obtained after including all the assumptions that would occur if ART is initiated. The life expectancy was taken to be 20 years giving a value of  $\mu^+ = 0.05$  per year as in [34]. The other parameters were taken to be  $a_1^+ = a_2^+ = \sigma_1^+ = \sigma_2^+ = 0.08/4 = 0.02$  per year and  $m^+ = 1.6/2 = 0.8$  per year. The results show that decreasing the maximum transmission rate  $d$  by 50% with the above assumptions leads to a 60.0% reduction in the TB notification rate in 5 years. Decreasing  $d$  by 75% leads to a 62.8% reduction in the TB notification rate in 5 years. The HIV prevalence decreases when the transmission rate  $d$  is reduced by 50% or more. A decrease of 50% and 75% in  $d$  leads to a 12.9% and 20%

reduction in the HIV prevalence respectively in 5 years.

### 4.5.3 Isoniazid preventive therapy (IPT)

Isoniazid preventive therapy (IPT) is used for treating latent tuberculosis. It reduces the reactivation rate of individuals that are latently infected with TB. Fig. 4.9 shows the graphs of the TB prevalence obtained after the initiation of Isoniazid preventive therapy on HIV-positive individuals. There is a significant reduction in the TB prevalence as the

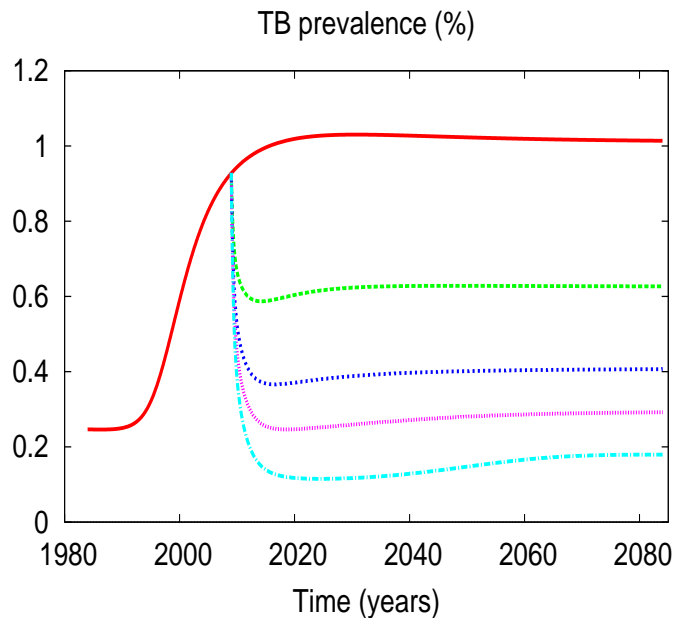


FIG. 4.9. The impact of Isoniazid preventive therapy on HIV-TB coinfecting individuals assuming that treatment starts in 2009. The parameter  $a_1^+$  is replaced by  $a_1^+, a_1^+/2, a_1^+/4, a_1^+/8, 0$ , the parameter  $a_2^+$  by  $a_2^+, a_2^+/2, a_2^+/4, a_2^+/8, 0$ , the parameter  $\sigma_1^+$  by  $\sigma_1^+, \sigma_1^+/2, \sigma_1^+/4, \sigma_1^+/8, 0$  and the parameter  $\sigma_2^+$  by  $\sigma_2^+, \sigma_2^+/2, \sigma_2^+/4, \sigma_2^+/8, 0$  from top to bottom. Parameter values are given in Table 4.2.

reactivation rate decreases. Decreasing the reactivation rate of all HIV-positive individuals latently infected with TB by 50% and 75% leads to a 40.4% and 62.6% reduction in the TB prevalence respectively in 5 years. 87.5% decrease in the reactivation rate of HIV-positive individuals takes the TB prevalence close to the one obtained at the TB steady state in about 10 years.

