Mathematical Studies of Persistence and Cost Effectiveness of Active Case Finding of Tuberculosis

by

Nibiao Zheng

Under the direction of Professor Andreas Handel

Abstract: Tuberculosis (TB) has been a human infectious disease for a long time. Yet, there are currently 2 billion persons infected with TB in the world. About 2 million people died in 2008 due to TB. It is essential to study why TB can survive a long time in human history and explore TB controls that might help eliminate TB in the future. This thesis is composed of three projects of mathematical studies of TB transmission and controls. The first project explores the possible reason for TB persistence. Simulation results suggest that TB has the optimal strength for persistence with a prolonged latency period. The second project studies the impact of HIV prevalence on TB epidemic. Simulation results show that the majority of TB cases are HIV negative when the HIV prevalence is below 25%. The number of HIV positive TB cases outnumbers the number of HIV negative TB cases when the HIV prevalence is over 25%. The third project analyzes the cost effectiveness of active case finding (ACF) in urban and rural Uganda areas. Results suggest that ACF implementation is more cost effective in the urban area than in the rural in terms of cost per TB case averted and ACF is more cost effective if implemented for a longer period.

Index words: Tuberculosis, HIV, Persistence, Latency, Active Case Finding (ACF), Passive Case Finding (PCF), TB Detection, Cost-effectiveness, Mathematical model, Modeling,

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Chapter 1

Introduction

Tuberculosis is an ancient infectious disease. TB could have been a human infectious disease for thousands of years [1]. Since ancient humans tended to live in small communities, TB must persist in these small host communities in human history. No previous studies have unraveled the potential reasons for the persistence of TB over human history. One potential reason is that TB has its own way to survive in human history.

One unique feature of TB is that the TB bacteria can stay in human body for a long time without making its host sick. Among human hosts infected with TB, only a small fraction of host will eventually develop active disease, and most of the infected hosts will stay latent for the rest of their life. This first appears to be a disadvantage to TB for better survival. Is it really so or the latency can actually help TB persist better at the population level? In the first part of the thesis, I built a mathematical model to explore the impact of latency and activation rate on TB persistence. Simulation results suggest that TB has the optimal strength for persistence with a prolonged latency period.

TB prevalence started to rise in the 1980s, which was mainly caused by the epidemics of HIV. WHO reported that about 13% of TB patients are co-infected with HIV. Among TB

patients who dies in 2011, about 1/3 of them are co-infected with HIV [2]. TB also caused the most deaths among HIV positive individuals.

TB control policy has emphasized the importance of treating TB patient who are co-infected with HIV. However, should TB control for TB patients who are HIV negative be put in the less important agenda? In the second part of the project, I used a mathematical model to explore the impact of HIV prevalence in TB epidemic. Simulation results show that the majority of TB cases are HIV negative when the HIV prevalence is low (below 25% in our results).

World health organization (WHO) has targeted to eliminate TB in the near future. WHO recommended directed observed therapy, short course (DOTS) for TB treatment practice. As for TB detection, the default method is pass case finding (PCF). Under PCF, individuals voluntarily go to hospital after coughing for some time. These individuals are tested for TB and placed for treatment if diagnosed with active TB disease. The delay from the onset of disease to the TB diagnosis and treatment normally lasts several months and up to two years [3]. During the duration of the delay, undiagnosed TB patients cough and potentially infect uninfected individuals in contact. Detection and diagnosis techniques have been developed to help detect and treat TB patients earlier. One approach to detect TB patients earlier is active case finding (ACF). Under ACF, health care workers go out to the communities and seek suspected TB patients who have coughed for some time for TB test and diagnosis.

To implement ACF for TB case detection, economic cost is one factor needed to be considered, especially in Africa countries where resources are limited. The additional cost for ACF implementation includes costs for surveys, door to door visits, TB tests, and TB treatments. The first part of cost involves the cost for health care personnel to detect individuals for TB tests. The second part of the additional cost is the cost of TB tests. ACF normally recommends individuals that cough for a certain period time for TB test. Obviously not

all recommended individuals have active TB disease. The number of additional TB tests needed to detect an active TB patient is different for various ACF strategies. This number is possibly different for rural and urban areas. Rural individuals tend to live far away from the health center. The transportation fee for conducting ACF surveys is potentially higher. Many TB test might be needed to detect an active TB case as the TB prevalence is relatively lower in the rural area.

TB and HIV transmission dynamics are different among rural and urban residents. Rural residents tend to live less crowded, have shorter life expectancy, and have limited access to health care compared with urban residents. This will lead to difference in the impact of ACF on TB incidence between rural and urban areas. Results suggest that ACF implementation is more cost effective in the urban area than in the rural in terms of cost per TB case averted and ACF is more cost effective if implemented for a longer period.

For health policy maker in Uganda, the key questions to implementing ACF would be whether ACF implementation will significantly reduce TB prevalence and where money can be better spent. I used a mathematical model to simulate TB epidemic in Uganda. We analyzed cost effectiveness for ACF implementation in rural and urban areas. We also compared the short term and long term benefits of ACF implementation in both rural and urban areas.

Chapter 2

Background

2.1 Tuberculosis Transmission Mechanism

Tuberculosis is caused by *Mycobacterium tuberculosis*. When an active TB infectious patient coughs, he spray TB bacteria into the air. If an uninfected individual inhales some of these TB bacteria, he might be infected with TB. A small fraction of TB infected individuals will develop active disease in a short time. However many might develop a long time after infection. Among all infected individuals, only a small fraction will develop active disease.

2.2 Epidemiology

Currently there are about 2 billion people infected with TB. Most of these people are latently infected, which means they are asymptomatic and will not cause new infection. There are 8.7 million new TB cases and 1.1 million persons die due to TB in 2012 [2]. Despite of efforts for TB controls, the number of TB patients are increasing, partly due to the growth

of the world population. TB are well controlled in developed countries such as USA and European countries. The TB incidence is 3.2 cases/100,000 in USA in 2012 [4]. However, some scientists are concerned about the impact of immigrants on the TB epidemic in USA as there are still many countries with relatively high TB incidences [5, 6]. There are 22 countries on the WHO's list of most TB burden countries. Many of these countries are in Africa, where co-infection of HIV and TB has made TB epidemics harder to control.

2.3 HIV and TB co-infection

TB prevalence started to rise in the 1980s, which was mainly caused by the epidemics of HIV. WHO reported that about 13% of TB patients are co-infected with HIV. Among TB patients who dies in 2011, about 1/3 of them are co-infected with HIV [2]. TB also caused the most deaths among HIV positive individuals.

HIV and TB confection increases TB transmission in a population for several reasons. About 5% of HIV negative hosts develop TB shortly after infection whereas 18% of HIV positive hosts develop TB shortly after infection [7]. Activation of latent TB is much faster in HIV positive hosts than in HIV negative hosts [8]. Larger fraction of latent hosts who are HIV positive will develop TB disease than those who are HIV negative [8]. These all contribute to higher transmission of TB. On the other hand, TB patients who are HIV positive are normally less infectious and the duration of infectious are normally shorter. Studies shows that population of higher HIV prevalence tend to have higher TB prevalence [9].

TB plays an important role in HIV epidemics. A meta-analysis by Straetemans *et al* summarized the current understandings on impacts of TB on HIV mortality [10]. In this meta-analysis, 15 studies showed that hazard ration of HIV patients with TB to those without TB was 1.8.

The co-infection of HIV and TB represents a case of "tragedy of commons" as both HIV virus and TB bacteria need human hosts for transmission but the interaction of the two diseases can significantly accelerate the death of their human hosts. However, the impact of one on another is different. HIV accelerates the death of hosts infected with TB, however it also increase the progression of TB onset and makes large fraction of TB latent hosts develop disease. Studies have suggested that higher HIV prevalence leads to higher TB prevalence in human population[9]. On the other hand, TB possibly accelerates the death of HIV positive hosts, but does not aid HIV transmission in human hosts.

2.4 TB controls

TB controls include prevention of TB uninfected hosts from infection and reduction of TB transmission from active TB patients. Prevention of new TB infections can be achieved through TB vaccinations and isolation of uninfected hosts from those with active disease. Reduction of TB transmission involve early detection and diagnosis, effective treatment, and isolation of TB patients.

2.4.1 Detection and Diagnosis

Early detection and accurate diagnosis of TB patients help identify TB patients and reduce possible new infections. Early detection of TB patients is not known in early human history as early detection is not possible and meaningless without proper diagnosis technique and effective TB treatment. In the recent decades, new methods and techniques have been developed to detect and diagnose TB patients earlier and place them in the health system.

Several approaches have been carried out to detect TB patients. One such effort is intensive

case finding (ICF). Under ICF, hospital staff recommend those individual tested HIV positive for TB tests. The limitation of ICF is that it only recommends TB test to those infected with HIV and seeking for health care. A larger fraction of TB patients are not infected with HIV [7] and will not be recommended for TB under ICF. Another approach is active case finding (ACF). Under ACF, hospital workers go to communications and find hosts who have coughed for more than two weeks and ask them for TB test. ACF might significantly reduce the time it takes from onset of disease to treatment of a TB patient.

2.4.2 Prevention

TB vaccines can help prevent or treat TB. There is only one TB vaccine available now, bacillus Calmette-Guerin(BCG). BCG was first used in humans in 1921 and has been used since then. BCG has been recommended to use for children. However, the protection results of BCG have not been consistent [11]. Several new TB vaccines are being developed and a couple are in phase III clinical trials[12].

2.4.3 Treatment

Antibiotic drugs are used to treat TB. There are different treatment strategies targeting various TB patients. For new TB patients, the recommended treatment is the first line drugs. The treatment standard is a combination of antibiotics containing rifampicin, isoniazid, pyrazinamide and ethambutol for the first two months, and rifampicin and isoniazid for the following four months [13]. When the treatment with first line drugs fails, second line drugs are recommended.

Drug-resistant TB occurs when TB treatment fails and TB becomes resistant to the antibiotic. Drug resistant TB arises because TB patients do not finish the whole treatment

process. To avoid drug resistant TB, World Health Organization (WHO) has recommended direct observed therapy, short-course (DOTS) for TB treatment. Under DOTS, health workers will supervise TB patients to take the drugs. Longer treatment time is generally required for drug resistant TB[13].

2.5 Mathematical Modeling of TB Epidemics

Mathematical models have been widely used to study various aspects of infectious diseases. Mathematical modeling can offer insights to epidemiological studies such as prediction of TB prevalence in the future and prediction of MDR TB in the future.

Mathematical models of infectious disease have different approaches,

- Compartmental Deterministic Model. Each group of individuals is considered well mixed in a compartment. Changes are in continuous time.
- Stochastic Model. Each host is modeled individually. Simulation is in discrete time.
- Agent-based Model. Each host is placed in a network in contacts of other hosts.

2.5.1 TB only

With regard to TB infection, human hosts can be characterized into three groups, uninfected (susceptible), infected but no disease (latent), and infected with active disease. Each group can have sub-groups. For example, human hosts with active TB can be smear positive or smear negative. Mathematical modeling of TB normally models transition and interaction among these groups of hosts and sometimes with human interventions.

Figure 2.1 shows the schematic diagram of TB transmission. A mathematical model might

include some or all processes in the diagram depending on the purpose of the study.

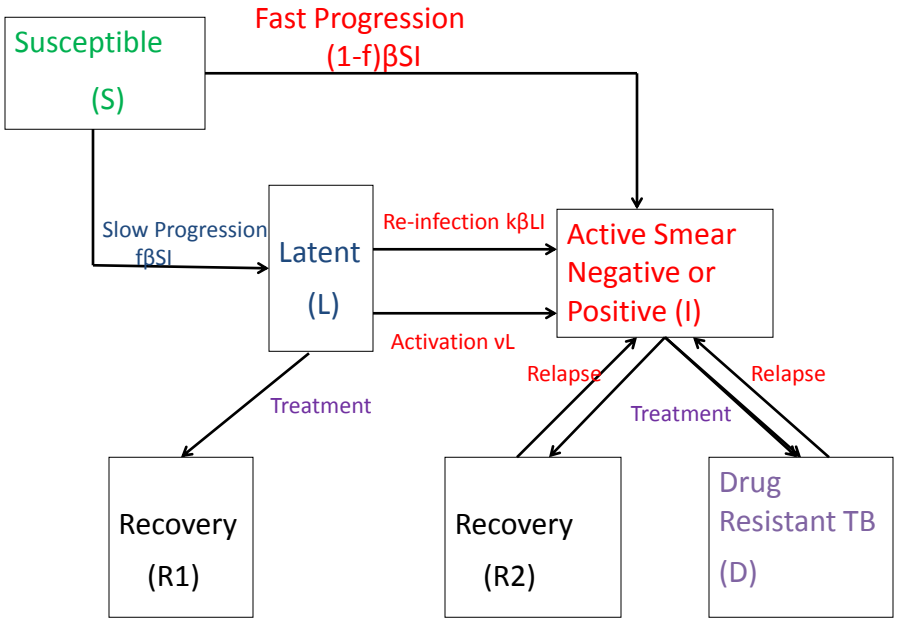


Figure 2.1: Schematic diagram for TB transmission

Compartmental deterministic models generally use ordinary differentiation equations (ODE) to simulate the change of the number of hosts in a compartment. The change of the number of hosts in a compartment is simply the sum of inflows to the compartment and outflows from the compartment. Equations 2.1 2.2 show simple examples to construct ODE equations for the susceptible and latent compartments.

$$\underbrace{\frac{dS}{dt}}_{\substack{\text{Change of number of TB susceptible hosts with time}}} = \underbrace{\pi}_{\substack{\text{Inflow of TB susceptible Assumed constant inflow}}} - \underbrace{\beta SI}_{\substack{\text{Outflow due to TB Infection } \beta\text{: Transmission coefficient}}} - \underbrace{\mu S}_{\substack{\text{Outflow due to death}}} \tag{2.1}$$

$$\underbrace{\frac{dL}{dt}}_{\substack{\text{Change of number of TB latent hosts with time}}} = \underbrace{f\beta SI}_{\substack{\text{Inflow of TB latent hosts} \\ \text{f:fraction of slow progression}}} - \underbrace{vl}_{\substack{\text{Outflow due to latent activation} \\ \text{v: activation rate}}} - \underbrace{\mu S}_{\substack{\text{Outflow due to death}}} \tag{2.2}$$

For stochastic and agent-based models, there is no inflow or outflow to model. Instead, each individual has a certain rate or probability to transit with another TB status in every time step.

2.5.2 TB and HIV

Mathematical models for TB and HIV co-infection basically add HIV transmission on top of the TB models described in the previous section. With regard to HIV infection, each human host can be characterized in three states, HIV negative (uninfected), HIV positive untreated, and HIV positive on ART treatment. Some models split the HIV positive state into several sub-states based on CD4 counts. The inflow to and the outflow from each compartment are of different forces.

Figure 2.2 shows the schematic diagram of HIV transmission according to [14]. A mathematical model might include some or all processes in the diagram depending on the purpose of the study.