#### 4.5.4 TB detection

Recovery from active TB was considered to be through self cure and successful treatment of detected cases. This implies that increased TB detection increases the recovery rate from active TB for both HIV-negative and positive individuals. Fig. 4.10 (a) shows the effect of increased TB detection rate in HIV-positive individuals and Fig. 4.10 (b) shows the effect of increased TB detection rate in all TB infected individuals regardless of their HIV status. The two graphs show that the incidence rate decreases with an increase in

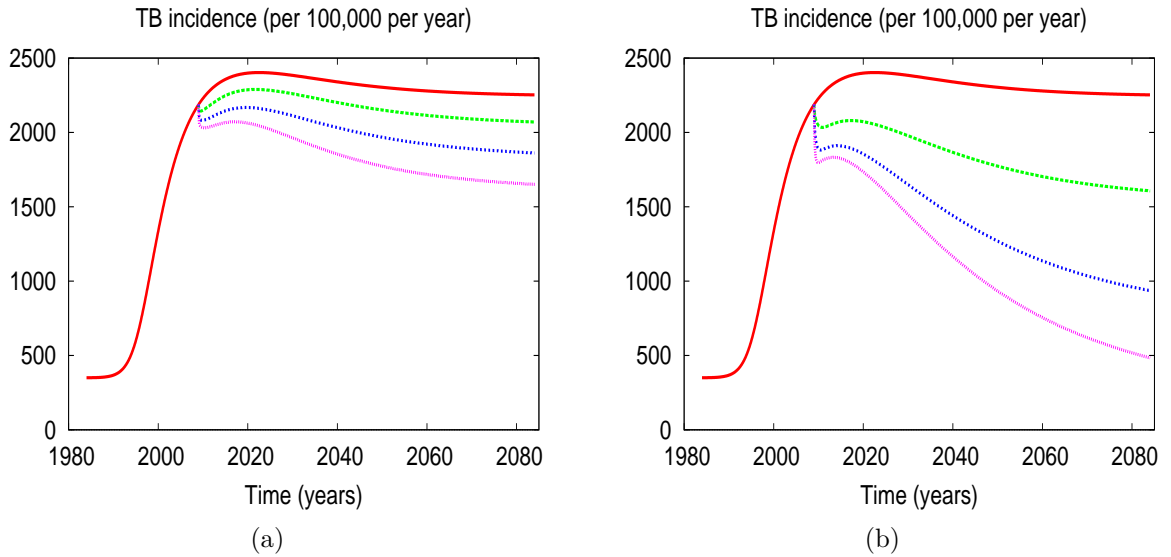


FIG. 4.10. TB detection. Assuming that there is an increase in TB detection rate starting in 2009. TB incidence rate obtained due to an increase in TB detection for HIV-positive individuals only (a), all TB infected individuals (b). The parameters  $\gamma_1^+$  and  $\gamma_2^+$  are replaced by  $\gamma_1^+, 2\gamma_1^+, 4\gamma_1^+, 8\gamma_1^+$  and  $\gamma_2^+, 2\gamma_2^+, 4\gamma_2^+, 8\gamma_2^+$  respectively from top to bottom for case (a). The parameter  $\gamma_1^-$  is replaced by  $\gamma_1^-, 2\gamma_1^-, 4\gamma_1^-, 8\gamma_1^-$ , the parameter  $\gamma_2^-$  by  $\gamma_2^-, 2\gamma_2^-, 4\gamma_2^-, 8\gamma_2^-$ , the parameter  $\gamma_1^+$  by  $\gamma_1^+, 2\gamma_1^+, 4\gamma_1^+, 8\gamma_1^+$  and the parameter  $\gamma_2^+$  by  $\gamma_2^+, 2\gamma_2^+, 4\gamma_2^+, 8\gamma_2^+$  from top to bottom for case (b). Parameter values are given in Table 4.2.

the detection rate. Increasing the TB detection rate of HIV-negative individuals by 50% and 75% leads to a 4.6% and 8.8% reduction in the TB incidence respectively in 5 years. Increasing the TB detection rate of both HIV-negative and HIV-positive individuals by 50% and 75% leads to a 11.8% and 18.3% reduction in the TB incidence respectively in 5 years. The increase in detection rate of all TB infected individuals looks to be more appropriate than increasing the detection rate of HIV-positive individuals only since the

effect in the latter is significantly small.

## 4.6 Summary

This chapter gives a mathematical model used to describe the interaction between HIV and TB epidemics. The model consists of two strains of *M. tuberculosis* and includes in the possibility of TB superinfection. The analysis of the HIV-only model shows that the disease-free equilibrium is locally asymptotically stable whenever the reproduction number is less than one and unstable otherwise.

Numerical simulations were carried out and it was established that HIV drives the TB epidemic with the TB notification rate increasing to almost 1,519 cases per 100,000 persons per year in the absence of TB superinfection, and almost 1,454 cases per 100,000 persons per year in the presence of TB superinfection. Approximately 2.0% of the active cases were found to be due to TB superinfection. The HIV prevalence was estimated to be approximately 24.5% and 23.5% in the absence and presence of TB superinfection respectively. It was also found that TB superinfection leads to strain coexistence, a similar result that was obtained in chapter 3.