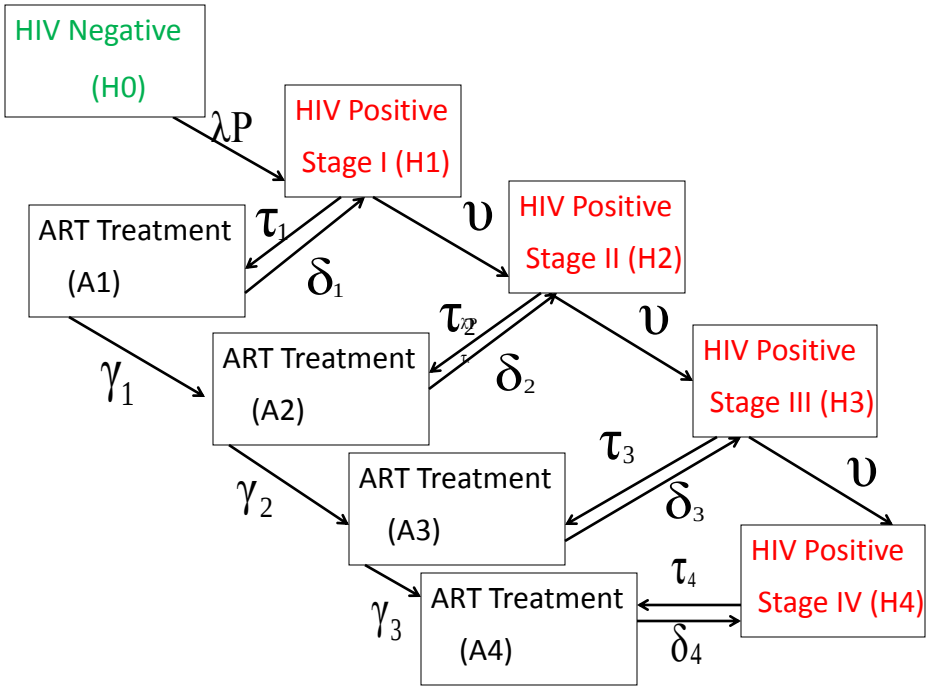


Figure 2.2: Schematic diagram for HIV transmission

2.5.2.1 Summary of TB and HIV models

Table 2.1 summarizes the modeling literatures in recent years.

Table 2.1: HIV and TB co-infection Models summary

Year	Authors	Setting	Model	Main Findings
2013	Sergeev, Cohen, etc	Swaziland	3 TB stages, 2 HIV stages and	HIV positive individuals infected with TB is at lower risk of MDR TB at the earlier stage of co-infection. The rise of HIV can increase the MDR TB prevalence in a population[15]
2011	Mills, Cohen, Colijn	Europe	Network	Population with clustering respiratory network have aggregation of TB cases and high number of re-infection. Impact of isoniazed preventive therapy is highly heterogeneous in populations with highly clustered network [16].
2010	Williams, Dye, etc	9 African Countries	4 HIV infection stages, 4 ART treatment stages, 2 TB stages, 18 compartments	Predict TB prevalence based on ART treatment [14]

Table 2.1: (continued)

Year	Authors	Setting	Model	Main Findings
2010	Sanchez, getz, etc	N/A	Modeling statistical approach	Define R_0 for HIV and TB co-infection [17]
2009	Basu, Galbani, etc	Botswana	4 TB stages, 3 HIV stages, 15 compartments	Isonaized preventive therapy (IPT) implemented through antiretroviral clinics can effectively lower TB prevalence[18]
2009	Bhunu, Mukandavire	N/A	4 TB stages, 3 HIV stages, 10 compartments	Treatment of HIV positive individuals significantly reduces number of individuals progressing to active TB. Treatment of infectious and latent TB individual delays onset of AIDS stages of HIV infection[19].
2008	Bacaer, Williams, etc	South Africa township	Deterministic, 3 TB stages, 2 HIV stages, 6 compartments	Studied impacts of various measures on HIV and TB epidemics. Suggested that antiretrovial therapy can greatly reduce TB notification rate.[9]
2008	Sharomi, Podder, Gumel	N/A	Deterministic, 4 TB stages, 4 HIV stages, 15 compartments	The HIV-only treatment strategy saves more mixed infection than the TB-only strategy. The mixed-only strategy saves the least cases for low treatment rate [20].

Table 2.1: (continued)

Year	Authors	Setting	Model	Main Findings
2006	Dowdy, Dorman, etc	N/A	4 TB stages, 3 HIV stages	Enhanced TB diagnostic techniques have great impacts on TB mortality and morbidity in HIV endemic areas. Enhanced TB diagnostic techniques might be a consideration for TB control. [21]
2006	Cohen, Murray, etc	sub-Saharan Africa	3 drug resistant stages, 2 latency stages, 2 detection stages, 45 compartments	Community-wide isonaized preventive therapy (IPT) can reduce TB incidence in the short term, but might speed the emergence of drug resistant TB.[22]
2005	Williams, Dye, etc	India	4 TB stages, 4 HIV stages	India's Revised National TB Control Program (RNTCP) could substantially reduce TB prevalence. Antiretrovial treatment is recommended to reduce TB mortality [23].
2004	Guwatudde, Whalen, etc	sub-Saharan Africa	Deterministic, 5 TB stages, 2 HIV stages, 11 compartments	The impact of preventive therapy (PT) in the population might be smaller than previously suggested [8]

Table 2.1: (continued)

Year	Authors	Setting	Model	Main Findings
2003	Williams, Dye	N/A	Statistical method	Antiretroviral drug could enhance TB treatment and TB program provides entrants points for HIV AIDS treatment [24]
2003	Currie, Dye, etc	N/A	Basian fitting for compartmental models	Finding and treating active TB cases is the most effective way to reduce TB deaths in the following ten years [25]

2.5.2.2 Challenges

For mathematical modeling, the saying is that a model is as good as its assumptions. With the complex of a HIV TB co-infection model, model assumption and parameter selection are the most important base before any simulations. Parameter value selection is very important part for a model, but generally ignored or not paid enough attentions to. Results of a mathematical modeling study is only as good as its selections of parameter values. For TB-HIV mathematical models, many parameter values are hard to obtain from field studies. Uncertainty and sensitivity analysis can somehow offset the uncertainty of parameter values. But the better approach is to increase corporation with field scientists. Certain parameter values can be obtained with designed field studies.

Studies of TB epidemic in the future can not leave HIV TB co-infection out. There are many topics about HIV TB co-infection to be studied. Figure 2.3 shows the topics of interest for TB transmission, HIV transmission, and public health. A combination of any three would be a project to explore. However, many have not been studied. For example, with the emergence of new TB vaccines, will it have any impact on HIV epidemics? Many studies explore the impact of HIV transmission on TB epidemic, however, no study has been done to explore the impact of HIV treatment on TB epidemic.

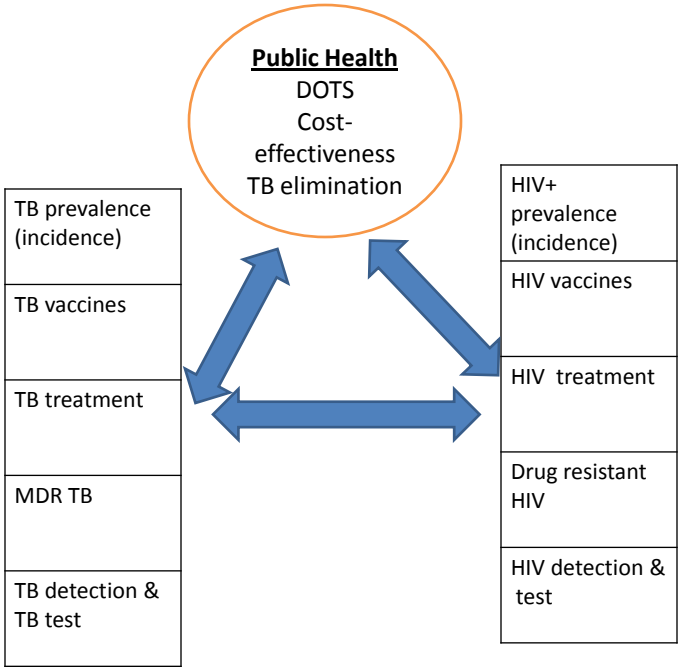


Figure 2.3: Topics of interest for HIV and TB co-infection

2.5.3 Cost-effective analysis of active case finding of TB

World health organization (WHO) has recommended directed observed therapy (DOTS) for TB treatment. Under this recommendation, TB cases are normally detected with passive case finding (PCF). TB patients are detected only when they go to hospital for health care. Intuitively, these patients only go to hospital when they are very sick. It is very likely that these TB patients have been active and have been infecting other persons before they seek for health care. Active case finding (ACF) has been recommended for early detection of these patients. With ACF, health workers go to the home of suspected TB patients and recommend suspected individuals for TB test.

The benefits of active case finding have been studied with mathematical modeling. Murray

et al studied the impact of various TB control strategies on global TB epidemics [26, 27]. They explored the impacts of various TB control strategies in different country settings. Their results suggested that ACF will not help detect more TB cases in low TB settings and ACF will be too expensive to implement in high TB developing countries. They also recommended that TB treatment is an optimal strategy compared with ACF for fixed budget. Currie et al confirmed this finding that TB treatment is the most cost effectiveness way for TB controls; however they also emphasized that to reduce TB incidence in high HIV setting, the immediate goal is to increase TB detection rates[28, 29]. Dowdy *et al* used a compartmental model to explore the impact of enhanced TB diagnosis in high HIV settings. Their results suggested that enhanced TB diagnosis including enhanced case finding can substantially reduce TB prevalence [21, 30, 31]. Mupere *et al* built a mathematical model to study the cost effectiveness of TB ACF strategy in Kampala, Uganda. They found that ACF is an effective strategy for TB controls and is cost effective in Uganda [32].

Chapter 3

Prolonged latency and reduced disease activation can improve population-level survival of *M. tuberculosis*

3.1 Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (MTB). It is estimated that there are currently about 2 billion people worldwide infected with TB [33]. Of those 2 billion people, most are latently infected. Those hosts do not show signs of disease, however, they still harbor live MTB, which can activate and lead to disease at any time [34–36]. The process of this activation might take a long time to occur, and the majority of TB infected hosts die without ever developing disease. Unlike other long-term infections, such as HIV, individuals latently infected with MTB cannot in-

fect other individuals. Therefore, at first glance, latency does not seem to be beneficial for the pathogen. One possible explanation for the long latency and the fact that activation to disease only occurs in a fraction of hosts is based on the host immune response [37–39]. It is known that a competent immune response is needed to contain infection and avoid disease, as dramatically illustrated in HIV infected hosts with weakened immune responses, who activate much faster [7, 40, 41]. Evolutionary speaking, this would mean that in the co-evolutionary arms race between MTB and its human hosts, the host immune response is successful enough to contain MTB in a state of suboptimal fitness, though not successful enough to keep MTB from causing disease and continuing to spread [42, 43]. The fact that there seems to be local adaptation on both the pathogen and host side lends support to this idea [43–47].

Although host immune pressure is a plausible explanation for reduced activation rates, such reduced activation might also be advantageous to MTB [48, 49].Pathogens like MTB replicate rapidly (compared to their human hosts) and often reach large population sizes; both features are known to foster rapid evolution, especially under strong selective pressure [50, 51]. This is at vivid display in the evolution of drug resistance for MTB and many other pathogens [52, 53]. Therefore, one could argue that if long latency and low activation rates were evolutionary strongly suboptimal for MTB, evolution would have led to higher rates of activation. Long latency and low activation rates might instead be strategies that are evolutionary beneficial to MTB. Since MTB is an ancient organism that has infected humans for a millenia [42, 54–57], it had to evolve strategies that allowed it to persist in relatively small host populations. It has been previously proposed that a prolonged latency might have been one of those survival strategies [49, 58]. Here, we use a mathematical model to explore this idea. We find that indeed, TB persistence is optimal for an intermediate duration of latency and level of activation, however this level is still above the observed value, suggesting that host immunity plays a role in keeping MTB in check. We also show how characteristics of the

pathogen and host, such as healthy and diseased host mortality, recovery rate, level of infectiousness and fraction of fast progression affect persistence and optimal latency and activation. We discuss the consequences of these findings in light of recent developments over the last hundreds of years, such as longer life-span, better nutrition, vaccine and drug interventions and HIV.

3.2 Method

3.2.1 The mathematical Model

We use a compartmental mathematical model formulated as a set of ordinary differential equations to describe the population-level infection dynamics of TB. The model is shown schematically in figure 3.1. Our model has the same structure as another recently studied TB model [18]. We chose this model as it represents a good balance between model simplicity and inclusion of the most important features of TB transmission dynamics. We consider 3 types of hosts (compartments) in our model: susceptible hosts, S, latently infected hosts, L, that harbor MTB but are not infectious and show no signs of disease, and infectious hosts with active disease, I. Susceptible individuals are born at a rate π, which we chose such that the disease-free population size remains constant. All hosts die due to causes other than TB after an average life-span of $1/m_n$ years. Uninfected hosts can become infected through contact with an infectious host at rate b. After infection, a small fraction f of hosts rapidly develop infectious disease (fast progression) and move into active disease compartment I. The majority of hosts enters the latent state L (slow progression). Latently infected hosts can convert to infectious hosts later in their life at rate a (activation) or through re-infection, with a re-infection coefficient k. The duration of latency (latency period) is mathematically the inverse of the activation rate. Infectious hosts with the disease either die due to disease after

on average $1/m_d$ years, or might regress and return to the latent stage at rate w. Following previous models, we assume that recovered individuals do not fully clear the infection but instead return to the latent stage [9, 18, 23, 59]. Table 3.1 summarizes the model variables and parameters and provides references for the parameter values used for most of our analysis. The model equations are

$$\frac{dS}{dt} = \pi - bSI - m_n S \tag{3.1}$$

$$\frac{dL}{dt} = (1-f)bSI + wI - aL - kfbLI - m_n L \tag{3.2}$$

$$\frac{dI}{dt} = fbSI + aL + kfbLI - wI - (m_n + m_d)I \tag{3.3}$$

We implemented model simulations in R [60], the code is available from the authors upon request.

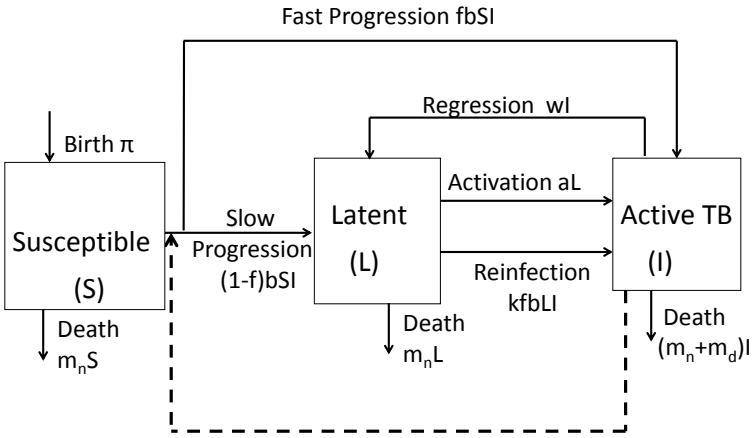


Figure 3.1: Flow diagram for our TB transmission model. Susceptible individuals (S) are born at rate π, can be infected at rate b with TB upon contact with TB infectious individuals (I). After TB infection, individuals can either develop active TB in a short time (Fast progression), or stay latent (L). Latent individuals can either activate and develop active TB sometime later (slow progression) or stay latent for the rest of their life. Latent individuals can also develop active TB after re-infection with TB. An infectious individual might lose its symptoms and infectiousness and return to the latent stage. Susceptible and latent individuals die with natural mortality rate m_n, while individuals with active disease also die due to diseased induced mortality at rate m_d.