Analysis of the control measures show that condom use, isoniazid preventive therapy (IPT) and antiretroviral therapy (ART) have a positive impact in controlling tuberculosis. Condom use largely decreases the HIV prevalence compared to antiretroviral therapy (ART). Increased TB detection rate is less effective in controlling TB in HIV-TB coinfecting individuals.

# Chapter 5

## Conclusions

In this thesis we developed a mathematical model for the dynamics of HIV-TB coinfection with a view of gaining a better understanding of the impact of TB superinfection on the prevalence and incidence of tuberculosis in both HIV-negative and HIV-TB coinfecting individuals. This is the first attempt to use a mathematical model to do such an evaluation. Chapter 3 of this project concentrated on the analysis of TB superinfection in HIV-negative individuals only. We demonstrated that the impact of superinfection on tuberculosis can not be ruled out as other modellers have been doing since it increases the prevalence and incidence tuberculosis.

By considering sensitive tuberculosis alone (one-strain TB model), it was established that most of the active cases arise from primary progression (about 75%), but as drug-resistance comes in (two-strain TB model), active cases due to primary progression goes down (about 71%) and become even smaller when superinfection is put into consideration (about 57%). Due to TB superinfection, a great number of active cases through reactivation (about 24%) were observed.

In the two-strain TB model, it was observed that resistant strains can not compete in the absence of TB superinfection. Coexistence of sensitive and resistant strains was shown to happen in the presence of TB superinfection only. This result do not differ significantly from the one obtained by Rodrigues *et al.* [39] and Castillo-Chavez *et al.* [7] in which they found that superinfection promotes strain coexistence. The same result was obtained after introducing HIV in the model. The dependency of the basic reproduction number



of the two-strain TB model with superinfection on some key parameters was analytically and numerically investigated. It was established that progression to active TB of the drug-sensitive strain would accelerate the TB epidemic at a higher rate compared to progression to active TB of the drug-resistant strain after superinfection if the transmission rate of the sensitive strains is higher than that of the resistant strains. However, if the transmission rate of resistant strains is higher than that of sensitive strains, then progression to active TB of the resistant strain after superinfection accelerates the epidemic at a much higher rate than progression to active TB of the sensitive strain after superinfection.

Chapter 4 concentrated on the analysis of TB superinfection in HIV-TB coinfecting individuals. The impact of TB superinfection in HIV-TB coinfecting individuals was found to be relatively smaller than the one in HIV-negative individuals. The impact of HIV on tuberculosis was shown to be high, with the TB prevalence rising to 0.82% and 1.0% in absence and presence of TB superinfection. The TB incidence was found to increase to 2,145 and 2,246 per 100,000 per year in the absence and presence of TB superinfection. Due to this high impact, it was found that the effect of TB superinfection on the prevalence and incidence of TB in HIV-TB coinfecting individuals is less.

Although increased TB detection rate led to a high decrease in the number of TB cases in HIV-negative individuals, it was noticed that the effect of increasing TB detection rate in HIV-TB coinfecting individuals does not give a clear result. Increased TB detection rate and Isoniazid preventive therapy (IPT) looks to be more appropriate in changing the course of the TB epidemic in HIV-negative and HIV-positive individuals respectively. This result looks to be different from what Bacaër *et al.* [34] obtained in their model where increased TB detection in HIV-positive individuals was shown to decrease the TB incidence. This could be due to drug-resistance and TB superinfection which is considered in our model.

It was also established that increased condom use has a greater impact on HIV prevalence and TB notification rate. Antiretroviral therapy (ART) was also found to decrease the TB notification rate and its impact on HIV prevalence requires high coverage. A similar result was obtained by Bacaër *et al.* [34].

Although the model was developed in accordance with previous models in the literature, there is also need to evaluate the model using experimental data. This would help in getting good estimates for the parameters used most especially the reactivation rate of

individuals latently infected with two strains, the proportion of individuals who progress to active TB soon after superinfection and the proportion of individuals that progress to active tuberculosis of each strain after superinfection.

As a future perspective, it would be important to know the impact of HIV superinfection and viral diversity on the prevalence and incidence of tuberculosis. To reduce on the number of compartments and parameters, we considered TB superinfection only. A case with both TB and HIV superinfection would also give interesting results.

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