3.2.2 Parameters

Our analysis focused on studying the persistence of TB in the thousands of prehistoric period. In the first part of our analysis, we used parameter values that described the ancient human and TB dynamics . Later on we varied the parameter value of each parameter to explore the impact of each one on TB latency period and TB persistence. Generally, researchers use rate in disease modeling. For our study, we used durations instead of rates. Durations are simply the inverse of rates. For example, life expectancy is the inverse of mortality rate. Latency period is the inverse of the activation rate or progression rate defined in previous TB models [61]. Table 3.1 shows the parameters in our model and their values we use for our simulations.

Symbol	Interpretation	Value	Note
S_0	initial susceptible hosts	1	population size scaled to 1
L_0	initial latent hosts	0	arbitrary choice
I_0	initial infectious hosts	1E-3	one infected per 1,000 hosts
m_n	natural mortality rate	1/(50 years)	assuming a life-span of 50 years for healthy hosts [9, 62]
m_d	disease-induced mortality rate	1/(3 years)	assuming 3 years life-span for untreated diseased hosts [63]
π	birth rate	$S_0 m_n$	maintaining a disease-free population
r	number of susceptible hosts that an infectious person infects annually	7 per year	[31, 61]
b	transmission coefficient	$\frac{r}{S_0}$	[61]
w	rate of regression	0.058/year	[61]
f	fraction of TB infections that develop active disease via fast progression	0.11	[9, 64]
k	reduced fraction of reinfection that develop active TB disease	0.28	[21, 65]
a	rate of TB activation in latent hosts	varied	

Table 3.1: Initial conditions of model variables and values of model parameters. These values are chosen for all simulations unless indicated otherwise.

3.2.3 Steady State Equations

While analytic expressions for the steady states for the full model can be derived, the expressions are unwieldy and not very insightful. We therefore show below the expressions for the simpler model without re-infection, fast progression and recovery ($k = f = w = 0$). We find for the number of susceptible, latent and infectious hosts at steady state (endemic equilibrium) the following expressions:

$$\hat{S} = \frac{(m_n + a)(m_n + m_d)}{ab} \tag{3.4}$$

$$\hat{L} = \frac{ab\pi - m_n^3 - m_d m_n^2 - a m_n^2 - a m_d m_n}{ab(m_n + a)} \tag{3.5}$$

$$\hat{I} = \frac{ab\pi - m_n^3 - m_d m_n^2 - a m_n^2 - a m_d m_n}{b(m_n + a)(m_n + m_d)} \tag{3.6}$$

The total population at steady state is given by $\hat{N} = \hat{S} + \hat{I} + \hat{L}$. The dependence of any of the steady state values on activation rate a is the same for the full model, therefore all conclusions hold for the general case, as we show with numerical simulations in the main text.

3.2.4 Reproductive Number

The basic reproductive number, R_0, is defined as the expected number of new infectious cases produced by one infectious case in a fully susceptible population. For our model (with $k = f = w = 0$), R_0 was derived earlier in [18] and found to be

$$R_0 = \frac{ab}{(m_n + m_d)(m_n + a)} \tag{3.7}$$

One can express R_0 in terms of the number of infectious hosts at steady state,

$$R_0 = \hat{I}\frac{r}{m_n S_0} + 1 \tag{3.8}$$

This shows that R_0 and $\hat{I}$ have the same functional relationship with respect to the latent period. R_0 is a frequently used measure of pathogen fitness. Specifically, if two strains with different R_0 compete in the same population, the one with the higher R_0 is expected to win. This would suggest evolutionary pressure toward high R_0 and low latency. However, as we show in the main text, persistence of a single strain is better for intermediate latency duration. This is reminiscent of other findings suggesting that locally "prudent" behavior might be overall beneficial [66, 67].

3.3 Results

3.3.1 Persistence of TB as a function of latency

Persistence (non-extinction) of MTB requires both non-extinction of the host species (i.e. humans) and the pathogen. Host persistence increases as population size increases. For our model, the host population size at steady state, $\hat{N}$, increases as the activation rate a from latency to disease decreases and therefore the duration of latency increases (equation 3.4). The reason for this is that increased latency leads to fewer infectious, diseased hosts and therefore reduced excess host mortality and in turn larger population size. Since larger population sizes reduce the chance of population extinction, this suggests that MTB should evolve towards a very long latency period and low activation rate. This corresponds to the idea that in the absence of a connection between virulence and fitness, the ideal strategy for obligate parasites is to evolve toward minimal virulence [68, 69].

However, for MTB to transmit it needs to induce disease in the host. The number of infectious, diseased hosts at steady state, $\hat{I}$, is found to increase as the activation rate from latency to disease increases (see appendix). Similarly, the reproductive number, R_0 – an often used measure of pathogen fitness – increases with increased activation rate (see appendix). The pathogen strain with the higher R_0 generally outcompetes the one with the lower R_0. Therefore, in direct competition between strains, the high R_0 pathogen usually wins [70].

However, in the absence of direct competition, strains with lower R_0 might sometimes be more advantaged as they can sometimes better avoid local extinction and therefore win through indirect competition against higher R_0 strains [66, 67]. For MTB, local extinction occurs if no more latently infected hosts, L, and infectious, diseased hosts, I, are present. To be more precise, since only a fraction of latently infected hosts will become infectious and contribute to ongoing transmission, a good measure of persistence is given by the quantity P, as $P = I + \alpha L$, where I and L are the number of infectious and latently infected hosts, and α represents the fraction of latently infected hosts that will develop TB disease and become infectious. The fraction of hosts becoming infectious, α, can be computed as the ratio of the rate at which hosts leave the latent stage and enter the infectious stage, divided by the total rate at which hosts leave the latent stage, which is given by

$$\alpha = \frac{a + \frac{kfrI}{S_0}}{a + m_n + \frac{kfrI}{S_0}}. \tag{3.9}$$

The measure of persistence we just defined can be numerically determined at any time. One especially interesting time point is the endemic equilibrium at steady state. We initially focus on evaluating P at the endemic state, we consider another scenario toward the end.

It is in principle possible to obtain analytical expressions for the steady state values of L and I and therefore P for the full model. However, the equations are too large and cumbersome

to be insightful. We will therefore show expressions for a simplified model without re-infection, fast progression and recovery ($k = f = w = 0$) to illustrate how persistence and the activation rate at which persistence is optimized can be determined. Using the expressions for the steady state values of L and I (see equations in appendix), we find the persistence measure P to be

$$P = \frac{m_n S_0 a}{(m_n + a)(m_n + m_d)} + \frac{m_n S_0 a}{(m_n + a)^2} - \frac{m_n S_0}{r} - \frac{m_n S_0 (m_n + m_d)}{r(m_n + a)} \tag{3.10}$$

Using this expression, we can also compute the value of the activation rate, a, for which persistence, P, is optimized (i.e. P has its maximum) by setting the derivative of P with respect to a to zero and solving for a. We find for the optimum value of the activation rate to be

$$a_0 = \frac{r m_n (2m_n + m_d) + m_n (m_n + m_d)^2}{r m_d - (m_n + m_d)^2}. \tag{3.11}$$

Substituting this expression and the result for I at steady state into equation 3.9 gives the optimal value for the fraction of hosts that activate

$$\alpha_o = \frac{r(2m_n + m_d) + (m_n + m_d)^2}{2r(m_n + m_d)}. \tag{3.12}$$

Similarly, substituting equation 3.11 into the expression for persistence, we find persistence at this optimum to be

$$P_0 = \frac{(2m_n r + m_d r - {m_n}^2 - 2m_n m_d - {m_d}^2)^2 S_0}{4(m_n + m_d)^2 r^2} \tag{3.13}$$

Figure 3.2a shows two curves of P as a function of the activation rate, with both optimal persistence, P_0, and optimal activation rate, a_0, indicated. The dashed lines corresponds to the analytical expressions just derived (i.e. with $k = f = w = 0$), the solid line shows

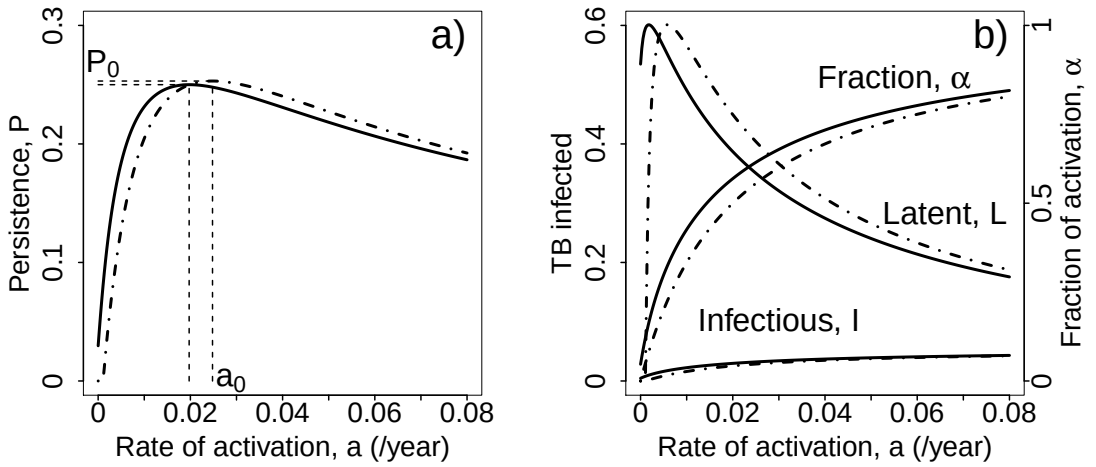


Figure 3.2: a) Persistence, P, as a function of activation rate. b) Latent and infectious hosts, $\hat{L}$ and $\hat{I}$, as functions of activation rate. Figure also shows the fraction of activation, α, as a function of activation rate. α is plotted as the second vertical axis on the right. Dashed lines show case with no re-infection, fast activation and recovery ($f = w = k = 0$), all other parameters are as given in table 3.1). Solid line shows case with all parameter values as reported in given in table 3.1).

P for the general scenario using the parameter values listed in table 3.1. The main finding shown through both the equations and the figure is that optimal persistence is achieved at intermediate rates of activation. Figure 3.2b shows the three components that make up P. The number of infectious host at steady state, as well as the fraction of hosts activating, α, increase with increasing activation rate. The number of latent hosts first increases and then decreases with larger activation rate. The combination of these three quantities leads to a maximum for persistence P at intermediate values.

Optimal persistence at an intermediate rate of activation also implies via equation 3.9 that instead of having every latent host activate and become infectious, it is beneficial for the pathogen to let some infections "go to waste" by way of latent hosts dying before they become infectious. This helps with overall persistence and is worth the "loss" of a fraction of latent hosts due to natural death before they activate and are able to transmit. Figure 3.3 shows persistence as a function of the fraction of hosts that activate. The figure also

illustrates another interesting point: The optimal fraction of hosts that activate is slightly above 50%. This is higher than the observed ≈10%, suggesting that MTB is not able to achieve the activation rate that would optimize its persistence. This can likely be attributed to the host immune response playing a role at reducing activation.

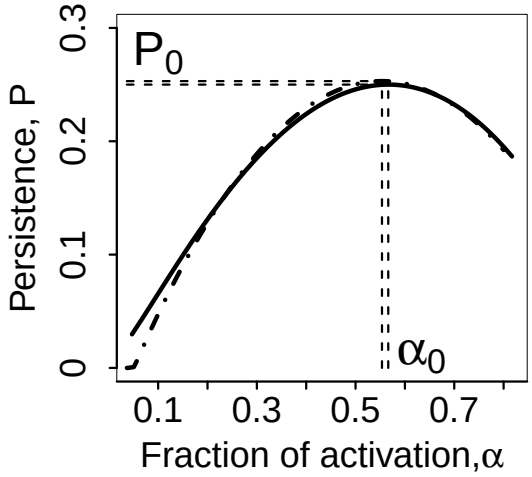


Figure 3.3: Persistence as function of fraction of hosts that activate. Dashed lines show case with no re-infection, fast activation and recovery ($f = w = k = 0$), all other parameters are as given in table 3.1). Solid line shows case with all parameter values as reported in given in table 3.1).

3.3.2 The deterministic persistence measure is well reproduced with a stochastic model

So far, and again in the results we show below, we consider a persistence measure, P, derived from a deterministic model. Of course, non-persistence, i.e. extinction, is an inherently stochastic process. While it is generally well known that larger populations – which is essentially what P measures – lead to less chance of extinction [71–73], it is useful to test our deterministic measure with a stochastic model. To that end, we implemented the differential equations as a compartmental stochastic model, with transition rates of the deterministic model becoming transition probabilities. We simulated the stochastic model using an efficient

form of the Gillespie algorithm (the adaptive-τ leap method as implemented in the R package adaptivetau [74, 75]). Starting at the equilibrium state, we simulated the model for a fixed number of years and record the fraction of simulations for which at least one infectious or latent individual was still present at the end of the simulation. Note that in contrast to the deterministic model, for the stochastic simulations we do not discount the latent class by considering only those that become active TB cases. Figure 3.4 shows that despite this minor difference in definition, the fraction of simulations for which persistence was found in the stochastic model has a very similar functional shape as our deterministic persistence measure, P. Having shown that P is an appropriate way to quantify persistence, we focus – for reasons of numerical feasibility – on P as derived from the deterministic model in the remainder of the paper. In the following sections, we explore how optimal activation rate and persistence depend on other characteristics of host and pathogen.

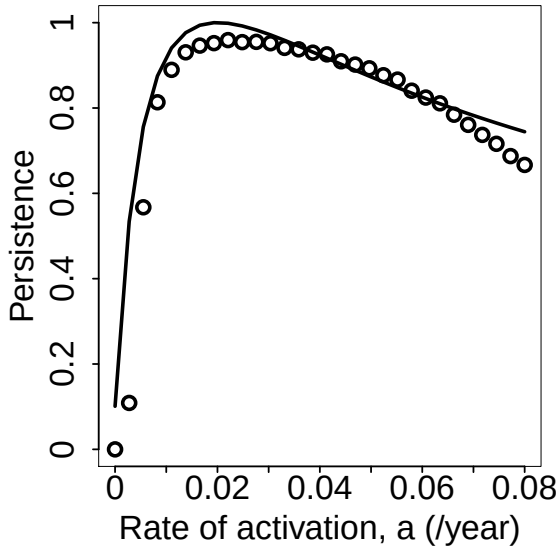


Figure 3.4: Persistence probability obtained from the stochastic model as a function of activation rate. Symbols show results obtained from stochastic simulations. Starting at the steady state, we ran the model for 1000 years and counted the numbers of runs for which any latent or infectious hosts were still present at the end of the simulation. The model was run 10,000 times, and a population of size 50 was used. The line shows the deterministic persistence measure, P. Note that because the absolute magnitude of P is arbitrary and scales with population size, for better comparison with the stochastic extinction probability we rescaled P to be between 0 and 1.

3.3.3 The impact of natural and disease induced mortality on TB persistence and optimal activation

As equations 3.11 and 3.13 indicate, optimal persistence and activation rate depend on both natural and disease induced mortality rates, m_n and m_d. Figure 3.5 shows heat map plots of persistence, P, as a function of these mortality rates and the rate of activation. In general, a higher natural mortality rate, i.e. a shorter life-span, leads to better persistence. This potentially non-intuitive finding stems from the fact that we consider a constant population size, and a longer lifespan implies a lower birth rate. The slower replenishment of new susceptible hosts at lower mortality rates leads to worse persistence. If we increased life-span while keeping birthrate the same, the size of the total population would increase and therefore persistence would improve (not shown). As mortality rate increases, so does the optimal rate of activation (black line). This makes intuitive sense as a shorter life expectancy of latently infected hosts requires faster activation, otherwise most hosts die before activation is possible.

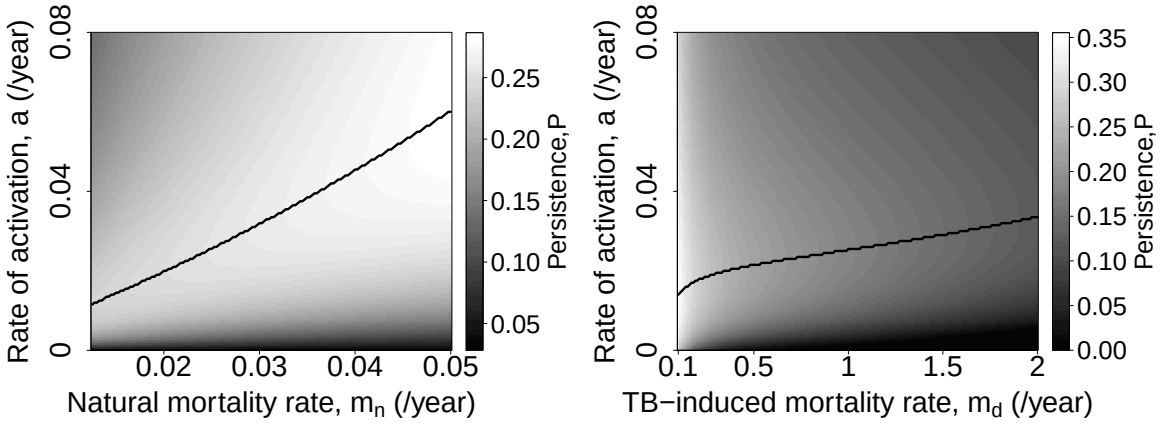


Figure 3.5: The impact of natural (left) and disease induced (right) mortality rate on TB persistence and optimal rate of latent activation. Remaining parameter values are as given in table 3.1. The black line shows the rate of activation which optimizes persistence for every value of the mortality rates.

For disease induced mortality, we find that an increase leads to reduced persistence, and the optimal rate of activation slightly increases. This can be explained by the fact that for

short life expectancies of infectious hosts, the pathogen "burns through" infectious hosts so quickly that it cannot afford a long latency period without going extinct. While good historic estimates for the mortality rate of TB are not readily available, it is reasonable to assume that improved nutrition and overall health have in general reduced TB induced mortality. Our results suggest that – all else being equal – a reduction of mortality rate and thereby an increase in infectious hosts favors TB persistence. In recent years, HIV has had a strong impact on TB infection dynamics. TB patients infected with HIV tend to have a strongly reduced life expectancy [41]. Our results imply that for such a situation, TB would benefit from an increased activation rate. Indeed, TB infected hosts who are also infected with HIV activate at a rate almost 100 times faster than those not infected with HIV [16]. While this is unlikely an evolutionary strategy of TB – the timespan is simply too short for this – but instead a side-effect of HIV's immunosuppressive features, our model suggests that this shorter latency helps the persistence of TB. For a complementary analysis, which focuses on disease-induced mortality (i.e. virulence) as the main outcome and investigates how other factors affect the potential evolution of virulence, see [18].

3.3.4 The impact of infection and reinfection rate on TB persistence and optimal activation

The transmissibility (infectiousness) of any disease is known to have a major impact on disease dynamics. As figure 3.6 shows, it also affects persistence and optimal activation rate. As infection rate increases, the optimal rate of activation decreases. This is in some way the flip side to the finding above where increased disease mortality required increased activation to ensure enough infectious hosts are present. Here, as infection rate increases, fewer infectious hosts are required to maintain the chain of transmission and therefore a reduced rate of activation becomes the better strategy. Along the line of optimal activation,

persistence increases with infection rate. This is expected as higher number of transmission means better transmission, which will lead to better pathogen persistence. The increase in persistence is most pronounced for small values of the infection rate. This suggests that as control measures reduce infection rates, little potential impact on persistence might be expected initially, until transmission is reduced far enough. Once such a critical level has been reached, any further reduction will make extinction much more likely. The figure also shows that extinction is most likely if a reduction in infection rate could be achieved for low activation rates (bottom left part of infection rate plot). While potential future TB vaccines are likely not sterilizing, they might be able to reduce the activation rate or infectiousness of hosts, which, combined with treatment of infectious hosts, might be a very promising strategy toward driving MTB to extinction [76, 77].

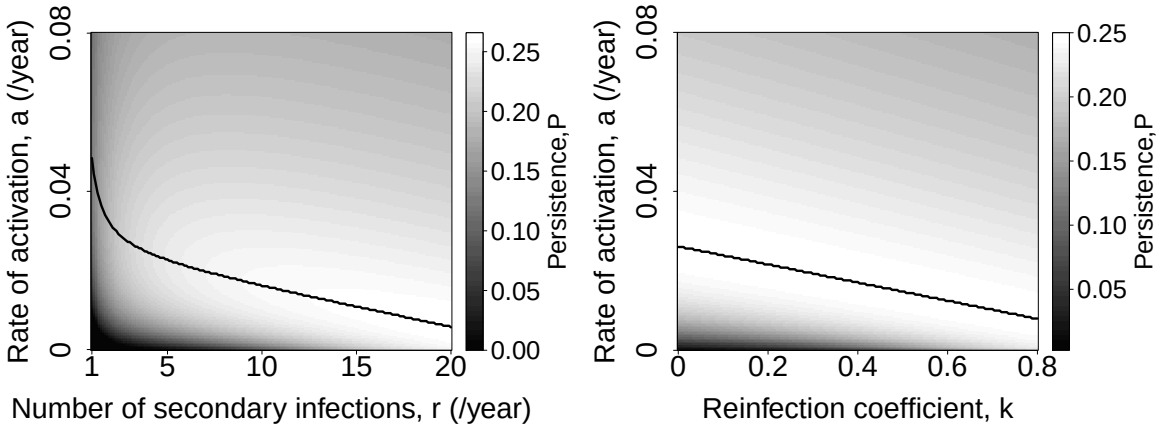


Figure 3.6: The impact of infection (left) and reinfection (right) on TB persistence and optimal rate of latent activation. Infection rate is measured by the annual number of secondary infections caused by an infectious host (r), reinfection is measured by the parameter k. Remaining parameter values are as given in table 3.1. The black line shows the rate of activation which optimizes persistence for every value of the infection and reinfection parameter.

In areas of high TB incidence and prevalence, it is likely that an already infected host in the latent stage is exposed to further TB infectious individuals and can become reinfected [78, 79]. In some hosts, this can lead to subsequent progression to disease [80]. As reinfection increases, the optimal rate of activation decreases to maintain the optimal balance between hosts in the latent and infectious stage (right panel in figure 3.6). Along the line of optimal

activation, increases in reinfection have almost no impact on persistence. Overall, optimal activation rate and persistence depend on reinfection rate in a manner very similar to the infection rate, and therefore the same considerations about extinction being most likely for low (re)infection and low activation rates apply again.

3.3.5 The impact of fast progression and regression on TB persistence and optimal activation

While most individuals infected with TB develop disease after a fairly long latent period (or never), some individuals progress to disease rapidly [7, 64, 65]. Figure 3.7 shows the impact of changing the fraction of fast progressors, f, on persistence and optimal activation rate. Optimal activation rates are highest when fast progressors are rare. This is expected, since both activation of latent and fast progression have similar effects by moving latent hosts into the infectious compartment. Therefore, as fast progressors increase, a reduction in activation rate compensates to maintain the optimal balance between latent and infectious hosts. Persistence along the optimal activation rate curve slightly decreases as fast progressors increase. This suggests that fast progression is not beneficial for MTB persistence. Instead, having all hosts move through a latent stage is best. It is likely host heterogeneity which leads to a small fraction of hosts that develop disease rapidly, and not an evolutionary strategy of MTB.

Regression describes the process by which infectious, diseased hosts can revert to the asymptomatic and non-infectious latent stage, either spontaneously or through treatment [18]. Regression of TB infectious hosts acts as the reverse process of TB activation. Because of this, one expects that as regression increases, so does the optimal rate of activation. Figure 3.7 shows that this is indeed the case. Further, one finds that as regression rate increases,

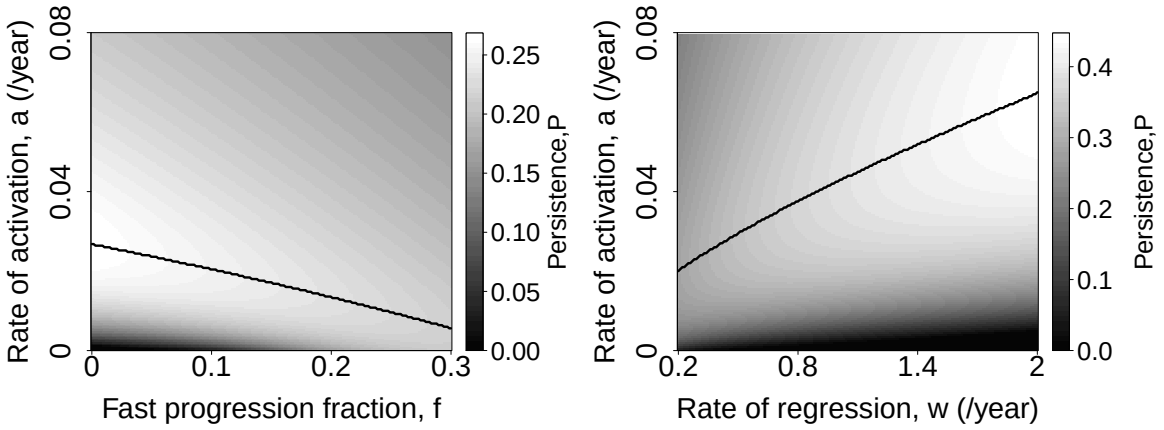


Figure 3.7: The impact of fast progression (left) and disease regression (right) on TB persistence and optimal rate of latent activation. Remaining parameter values are as given in table 3.1. The black line shows the rate of activation which optimizes persistence for every value of the fast progression and regression parameters.

persistence is improved. This suggests that increased treatment, which increases rates of movement from the infectious to the latent stage, could lead to higher persistence *if* TB is able to evolve toward higher activation rates. In contrast, if it were possible to increase regression rates and reduce the rate of activation, one could drive MTB toward the lower right corner of the figure which shows very low persistence, i.e. a high chance of extinction.

3.3.6 Persistence during epidemic cycles

We have so far focused on MTB persistence at the endemic state. Equally important for pathogens is the ability to persist after introduction to a newly susceptible population. Upon entering a fully susceptible population, pathogens usually cause an outbreak. This outbreak is often followed by a fade-out once most susceptibles have been depleted. For the pathogen to not go extinct, it needs to persist long enough until the number of susceptibles has built up again sufficiently, usually leading to consecutive smaller outbreaks until the endemic state is reached. Extinction can often occur during the fade-out right after the first outbreak. We

can quantify persistence during epidemic cycles by evaluating our expression for persistence not at the steady state but instead at the overall minimum occurring between introduction of the disease in a susceptible population and eventual attainment of the endemic equilibrium, i.e. we determine the overall minimum $P_m = \min_t[P]$. Figure 3.8 shows the same heat map plots as previously shown in figures 3.5-3.7, only instead of evaluating P at the steady state, we now plot the minimum persistence measure for all times P_m. The results are very similar to our findings in the previous section. The main reason for the similarity is that TB has a relatively "slow" disease dynamics [61], without pronounced outbreak peaks and minima. Therefore for most parameter values, the disease reaches the steady state without a large contraction after the first outbreak, leading to essentially the same results as for the steady state. The only exceptions are observed for high infection, reinfection and fast progression rates (panels d-f). At those parameter values, there is indeed a minimum after the first peak, leading to slightly different values for persistence and the optimal rate of activation. However, the differences between these values and the steady state results are minor.

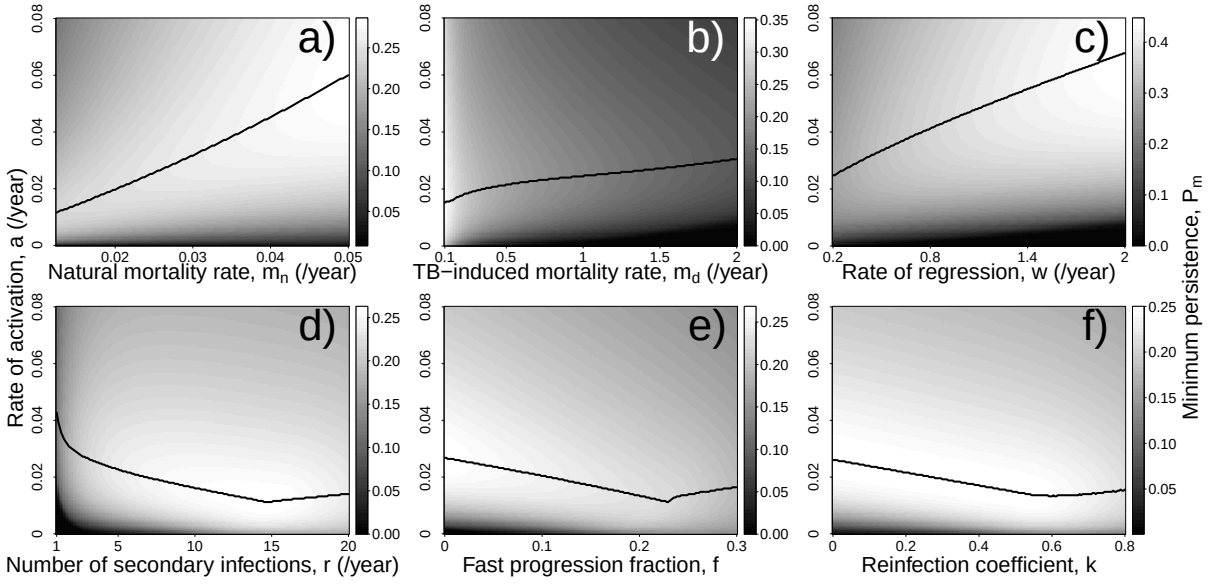


Figure 3.8: Persistence and optimal activation rates as function of model parameters. Figures are as shown previously in 3.5-3.7, with the difference that persistence P is determined at the overall minimum, defined as the lowest value for P after the peak of the first outbreak. Everything else is as explained for the previous figures.

3.4 Discussion

We used a mathematical model to investigate the role of activation rate and latency duration on the ability of MTB to persist in a host population. Our results support the previously proposed idea that the prolonged latency observed for TB infections might provide MTB an evolutionary advantage, namely improved persistence in a host population [49, 58]. We found that an intermediate rate of activation is optimal for persistence. Interestingly, this optimal rate ($a \approx 0.02$) suggests an optimal fraction of about 50% of host that eventually become cases (equation 3.9). This value is higher than the ≈10% generally seen for TB, suggesting that the host immune response plays some role in keeping TB disease in check, lowering activation rate below what would be the evolutionary optimal level for the pathogen. It is likely that some level of co-evolution between pathogen and host occurred and that humans who have been exposed to MTB for a long time evolved some level of resistance that potentially prevents MTB from reaching its evolutionary optimal activation rate [42]. This also agrees with the observation that upon contact with novel MTB strains, some populations have been shown to experience much higher rates of disease than the usually observed 10% [81]. It is further interesting to note that the optimal rate of activation we find in our study is similar to values reported for HIV positive TB patients [82–84]. While the simplicity of our model is a caveat in interpreting this agreement too quantitatively, this is another indication that the host immune response is responsible for keeping MTB activation rates below a value that would be optimal for MTB, and once the immune protection fails, as in HIV infected hosts, MTB activates at rates close to its optimum value.

We further investigated optimal persistence and activation rate as function of other host and pathogen phenotypes. It is of interest to discuss these results in light of important changes in TB dynamics over the last decades. Arguably one of the most important events was the emergence of HIV, leading to HIV-TB co-infections and subsequently altered infection

dynamics. In general, hosts infected with HIV (excluding the AIDS stage) seem to have similar susceptibility compared to non-HIV infected hosts [7], but higher disease induced mortality [41, 63, 85], higher fraction of fast progressors [7], possibly lower level of infectiousness [86, 87] and lower risk of reinfection [21, 22]. The rates of activation are also much higher [41, 84]. We find that an increase in disease induced mortality leads to reduced MTB persistence, no matter the rate of activation (figure 3.5). An increase in fast progressors, reduction of infectiousness and reduction of reinfection risk – with concomitant increase in activation rate – also leads to reduced persistence in most instances (figures 3.6,3.7). This suggests that while the resurgence of TB induced by the HIV epidemic is certainly a serious public health problem, it does not seem to improve MTB persistence.

Another important recent event is the increased prevalence of MTB strains resistant to some or all of the commonly used drugs. Those strains, knows as MDR-TB and XDR-TB, lead to reduced treatment success, i.e. reduced regression from the infectious to the latent stage in our model [53, 88, 89]. It is as of yet not completely clear if drug resistant strains differ in other infection characteristics. A reduced rate of regression implies a lower level of persistence. So again, as for HIV, with regard to persistence phenotype, drug resistance does not seem to be "helpful" for MTB – though obviously it provides the pathogen a large fitness advantage in the presence of drug treatment.

As all models are, ours is a simplified representation of the real world dynamics of TB transmission. As mathematical models for TB go, ours is on the simpler side, though it still incorporates all the important aspects of TB transmission dynamics [18]. We kept the model simple to allow for a thorough analysis. One feature inherent in our and more complicated models based on ordinary differential equations is the assumption of exponentially distributed periods. Most relevant for our study, the way the model is formulated assumes an exponentially distributed latency period. This is of course a somewhat unrealistic simpli-

fication. Models with more realistic distributions for the latent period have been proposed and studied [90, 91]. In that study, the authors found that the system behaved qualitatively similar to a simple ODE model. We expect the same for our system. While absolute values for our persistence measure might change, we expect the functional dependence of persistence and optimal latent period to be fundamentally preserved. While we are fairly certain that this will hold, it might nevertheless be worth checking this in a future study, as the assumptions about the distribution times have been shown to lead to some different results in certain infectious disease models [92, 93]. Other details could also be added to the model, such as more detailed population structure. While this will again likely change the details, we expect the overall result of optimal persistence at intermediate activation rates to hold.

In summary, our results suggest that an intermediate level of activation from latency to disease is optimal for MTB persistence, that the optimal level depends on the detailed pathogen, host and environment characteristics, and that it tends to be higher than the observed value, suggesting an important role for the immune response to keep MTB in check. While increasing activation rates beyond the optimum to reduce MTB persistence is not a suitable goal from a public health perspective, a reduction in activation rate is much more promising. This would lower the number of hosts with disease, and thereby reduce incidence and prevalence for TB cases and at the same time reduce persistence potential. Potential TB vaccines currently under consideration might help us to achieve such a shift in activation rate. If this shift is strong enough, eradication of MTB might become a possibility.

Chapter 4

Undetected Seronegative Cases May be "Hidden" Drivers of the Tuberculosis Epidemic in an Urban African Setting with High HIV Prevalence

4.1 Introduction

TB prevalence started to rise in the 1980s, which was mainly caused by the epidemics of HIV. WHO reported that about 13% of TB patients were co-infected with HIV. Among TB patients who dies in 2011, about 1/3 of them were co-infected with HIV [2]. TB also caused the most deaths among HIV positive individuals.

HIV and TB confection increases TB transmission in a population for several reasons. About 5% of HIV negative hosts develop TB shortly after infection whereas 18% of HIV positive host develop TB shortly after infection [7]. Activation of latent TB is much faster in HIV positive hosts than in HIV negative hosts [8]. Larger fraction of latent hosts who are HIV positive will develop TB disease than those who are HIV negative [8]. These all contribute to higher transmission of TB.On the other hand, TB patients who are HIV positive are normally less infectious and the duration of infectious are normally shorter. Studies shows that population of higher HIV prevalence tend to have higher TB prevalence [9].

TB control policy has emphasized the importance of treating TB patient who are co-infected with HIV. However, should TB control for TB patients who are HIV negative be put in the less important agenda? In the second part of the project, I used a mathematical model to explore the impact of HIV prevalence in TB epidemic.

4.2 Method

Brief overview of the mathematical model

Our mathematical model describes infection dynamics of TB and HIV in the presence of TB and HIV treatment. The general form follows models previously described and studied by others (see e.g. table 2 in [9] for a review of such models). We consider human hosts in one of 3 states with regard to TB infection, namely non-infected and susceptible, latently infected, and diseased and infectious. In addition, each person is characterized according to 3 possible states with regard to their HIV status. We consider HIV negative hosts, hosts that are infected with HIV and do not receive antiretroviral therapy (ART), and hosts infected with HIV that do receive ART. The classification according to one of 3 TB infection states

and one of 3 HIV states leads to a total of 9 model compartments. The flowchart for the model is shown in figure 4.1. Detailed descriptions for each of the model components are provided in the following sections. Tables for all model variables and parameters and the set of differential equations used to implement and simulate the model are shown at the end of this supplementary material.

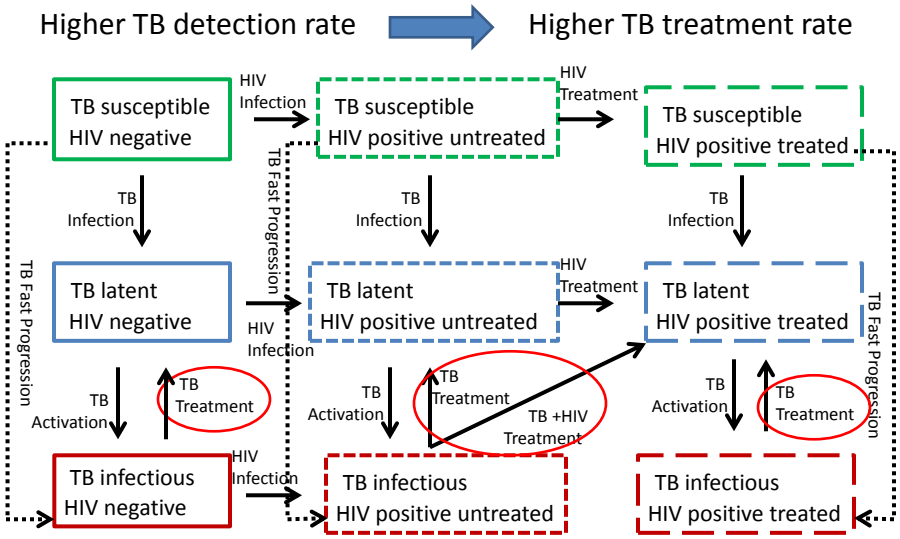


Figure 4.1: Flow chart for the mathematical model describing TB and HIV infection dynamics. Susceptible hosts not infected with TB can come in contact with a TB-infectious host. A fraction of newly infected hosts immediately progress to full blown infectious TB, while the majority enters the TB latency stage. Hosts with latent TB can activate and become TB diseased and infectious. As is commonly assumed, treatment of TB moves hosts from the active TB stage back to the latent stage. Rates and probabilities of transitioning between susceptible, latent and infectious TB compartments depends on HIV status, as described in more detail in the text. At any stage of TB infection, a host can become infected with HIV, and subsequently potentially receive antiretroviral treatment. Not shown in the flow chart are arrows for natural births and deaths, which are included in the model as described in the text. Table 4.1 lists all variables used in the model, the remaining tables list the various model parameters.

Population size, births and deaths

Consistent with the experimental study, our model describes an adult population in Uganda; more specifically, the Rubaga division of Kampala, Uganda's capital. The population of Rubaga was estimated to be about 295,000 in 2002 [94]. As was done in the experimental study, we only consider adults (age 15 or above). For Uganda, about 50 percent of the population is of age 15 or above [94]. For our model, we therefore assume a population size of $N = 147,500$.

The average life expectancy in Uganda is estimated to be about 50 years [94]. Since we only model adults, the average time a person spends in one of the compartments of the model is 50-15=35 years. We therefore set the natural mortality rate for uninfected hosts to $\mu = 1/35$ per year.

We assume that individuals enter our model (i.e. turn 15 years old) at a constant rate, consistent with the usual modeling approach [61, 95–97]. The rate is chosen to maintain a constant population in the absence of disease. For a population of size N, with death rate (inverse of average life expectancy) μ, the birth/entry rate is defined as $\pi = N\mu$, with N and μ values as just described.

Mortality is increased for hosts that either have TB disease or are HIV positive and do not receive ART. For hosts that do not have active TB disease but are HIV positive and do not receive ART, life expectancy has been estimated to be around 10 years [98], leading to $\mu_{+u} = 1/10$ per year. Hosts that have HIV and do receive ART have been estimated to live approximately twice as long as HIV infected hosts not on ART [99]. We therefore set $\mu_{+t} = 1/20$ per year.

Hosts with active (untreated) TB disease who are HIV negative live for approximately 3 years [63], which leads to a mortality rate of $\delta_{-} = 1/3$ per year. For active TB and HIV positive

hosts not on ART, the life expectancy is less than a year and possibly only a few months [41, 63, 85]. We chose a value of 9 months, which leads to a mortality rate of $\delta_{+u} = 4/3$ per year. Good data is lacking on the survival for HIV infected hosts with active TB who receive ART; we make the assumption that they have a life expectancy similar to HIV negative TB cases, i.e. we set $\delta_{+t} = 1/3$ per year.

The demographic parameters just described are summarized in Table 4.2.

TB infection

Persons who have TB disease are infectious and can infect uninfected hosts or re-infect hosts who harbor latent TB. HIV status of the TB infectious host is known to affect the level of infectiousness. In our model, the maximum number of new infections per year caused by one TB infectious host is given by a rate k_j, where the index j indicates the HIV status (1 = uninfected, 2 = HIV infected untreated, 3 = HIV infected treated). Recent estimates for the annual number of new infections caused by a TB case are in the range of 3-13 per year, with most estimates well below the often-made assumption of 10 per year [100, 101]. These estimates are for real world settings, which include detection and treatment and a not fully susceptible population. For our model, we need the maximum number of possible new infections assuming a fully susceptible population and no interventions. We therefore correct that value upward and set the maximum annual transmission rate as $k_1 = 15$ per year for HIV negative hosts. HIV infection seems to not increase, and maybe even decrease infectivity of TB cases [86, 87]. We assume a moderate reduction in infectiousness for HIV positive hosts not on ART and set $k_2 = 0.8k_1$. We further assume that HIV positive hosts receiving ART have an infectiousness that is intermediate between HIV negative and HIV positive untreated hosts and set $k_3 = (k_1 + k_2)/2$.

A recent study in Uganda indicated that susceptibility to TB infection (but not disease) is similar among individuals independent of HIV status [7]. We therefore assume in our model that the susceptibility for TB infection of TB uninfected individuals is the same regardless of HIV status, and can therefore omit additional parameters describing differential susceptibility from our model.

Table 4.3 summarizes the parameters discussed in this section.

Progression from TB latency to infectiousness

Upon TB infection, newly infected individuals either rapidly develop disease (fast progression) or remain latent for an extended period and possibly develop disease later in life (slow progression). The fraction of fast progressors depends on HIV status. Parameters p_1, p_2, and p_3 quantify the fraction of fast progressors for each HIV status (uninfected, infected untreated, infected treated). The fraction of TB-infected HIV negative persons that develop fast progression to active TB is generally between $0.05 - 0.1$ and has been estimated for Uganda at 0.053 [7], which we will use here, i.e. we set $p_1 = 0.053$. The estimated fraction of fast progression for HIV positive hosts not on ART has been estimated for Uganda to be 0.186 per year [7], which is the rate we use here ($p_2 = 0.186$). As far as we are aware, there are no studies on the impact of HIV treatment on TB progression. However, previous studies suggested that ART treatment was correlated with a reduction of TB incidence [102]. This suggests that HIV treatment might reduce the impact of HIV infection on TB progression. We therefore set the the fraction of fast progressors for HIV positive, treated hosts to a value between HIV negative and HIV positive untreated hosts. Specifically, we chose $p_3 = (p_1 + p_2)/2$.

Hosts that do not immediately progress to TB disease enter the latent stage. These hosts

can eventually transition into the TB disease stage. This transition again depends on HIV status. The rate of transition from latent TB to TB disease for HIV negative adult hosts was estimated to be broadly in the range of $0.0003-0.0034$ per year [103]. We use an intermediate value and set $\nu_1 = 0.001$ per year. For HIV positive hosts not on ART, transition from latent TB to TB disease occurs at faster rates [41]. Some estimates are 0.079 per year in [82], 0.054 per year in [83] and 0.034 in [84]. We use the value from [84] as this data comes from a Ugandan population, and set $\nu_2 = 0.034$ per year. While ART treatment of HIV positive hosts has been shown to reduce the incidence of TB [104], it is unclear if this is due to a reduced fraction of fast progressors or a reduced rate of slow progression. In the absence of more solid data, we assume that the presence of ART lowers the rate of slow progression by a moderate factor of two, i.e. we choose $\nu_3 = 0.5\nu_2$ per year.

Another transition from latent TB infection to TB disease can occur through re-infection. The risk of developing active TB following reinfection is smaller compared with TB disease following initial infection (i.e. fast progression). Therefore, the proportions for TB disease following reinfection, which we label q_1, q_2, and q_3, are lower than the corresponding fractions (p_i) for new infections. For HIV negative hosts, reported estimates are in the range of $16\% - 82\%$ [64, 65, 80]. We choose a intermediate value and assume a risk reduction of 50% for our model ($q_1 = 0.5p_1$). For HIV positive, untreated persons, data does not seem to exist. Two recent modeling studies [21, 22] assumed a reduction of risk by 25%, which we follow and set $q_2 = 0.75p_2$. For HIV positive hosts on ART, we again assume the value between HIV negative and HIV positive untreated hosts and therefore set $q_3 = 0.625p_3$.

Table 4.4 summarizes the progression parameters.

TB treatment

Hosts with TB disease can receive treatment and thereby be cured from active TB. Following e.g. [9, 23, 91, 95], we assume that those hosts return to the TB latent class. The population-level average for the time it takes to go from onset of infectiousness to cure depends on the time between start of infectiousness and detection, the duration between detection and successful treatment, and the fraction of hosts that are successfully treated. Estimates for these values will vary widely between settings and are difficult to come by. One recent study in Uganda found that index cases had a median cough duration of 90 days, with a wide range between 1 - 730 days [3]. Another recent study in Uganda found that only 21% of patients with prolonged cough where referred for TB testing and 71% of those testing positive received treatment [105]. Combining the values for duration between infectiousness and detection/treatment with the fraction of those receiving diagnosis/treatment, we choose as a conservative estimate a population level average time to treatment of 3 years, leading to $\rho_1 = 1/3$ per year. Cure rates for TB seem to be similar for HIV negative and HIV positive hosts not on ART [106]. Since there is no reason to assume that HIV positive hosts not on ART have more frequent contact with the health system than HIV negative hosts, we assume the fraction of those that are being treated and the timing for treatment is the same as in the HIV negative hosts , i.e. we set $\rho_2 = \rho_1$. Since HIV positive hosts who receive ART are already under "health surveillance", it is likely that they are detected and treated faster and at greater coverage once they develop TB disease. Our study finding that the proportion of cases detected through active case finding was greater among the HIV negative than HIV positive participants supports this notion. To reflect this, we assume that treatment rate in this class is higher, and set $\rho_3 = 2\rho_2$ per year. Finally, it is becoming common for a person receiving TB treatment to also be tested for HIV and if tested positive, potentially being placed on ART. We therefore assume that a fraction of the HIV positive

hosts that are not on ART, when receiving TB treatment are also placed on ART and move into the TB-latent, HIV positive, ART treated category. WHO reported that 48% of TB patients that are infected with HIV are on ART in 2011 [2]. We set the proportion for such double-treatment to $a = 0.48$.

Table 4.5 summarizes all treatment related parameters.

HIV transmission and treatment

As we do for TB transmission, we make the common assumption that HIV transmission can be modeled with a simple frequency-dependent term. The maximum rate of HIV transmission, d, is varied in our study to adjust the level of HIV prevalence, as explained further below. Note that several recent modeling studies described HIV transmission differently, namely using a term in which per-person transmission declined as HIV prevalence increased. This was used to better describe the observed data and justified by the fact that high HIV prevalence might lead to behavior changes that effectively reduce per-person transmissibility [9, 107]. For our model, our focus is not on HIV, and in fact we vary HIV prevalence to observe its impact on TB prevalence. We therefore did not implement this more complex transmission assumption, which would have no impact on our results. Since HIV positive hosts on ART are aware of their HIV status and are likely to take precautions, combined with a strongly reduced viral load, we make the approximate assumption that only HIV positive hosts not on ART are infectious. Again, changing this assumption would only impact HIV transmission and therefore HIV prevalence, and would not affect our results.

A fraction of HIV positive hosts receive ART. The estimated fraction of HIV positive hosts on ART in Uganda in 2005 was 21%, while this number was 33% in 2007 [108]. We assume 25% for our model. We assume that ART coverage is the same for TB uninfected and TB

latent hosts. We chose the rate of ART treatment in our model such that we observed a 25% ART coverage of HIV positive hosts at steady state for both TB uninfected and TB latent hosts, which lead to $\tau = 0.015$ per year. We assume that HIV positive hosts that also have TB disease do not receive ART only, they are assumed to always be treated for TB. A fraction of them is treated for HIV as well, as described in the previous section.

Table 4.6 summarizes the HIV related parameters.

Model Implementation

The model was implemented in the R programming language [60]. The R code is available upon request. We varied the HIV transmission rate, d, which allowed us to change the level of HIV prevalence in the population. For each value of d, we ran the simulation until we reached an endemic equilibrium. We then recorded HIV prevalence and prevalences of TB disease for HIV negative and HIV positive individuals in the population. These results were plotted with HIV prevalence as the x-axis and TB prevalences as the y-axis.

Tables of model variables and parameters

Symbol	Interpretation
S_-	number of TB susceptible and HIV(-) persons
L_-	number of TB latent and HIV(-) persons
I_-	number of TB infectious and HIV(-) persons
S_{+u}	number of TB susceptible and HIV(+,untreated) persons
L_{+u}	number of TB latent and HIV(+,untreated) persons
I_{+u}	number of TB infectious HIV(+,untreated) persons
S_{+t}	number of TB susceptible and HIV(+,treated) persons
L_{+t}	number of TB latent and HIV(+,treated) persons
I_{+t}	number of TB infectious and HIV(+,treated) persons
N	total population (sum of all above compartments)
H	total number of HIV positive, untreated persons ($S_{+u} + L_{+u} + I_{+u}$)

Table 4.1: Model variables

Symbol	Meaning	Value
N	Population size	147,500
μ	Mortality rate for HIV- and non-infectious TB adults	$\frac{1}{35}$ per year
π	Annual inflow ("births")	$\pi = N\mu$
μ_{+u}	Mortality rate for HIV+ untreated persons	$\frac{1}{10}$ per year
μ_{+t}	Mortality rate for HIV+ treated adults	$\frac{1}{20}$ per year
δ_-	Mortality rate for TB infectious HIV- persons	$\frac{1}{3}$ per year
δ_{+u}	Mortality rate for TB infectious HIV+ untreated persons	4/3 per year
δ_{+t}	Mortality rate for TB infectious HIV+ treated persons	δ_-

Table 4.2: Demographic parameters. See the text for references to sources for the chosen values.

Symbol	Meaning	Value
k_1	Maximum number of annual new TB infections by one TB infectious and HIV- person	15 per year
k_2	Maximum number of annual new TB infections by one TB infectious HIV+ untreated person	$0.8 * k_1$
k_3	Maximum number of annual new TB infections by one TB infectious HIV+ treated person	$(k_1 + k_2)/2$

Table 4.3: TB transmission parameters. See the text for references to sources for the chosen values.

Symbol	Meaning	Value
p_1	Fraction of fast progressors among HIV- hosts	0.053
p_2	Fraction of fast progressors among HIV+ untreated hosts	0.186
p_3	Fraction of fast progressors among HIV+ treated hosts	$(p_1 + p_2)/2$
ν_1	Rate of TB latent HIV- persons becoming TB infectious by slow progression	0.001 per year
ν_2	Rate of TB latent HIV+ untreated persons becoming TB infectious by slow progression	0.034 per year
ν_3	Rate of TB latent HIV+ treated persons becoming TB infectious by slow progression	$0.5\nu_2$
q_1	Fraction of reinfection of HIV- persons that will cause active TB	$0.5p_1$
q_2	Fraction of reinfection of HIV+ untreated persons that will cause active TB	$0.75p_2$
q_3	Fraction of reinfection of HIV+ treated persons that will cause active TB	$0.625p_3$

Table 4.4: TB progression parameters. See the text for references to sources for the chosen values.

Symbol	Meaning	Value
ρ_1	Rate at which TB infectious HIV- persons are treated	1/3 per year
ρ_2	Rate at which TB infectious HIV+ untreated persons are treated	ρ_1
ρ_3	Rate at which TB infectious HIV+ treated person are treated	$2\rho_1$
a	Fraction of TB infectious HIV+ untreated persons treated to TB latent HIV+ treated	0.48

Table 4.5: TB treatment parameters. See the text for references to sources for the chosen values.

Symbol	Meaning	Value
d	HIV transmission rate	varied
τ	HIV treatment rate for TB susceptible and latent, HIV+ hosts	0.015 per year

Table 4.6: HIV transmission and treatment parameters. See the text for references to sources for the chosen values.

Model equations

$$\underbrace{\frac{dS_-}{dt}}_{\boxed{\text{Change of number of HIV negative and TB susceptible hosts with time}}} = \underbrace{\pi}_{\boxed{\text{Inflow of HIV negative and TB susceptible}}} \underbrace{-(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{S_-}{N}}_{\boxed{\text{Outflow due to TB Infection}}} - \underbrace{d\frac{H}{N}S_-}_{\boxed{\text{Outflow due to HIV infection}}} - \underbrace{\mu S_-}_{\boxed{\text{Outflow due to death}}} \tag{4.1}$$

$$\underbrace{\frac{dS_{+u}}{dt}}_{\boxed{\text{Change of number of HIV positive untreated and TB susceptible hosts with time}}} = \underbrace{d\frac{H}{N}S_-}_{\boxed{\text{Inflow due to HIV infection of TB susceptibles}}} \underbrace{-(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{S_{+u}}{N}}_{\boxed{\text{Outflow due to TB Infection}}} - \underbrace{\tau S_{+u}}_{\boxed{\text{Outflow due to HIV treatment}}} - \underbrace{\mu_{+u} S_{+u}}_{\boxed{\text{Outflow due to death}}} \tag{4.2}$$

$$\underbrace{\frac{dS_{+t}}{dt}}_{\substack{\text{Change of number of HIV positive treated and TB susceptible hosts with time}}} = \underbrace{\tau S_{+u}}_{\substack{\text{Inflow due to treatment of HIV positive hosts}}} - \underbrace{(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{S_{+t}}{N}}_{\text{Outflow due to TB Infection}} - \underbrace{\mu_{+t} S_{+t}}_{\substack{\text{Outflow due to death}}} \tag{4.3}$$

$$\begin{aligned}\underbrace{\frac{dL_-}{dt}}_{\substack{\text{Change of number of HIV negative and TB latent hosts with time}}} = {} & \underbrace{(1-p_1)(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{S_-}{N}}_{\substack{\text{Inflow due to slow progression part of TB infection of susceptibles}}} + \underbrace{\rho_1 I_-}_{\substack{\text{Inflow due to treatment of TB patients}}} - \underbrace{v_1 L_-}_{\substack{\text{Outflow due to TB latent activation}}} \\ & - \underbrace{q_1(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{L_-}{N}}_{\text{Outflow due to TB reinfection}} - \underbrace{d\frac{H}{N}L_-}_{\substack{\text{Outflow due to HIV infection}}} - \underbrace{\mu L_-}_{\substack{\text{Outflow due to death}}}\end{aligned} \tag{4.4}$$

$$\underbrace{\frac{dL_{+u}}{dt}}_{\substack{\text{Change of number of HIV positive untreated and TB latent hosts with time}}} = \underbrace{(1-p_2)(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{S_{+u}}{N}}_{\text{Inflow due to slow progression part of TB infection of susceptibles}} + \underbrace{d\frac{H}{N}L_-}_{\text{Inflow due to HIV infection of TB latent hosts}} + \underbrace{(1-a)\rho_2 I_{+u}}_{\text{Inflow due to treatment of TB patients}}$$

$$\underbrace{-q_2(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{L_{+u}}{N}}_{\text{Outflow due to TB reinfection}} - \underbrace{v_2 L_{+u}}_{\text{Outflow due to TB latent activation}}$$

$$- \underbrace{\tau L_{+u}}_{\text{Outflow due to HIV treat-ment}} - \underbrace{\mu_{+u} L_{+u}}_{\text{Outflow due to death}} \tag{4.5}$$

$$\underbrace{\frac{dL_{+t}}{dt}}_{\substack{\text{Change of number of HIV positive treated and TB latent hosts with time}}} = \underbrace{(1-p_3)(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{S_{+t}}{N}}_{\text{Inflow due to slow progression part of TB infection of susceptibles}} + \underbrace{\tau L_{+u}}_{\text{Inflow due to HIV treatment}} + \underbrace{\rho_3 I_{+t}}_{\text{Inflow due to TB treatment}}$$
$$+ \underbrace{a\rho_2 I_{+u}}_{\text{Inflow due to TB+HIV treatment}} - \underbrace{-q_3(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{L_{+t}}{N}}_{\text{Outflow due to TB reinfection}}$$
$$- \underbrace{v_3 L_{+t}}_{\text{Outflow due to latent TB activation}} - \underbrace{\mu_{+t} L_{+t}}_{\text{Outflow due to death}} \tag{4.6}$$

$$\underbrace{\frac{dI_-}{dt}}_{\substack{\text{Change of number of HIV negative and TB infectious hosts with time}}} = \underbrace{p_1(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{S_-}{N}}_{\text{Inflow due to TB infection fast progression}} + \underbrace{q_1(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{L_-}{N}}_{\text{Inflow due to latent TB reinfection}}$$

$$\underbrace{+v_1 L_-}_{\text{Inflow due to latent TB activation}} - \underbrace{\rho_1 I_-}_{\text{Outflow due to TB treatment}} - \underbrace{d\frac{H}{N} I_-}_{\text{Outflow due to HIV infection}} - \underbrace{\delta_- I_-}_{\text{Outflow due to death}} \tag{4.7}$$

$$\underbrace{\frac{dI_{+u}}{dt}}_{\substack{\text{Change of number of HIV positive untreated and TB infectious hosts with time}}} = \underbrace{p_2(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{S_{+u}}{N}}_{\text{Inflow due to TB infection fast progression}} + \underbrace{q_2(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{L_{+u}}{N}}_{\text{Inflow due to latent TB reinfection}}$$

$$\underbrace{+v_2 L_{+u}}_{\substack{\text{Inflow due to latent TB activation}}} + \underbrace{d\frac{H}{N} I_-}_{\substack{\text{Inflow due to HIV infection}}} - \underbrace{\rho_2 I_{+u}}_{\substack{\text{Outflow due to TB+HIV treatment}}} - \underbrace{\delta_{+u} I_{+u}}_{\substack{\text{Outflow due to death}}} \tag{4.8}$$

$$\underbrace{\frac{dI_{+t}}{dt}}_{\substack{\text{Change of number of HIV positive treated and TB infectious hosts with time}}} = \underbrace{p_3(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{S_{+t}}{N}}_{\text{Inflow due to TB infection fast progression}} + \underbrace{q_3(k_1 I_- + k_2 I_{+u} + k_3 I_{+t})\frac{L_{+t}}{N}}_{\text{Inflow due to latent TB reinfection}}$$

$$+ \underbrace{v_3 L_{+t}}_{\substack{\text{Inflow due to latent TB activation}}} - \underbrace{\rho_3 I_{+t}}_{\substack{\text{Outflow due to TB treat-ment}}} - \underbrace{\delta_{+t} I_{+t}}_{\substack{\text{Outflow due to death}}} \tag{4.9}$$

4.3 Result

Figure 4.2 shows the impact of HIV prevalence on the TB epidemics. The data points are from a field study in Uganda. The figure suggests that for the HIV prevalence of about 9%, the main contribution of the TB prevalence is from the HIV- TB patients. HIV+ TB patients contribution only a small fraction to the overall TB prevalence. The figure also implies that when the HIV prevalence reaches about 25%, the contribution to the TB prevalence is about equally from HIV- and HIV+ TB patients. This result suggests that in the current world, TB controls should also emphasize controls for HIV- TB patients.

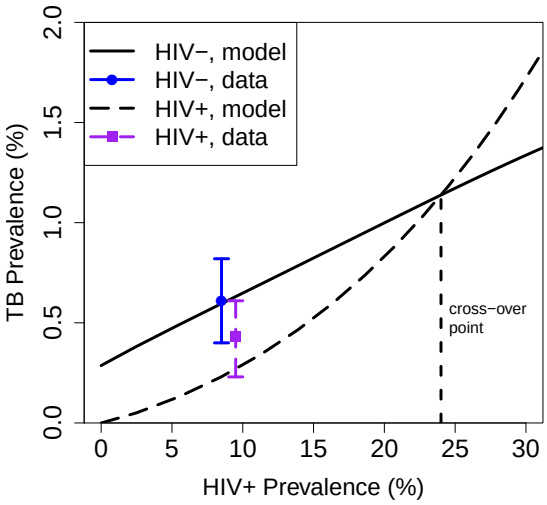


Figure 4.2: Impact of HIV prevalence on TB epidemics. The data line is from a field study from Uganda.

Chapter 5

Modeling Cost Effectiveness of Tuberculosis Active Case Finding for Urban and Rural Areas in Uganda

5.1 Introduction

Tuberculosis is an infectious disease that is still a burden in most part of the world. 1.3 million persons died due to TB and there were 8.7 million new TB cases worldwide in 2012 [2]. World health organization (WHO) has targeted to eliminate TB in the near future. WHO recommended directed observed therapy, short course (DOTS) for TB treatment practice. As for TB detection, the default method is pass case finding (PCF). Under PCF, individuals voluntarily go to hospital after coughing for some time. These individuals are tested for TB and placed for treatment if diagnosed with active TB disease. The delay from the onset of disease to the TB diagnosis and treatment normally lasts several months and up to two years [3]. During the duration of the delay, undiagnosed TB patients cough and potentially infect

uninfected individuals in contact. Detection and diagnosis techniques have been developed to help detect and treat TB patients earlier. One approach to detect TB patients earlier is active case finding (ACF). Under ACF, health care workers go out to the communities and seek suspected TB patients who have coughed for some time for TB test and diagnosis.

ACF helps detect TB patients earlier, which intuitively reduce the duration of infectiousness of TB patients. However it is not obvious whether implementation of ACF can significantly decrease TB prevalence in the population. Some studies suggested that ACF did not significantly impact TB incidence in a population[109–111]. This might be true as many studies were only conducted in a short period of time and the impact of ACF on TB prevalence might not have been fully realized yet. Mathematical modeling, on the other hand, can explore the impact of ACF for a longer time. Studies suggested that ACF can reduce TB incidence and deaths due to TB in high TB and high HIV settings [28, 29]. Although some studies suggested that TB treatment is the optimal TB control strategy, they also emphasized the importance of ACF for reducing TB prevalence and death due to TB.

To implement ACF for TB case detection, economic cost is one factor needed to be considered, especially in Africa countries where resources are limited. The additional cost for ACF implementation includes costs for surveys, door to door visits, TB tests, and TB treatments. The first part of cost involves the cost for health care personnel to detect individuals for TB tests. The second part of the additional cost is the cost of TB tests. ACF normally recommends individuals that cough for a certain period time for TB test. Obviously not all recommended individuals have active TB disease. The number of additional TB tests needed to detect an active TB patient is different for various ACF strategies. This number is possibly different for rural and urban areas. Rural individuals tend to live far away from the health center. The transportation fee for conducting ACF surveys is potentially higher. Many TB test might be needed to detect an active TB case as the TB prevalence is relatively

lower in the rural area.

TB and HIV transmission dynamics are different among rural and urban residents. Rural residents tend to live less crowded, have shorter life expectancy, and have limited access to health care compared with urban residents. This will lead to difference in the impact of ACF on TB incidence between rural and urban areas. Results suggest that ACF implementation is more cost effective in the urban area than in the rural in terms of cost per TB case averted and ACF is more cost effective if implemented for a longer period.

For health policy maker in Uganda, the key questions to implementing ACF would be whether ACF implementation will significantly reduce TB prevalence and where money can be better spent. I used a mathematical model to simulate TB epidemic in Uganda. We analyzed cost effectiveness for ACF implementation in rural and urban areas. We also compared the short term and long term benefits of ACF implementation in both rural and urban areas.

5.2 Method

5.2.1 Brief overview of the mathematical model

Our mathematical model describes infection dynamics of TB and HIV in the presence of TB and HIV treatment. The general form follows models previously described and studied by others (see e.g. table 2 in [9] for a review of such models). We consider human hosts in one of 4 states with regard to TB infection, namely non-infected and susceptible, latently infected, and diseased and infectious undiagnosed, diseased and infectious diagnosed. Undiagnosed TB patients can be detected with passive case finding (PCF) and moved to the diagnosed group. These patients can be detected and moved to diagnosed group with periodic active case finding (ACF). In addition, each person is characterized according to 3 possible states

with regard to their HIV status. We consider HIV negative hosts, hosts that are infected with HIV and do not receive antiretroviral therapy (ART), and hosts infected with HIV that do receive ART. The classification according to one of 3 TB infection states and one of 3 HIV states leads to a total of 9 model compartments. The flowchart for the model is shown in figure 5.1. Detailed descriptions for each of the model components are provided in the following sections. Tables for all model variables and parameters and the set of differential equations used to implement and simulate the model are shown at the end of this supplementary material.

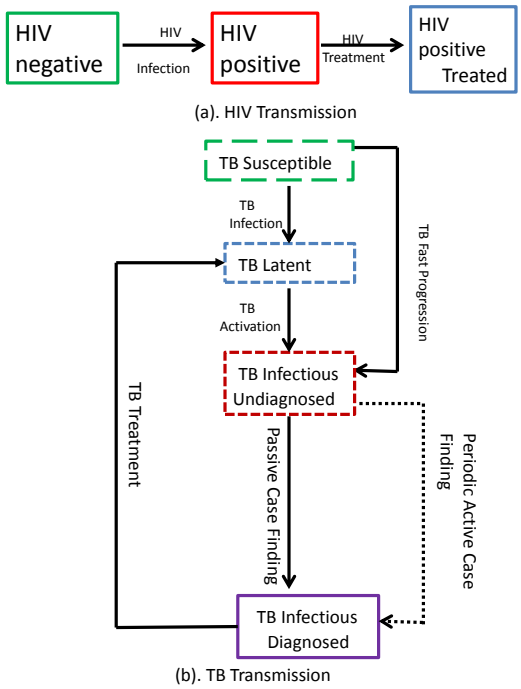


Figure 5.1: Flow chart for the mathematical model describing TB and HIV infection dynamics. Susceptible hosts not infected with TB can come in contact with a TB-infectious host. A fraction of newly infected hosts immediately progress to full blown infectious TB, while the majority enters the TB latency stage. Hosts with latent TB can activate and become TB diseased and infectious. As is commonly assumed, treatment of TB moves hosts from the active TB stage back to the latent stage. Rates and probabilities of transitioning between susceptible, latent and infectious TB compartments depends on HIV status, as described in more detail in the text. At any stage of TB infection, a host can become infected with HIV, and subsequently potentially receive antiretroviral treatment. Not shown in the flow chart are arrows for natural births and deaths, which are included in the model as described in the text. Table 4.1 lists all variables used in the model, the remaining tables list the various model parameters.

5.2.2 Model Symbols and Parameters

5.2.2.1 Model Symbols

The symbols we use to represent different groups of individuals are shown in table 5.1

Symbol	Interpretation
S_-	number of TB susceptible and HIV(-) persons
L_-	number of TB latent and HIV(-) persons
I_-	number of TB infectious and HIV(-) persons
S_{+u}	number of TB susceptible and HIV(+,untreated) persons
L_{+u}	number of TB latent and HIV(+,untreated) persons
I_{+u}	number of TB infectious HIV(+,untreated) persons
S_{+t}	number of TB susceptible and HIV(+,treated) persons
L_{+t}	number of TB latent and HIV(+,treated) persons
I_{+t}	number of TB infectious and HIV(+,treated) persons
N	total population (sum of all above compartments)
H	total number of HIV positive, untreated persons ($S_{+u} + L_{+u} + I_{+u}$)

Table 5.1: Model variables

5.2.2.2 Population size, births and deaths

To better compare differences between urban and rural settings, we choose to simulate a population of 100,000 persons for each setting. The average life expectancy in Uganda is estimated to be about 55 years [108]. No information on differences between urban and rural settings was available. While better access to health care might lead to higher life expectancy in urban areas, a less strong social net, increased pollution, accidents and similar factors might have a negative impact. Given the lack of solid information, we made the assumption that average life expectancy is the same in urban and rural settings. Since we only consider individuals older than 15 years in our study, the average time a person spends in one of the compartments of the model is 55-15=40 years. We therefore set the natural mortality rate for uninfected hosts to $\mu = 1/40$ per year in both urban and rural

populations. We assume that individuals enter our model (i.e. turn 15 years old) at a constant rate, consistent with the usual modeling approach [61, 95, 112, 113]. The rate is chosen to maintain a constant population in the absence of disease. For a population of size N, with death rate (inverse of average life expectancy) μ, the birth/entry rate is defined as $\pi = N\mu$, with N and μ values as just described.

Mortality is increased for hosts that either have TB disease or are HIV positive. Life expectancy of HIV infected individuals not on ART was estimated to be around 10 years in rural Uganda [114, 115]. While no such estimates specific for urban Uganda are available, studies in other populations report similar life expectancies, largely independently of setting [115]. We therefore set the mortality rate for HIV infected hosts not on ART to $\mu_{+u} = 1/10$ per year for both urban and rural populations.

A study of European individuals with HIV who receive ART estimated a life-span approximately twice as long as HIV infected hosts not on ART [99]. HIV progression was found to be similar between Uganda and developed countries [115]. We therefore assume that the impact of ART on the life expectancy of HIV positive hosts is similar between Uganda and developed countries and set $\mu_{+t} = 1/20$ per year for both the urban and rural scenario.

Hosts with active, untreated TB disease who are HIV negative are estimated to live for approximately 3 years in a recent systematic review [63]. Most studies underlying the systematic review came from pre-treatment Europe and the USA. Data for untreated TB in Uganda is not available. We use the 3 year estimate as the best available data and apply it to the urban setting, i.e. we set the mortality rate at $\delta_- = 1/3$ per year.

National data suggested that rural Uganda residents are generally poorer than urban Uganda residents [116, 117], which suggests that malnutrition are more likely to occur to rural residents. Since malnutrition was associated with shorter survival time in TB patients [118, 119], we assume a survival time that is 33% shorter (2 years) for hosts with active, untreated TB

disease in rural settings, i.e. we set $\delta_- = 1/2$ per year.

For individuals with active TB who are HIV positive and not on ART, the life expectancy is generally less than a year and possibly only a few months in various settings[63, 85, 120]. Detailed information specifically for Uganda is not available. We chose to set life expectancy to 9 months, which leads to a mortality rate of $\delta_{+u} = 12/9$ per year for the urban setting. For the rural setting, we again assume a 33% reduction, leading to a life expectancy of 6 months ($\delta_{+u} = 12/6$ per year). There is also no good data on the survival for HIV infected hosts with active TB who receive ART; we make the assumption that their life expectancy is similar to HIV negative TB cases, i.e. we set $\delta_{+t} = 1/3$ per year for the urban scenario and $\delta_{+t} = 1/2$ per year for the rural scenario.

The demographic parameters just described are summarized in Table 5.2.

Symbol	Meaning	Urban	Rural
N	Population size	100,000	100,000
μ	Mortality rate for HIV- and non-infectious TB adults (1/average lifespan)	$\frac{1}{40}$/year	$\frac{1}{40}$/year
π	Annual inflow ("births")	$\pi = N\mu$	$\pi = N\mu$
μ_{+u}	Mortality rate for HIV positive hosts not on ART	$\frac{1}{10}$/year	$\frac{1}{10}$/year
μ_{+t}	Mortality rate for HIV positive hosts on ART	$\frac{1}{20}$/year	$\frac{1}{20}$/year
δ_-	Mortality rate for TB infectious, HIV negative hosts	$\frac{1}{3}$/year	$\frac{1}{2}$/year
δ_{+u}	Mortality rate for TB infectious, HIV positive hosts not on ART	4/3/year	12/6/year
δ_{+t}	Mortality rate for TB infectious, HIV positive hosts on ART	1/3/year	1/2/year

Table 5.2: Demographic parameters for both rural and urban areas. See the text for references to sources for the chosen values.

5.2.2.3 TB infection

Hosts who have TB disease are infectious and can infect uninfected hosts or re-infect hosts who harbor latent TB. HIV status of the TB infectious host is known to affect the level of infectiousness. In our model, the maximum number of new infections per year caused by one TB infectious host is given by a rate k_j, where the index j indicates the HIV status (1 = uninfected, 2 = HIV infected untreated, 3 = HIV infected treated). For Uganda, the annual risk of infection (ARI) was estimated at about 3000/100,000, and the TB prevalence is about 200/100,0000 [2, 121]. From this, one finds that the number of annual infections by a TB patient is about $3000/200 = 15$. The data applies to all of Uganda, with 90% of the population living in the rural areas. We therefore set the annual transmission rate as $k_1 = 15$ with a range from 12 to 18 per year for HIV negative hosts in rural areas. Recent estimates for the annual number of new infections caused by a TB case are in similar ranges [101]. Urban areas are more crowded than rural areas. it is therefore reasonable to assume a higher rate of transmission in the urban setting. We assume the maximum annual transmission rate as $k_1 = 18$ with range from 15 to 21 per year for HIV negative hosts in the urban areas.

HIV infection seems to not increase, and maybe even decrease infectivity of TB cases [86, 87]. We assume a moderate reduction in infectiousness for HIV positive hosts not on ART and set $k_2 = 0.8k_1$. We further assume that HIV positive hosts receiving ART have an infectiousness that is intermediate between HIV negative and HIV positive untreated hosts and set $k_3 = (k_1 + k_2)/2$. We assumed these rules apply to both rural and urban areas.

A recent study in Uganda indicated that susceptibility to TB infection (but not disease) is similar among individuals independent of HIV status [7]. We therefore assume in our model that the susceptibility for TB infection of TB uninfected individuals is the same regardless of HIV status, and can therefore omit additional parameters describing differential susceptibility from our model.

Table 5.3 summarizes the parameters discussed in this section.

Symbol	Meaning	Urban		Rural	
		Value	Range	Value	Range
k_1	Maximum number of annual new TB infections caused by one TB infectious, HIV negative host	18/year	15 - 21	15/year	12-18
k_2	Maximum number of annual new TB infections caused by one TB infectious, HIV positive host not on ART	$0.8k_1$	$0.8k_1$	$0.8k_1$	$0.8k_1$
k_3	Maximum number of annual new TB infections caused by one TB infectious, HIV positive host on ART	$(k_1 + k_2)/2$	$(k_1 + k_2)/2$	$(k_1 + k_2)/2$	$(k_1 + k_2)/2$

Table 5.3: TB transmission parameters for urban and rural areas. See the text for references to sources for the chosen values.

5.2.2.4 Progression from TB latency to disease

Upon TB infection, newly infected individuals either rapidly develop disease (fast progression) or remain latent for an extended period and possibly develop disease later in life (slow progression). The fraction of fast progressors depends on HIV status. Parameters p_1, p_2, and p_3 quantify the fraction of fast progressors for each HIV status (uninfected, infected untreated, infected treated). The fraction of TB-infected HIV negative persons that develop fast progression to active TB is generally between $0.05-0.1$ and has been estimated for urban Uganda at 0.053 [7], which we will use here, i.e. we set $p_1 = 0.053$. The estimated fraction of fast progression for HIV positive hosts not on ART has been estimated for urban Uganda to be 0.186 per year [7], which is the rate we use here ($p_2 = 0.186$). As far as we are aware, there are no studies on the impact of HIV treatment on TB progression. However, previous studies suggested that ART treatment was correlated with a reduction of TB incidence in

a meta-analysis study[102]. This suggests that HIV treatment might reduce the impact of HIV infection on TB progression. We therefore set the the fraction of fast progressors for HIV positive, treated hosts to a value between HIV negative and HIV positive untreated hosts. Specifically, we chose $p_3 = (p_1 + p_2)/2$.

Hosts that do not immediately progress to TB disease enter the latent stage. These hosts can eventually transition into the TB disease stage. This transition again depends on HIV status. The rate of transition from latent TB to TB disease for HIV negative adult hosts was estimated to be broadly in the range of $0.0003 - 0.0034$ per year from a US study[103]. There is no data for this rate for Uganda population. We therefore use an intermediate value and set $\nu_1 = 0.001$ per year. For HIV positive hosts not on ART, transition from latent TB to TB disease occurs at faster rates [120]. Some estimates are 0.079 per year in [82], 0.054 per year in [83] and 0.034 in [84]. We use the value from [84] as this data comes from an urban Ugandan population, and set $\nu_2 = 0.034$ per year. While ART treatment of HIV positive hosts has been shown to reduce the incidence of TB [104], it is unclear if this is due to a reduced fraction of fast progressors or a reduced rate of slow progression. In the absence of more solid data, we assume that the presence of ART lowers the rate of slow progression by a moderate factor of two, i.e. we choose $\nu_3 = 0.5\nu_2$ per year.

Another transition from latent TB infection to TB disease can occur through re-infection. The risk of developing active TB following reinfection is smaller compared with TB disease following initial infection (i.e. fast progression). Therefore, the proportions for TB disease following reinfection, which we label q_1, q_2, and q_3, are lower than the corresponding fractions (p_i) for new infections. For HIV negative hosts, reported estimates are in the range of $16\% - 82\%$ for various settings[64, 65, 80]. We choose a intermediate value and assume a risk reduction of 50% for our model ($q_1 = 0.5p_1$). For HIV positive, untreated persons, data does not seem to exist. Two recent modeling studies [21, 22] assumed a reduction of risk

by 25%, which we follow and set $q_2 = 0.75p_2$. For HIV positive hosts on ART, we again assume the value between HIV negative and HIV positive untreated hosts and therefore set $q_3 = 0.625p_3$.

Since we did not find any studies suggesting differences between rural and urban populations for the TB progression parameters, we assume the same values for the rural areas.

Table 5.4 summarizes the progression parameters.

Symbol	Meaning	Value
p_1	Fraction of fast progressors among HIV negative hosts	0.053
p_2	Fraction of fast progressors among HIV positive host not on ART	0.186
p_3	Fraction of fast progressors among HIV positive hosts on ART	$(p_1 + p_2)/2$
ν_1	Rate of slow progression among HIV negative hosts	0.001 per year
ν_2	Rate of slow progression among HIV positive host not on ART	0.034 per year
ν_3	Rate of slow progression among HIV positive host on ART	$0.5\nu_2$
q_1	Fraction of reinfections of HIV negative hosts that will cause active TB	$0.5p_1$
q_2	Fraction of reinfections of HIV positive hosts not on ART that will cause active TB	$0.75p_2$
q_3	Fraction of reinfections of HIV positive hosts on ART that will cause active TB	$0.625p_3$

Table 5.4: TB progression parameters for urban and rural areas. Assume same values for urban and rural areas. See the text for references to sources for the chosen values.

5.2.2.5 TB detection and diagnosis

Under current TB diagnosis and treatment standards, most patients are diagnosed and treated after reporting to a healthcare facility (passive case finding, PCF). The time from onset of infectiousness to diagnose for TB treatment can vary widely. One recent study in Uganda found that index cases had a median cough duration of 90 days, with a wide range between 1 - 730 days [3]. Other studies found delay in diagnosis and treatment in the range of roughly 100 - 200 days [122, 123] in Tanzania. These estimates are for the delay following hospital visits, not including delays between onset of disease and hospital visit. Further,

not all individuals with TB disease will seek healthcare, some are likely to die without ever being picked up by the healthcare system. Our model parameter represents an average time between disease and diagnosis, including those that eventually seek care and those that do not. We assume that this average time 6 months ($a_1 = 12/6$ per year) with a range from 3 to 9 months for TB patients not infected with HIV living in urban Uganda. For the rural setting, lack of knowledge and access to healthcare has been shown [124], which in a different setting has been suggested to lead to prolonged delay in seeking care [125]. It was also observed that TB patients presented late and in severe conditions in a rural Ugandan hospital [126]. All of this suggests that the delay between disease onset and diagnosis is longer in the rural setting. We therefore assume an average time of 9 months ($a_1 = 12/9$ per year) with a range from 6 to 12 months for the rural setting.

Since co-infection with HIV leads to more rapid disease progression, we assume that for TB patients who are infected with HIV and not on ART, the faster and more severe progression of symptoms will lead on average to faster care-seeking behavior. We therefore reduce the 3-9 and 6-12 month ranges just described by a third.

For TB patients who are infected with HIV and already receive ART, the time for them to be detected and diagnosed for TB is likely to be shorter due to their already existing contact with the health care system. We assume that this reduces the time between disease and treatment by 50% for both the urban and rural settings.

Table 5.5 summarizes all detection and diagnosis related parameters.

Symbol	Meaning	Urban		Rural	
		Value	Range	Value	Range
a_1	Diagnose rate for TB infectious, HIV negative hosts	1/0.5/year	1/0.25-1/0.75	1/0.75/year	1/0.5-1/1
a_2	Diagnose rate for TB infectious, HIV positive host not on ART	a_1	a_1	a_1	a_1
a_3	Diagnose rate for TB infectious, HIV positive host on ART	$2a_1$	$2a_1$	$2a_1$	$2a_1$

Table 5.5: TB diagnose parameters for urban and rural areas. See the text for references to sources for the chosen values.

5.2.2.6 TB treatment

Individuals with TB disease can receive treatment and thereby be cured from active TB. Following e.g. [9, 127], we assume that those hosts return to the TB latent class. WHO recommends TB treatment time for 6 months. In our model, the treatment time is the time from the beginning of treatment to the time when the treated host stops to infect other persons. Theoretically, an infectious TB patient can stop infecting other persons days or weeks after being treated for TB. In reality, there might be a delay between diagnosis and treatment. At the population level, some TB patients might not initiate or quickly stop treatment. It was reported that 71% of those testing positive received treatment in Uganda in 2009 [105]. Therefore we choose as a conservative estimate a population level average time to treatment of 2 months ($\rho_1 = 12/2$ per year) with a range from 1 to 4 months. Cure rates for TB seem to be similar for HIV negative and HIV positive hosts not on ART [106]. Since there is no reason to assume that HIV positive hosts not on ART have more frequent contact with the health system than HIV negative hosts, we assume the fraction of those that are being treated and the timing for treatment is the same as in the HIV negative hosts , i.e. we set $\rho_2 = \rho_1$. Since HIV positive hosts who receive ART are already under "health

surveillance", it is likely that they are treated faster and show better treatment adherence. To reflect this, we assume that treatment rate in this class is higher, and set $\rho_3 = 2\rho_2$ per year.

Finally, it is becoming common for a person receiving TB treatment to also be tested for HIV and if tested positive, potentially being placed on ART. We therefore assume that a fraction of the HIV positive hosts that are not on ART, when receiving TB treatment are also placed on ART and move into the TB-latent, HIV positive, ART treated category. WHO reported that 48% of TB patients that are infected with HIV are on ART in 2011 [2]. We set the proportion for such double-treatment to $a = 0.48$.

In the absence of any studies suggesting differences in the time to treatment between urban and rural areas, we assume the same parameter values for the rural areas.

Table 5.6 summarizes all treatment related parameters.

Symbol	Meaning	Value	Range
ρ_1	Treatment rate for TB infectious, HIV negative hosts	12/2 /year	12/1-12/4
ρ_2	Treatment rate for TB infectious, HIV positive host not on ART	ρ_1	ρ_1
ρ_3	Treatment rate for TB infectious, HIV positive host on ART	$2\rho_1$	$2\rho_1$
a	Fraction of TB infectious, HIV positive hosts not on ART that receive both TB treatment and ART	0.48	0.48

Table 5.6: TB treatment parameters for both urban and rural areas. Assume same values for urban and rural areas. See the text for references to sources for the chosen values.

5.2.2.7 HIV transmission and treatment

As we do for TB transmission, we make the common assumption that HIV transmission can be modeled with a simple frequency-dependent term. Note that several recent modeling studies described HIV transmission differently, namely using a term in which per-person transmission declined as HIV prevalence increased. This was used to better describe the ob-

served data and justified by the fact that high HIV prevalence might lead to behavior changes that effectively reduce per-person transmissibility [9, 128]. For our model, our focus is not on HIV. We therefore did not implement this more complex transmission assumption. Since HIV positive hosts on ART are aware of their HIV status and are likely to take precautions, combined with a strongly reduced viral load, we make the approximate assumption that only HIV positive hosts not on ART are infectious. The maximum rate of HIV transmission, d, is obtained by fitting our model to the HIV prevalence of 8.7% in 2011 in urban Uganda areas ($d = 0.195$ per year) [129]. HIV prevalence in the urban areas of Uganda used to be about five times as high as that in the rural areas, but the difference is getting smaller [130]. HIV prevalence reflects the rate of HIV transmission in the population. The rate of HIV transmission in the rural area is obtained by fitting our model with the HIV prevalence of 7% in the rural Uganda area ($d = 0.185$ per year)[129].

A fraction of HIV positive hosts receive ART. The estimated fraction of HIV positive hosts on ART in Uganda in 2011 was 24.2% in urban and 17.4% in rural Uganda[129]. We assume that ART coverage is the same for TB uninfected and TB latent hosts. We chose the rate of ART treatment in our model such that we obtain these reported coverages of HIV positive hosts at steady state for both TB uninfected and TB latent hosts, which leads to an HIV treatment reate of $\tau = 0.015$ per year for the urban and $\tau = 0.01$ per year for the rural setting. We assume that HIV positive hosts that also have TB disease do not receive ART only, they are assumed to always be treated for TB. A fraction of them is treated for HIV as well, as described in the previous section.

Table 5.7 summarizes the HIV related parameters.

Symbol	Meaning	Urban	Rural
d	HIV transmission rate	0.195/year	0.185/year
τ	HIV treatment rate for TB susceptible and latent, HIV positive hosts	0.015/year	0.01/year

Table 5.7: HIV transmission and treatment parameters for urban areas. See the text for references to sources for the chosen values.

5.2.3 The Mathematical Model

We first calculate the force of infection for our model. Force of TB infection from TB infectious are the maximum number of possible new infections by all TB patients.

$$\lambda = k_1(I_- + D_-) + k_2(I_{+u} + D_{+u}) + k_3(I_{+t} + D_{+t}) \tag{5.1}$$

Change of number of TB Susceptible HIV negative host with time

$$\underbrace{\frac{dS_-}{dt}}_{\substack{\text{Change of number of HIV negative and TB susceptible hosts with time}}} = \underbrace{\pi}_{\substack{\text{Inflow of HIV negative and TB susceptible}}} - \underbrace{\lambda\frac{S_-}{N}}_{\substack{\text{Outflow due to TB Infection}}} - \underbrace{d\frac{H}{N}S_-}_{\substack{\text{Outflow due to HIV infection}}} - \underbrace{\mu S_-}_{\substack{\text{Outflow due to death}}} \tag{5.2}$$

TB Susceptible HIV positive

$$\underbrace{\frac{dS_{+u}}{dt}}_{\substack{\text{Change of number of HIV Positive untreated and TB susceptible hosts with time}}} = \underbrace{d\frac{H}{N}S_{-}}_{\substack{\text{Inflow due to HIV infection of TB susceptibles}}} - \underbrace{\lambda\frac{S_{+u}}{N}}_{\substack{\text{Outflow due to TB Infection}}} - \underbrace{\tau_1 S_{+u}}_{\substack{\text{Outflow due to HIV treatment}}} - \underbrace{\mu_{+u}S_{+u}}_{\substack{\text{Outflow due to death}}} \tag{5.3}$$

$$\underbrace{\frac{dS_{+t}}{dt}}_{\substack{\text{Change of number of HIV Positive treated and TB susceptible hosts with time}}} = \underbrace{\tau_1 S_{+u}}_{\substack{\text{Inflow due to treatment of HIV positive hosts}}} - \underbrace{\lambda\frac{S_{+t}}{N}}_{\substack{\text{Outflow due to TB Infection}}} - \underbrace{\mu_{+t}S_{+t}}_{\substack{\text{Outflow due to death}}} \tag{5.4}$$

$$\underbrace{\frac{dL_-}{dt}}_{\substack{\text{Change of number of HIV negative and TB latent hosts with time}}} = \underbrace{(1-p_1)\lambda\frac{S_-}{N}}_{\substack{\text{Inflow due to slow progression part of TB infection of susceptibles}}} + \underbrace{\rho_1 D_-}_{\substack{\text{Inflow due to treatment of TB patients}}} - \underbrace{v_1 L_-}_{\substack{\text{Outflow due to TB latent activation}}} - \underbrace{q_1\lambda\frac{L_-}{N}}_{\substack{\text{Outflow due to TB reinfection}}} - \underbrace{d\frac{H}{N}L_-}_{\substack{\text{Outflow due to HIV infection}}} - \underbrace{\mu L_-}_{\substack{\text{Outflow due to death}}} \tag{5.5}$$

$$\underbrace{\frac{dL_{+u}}{dt}}_{\substack{\text{Change of number of HIV positive untreated and TB latent hosts with time}}} = \underbrace{(1-p_2)\lambda\frac{S_{+u}}{N}}_{\substack{\text{Inflow due to slow progression part of TB infection of susceptibles}}} + \underbrace{d\frac{H}{N}L_-}_{\substack{\text{Inflow due to HIV infection of TB latent hosts}}} + \underbrace{(1-a)\rho_2 D_{+u}}_{\substack{\text{Inflow due to treatment of TB patients}}} \underbrace{-q_2\lambda\frac{L_{+u}}{N}}_{\substack{\text{Outflow due to TB reinfection}}} - \underbrace{v_2 L_{+u}}_{\substack{\text{Outflow due to TB latent activation}}} - \underbrace{\tau_2 L_{+u}}_{\substack{\text{Outflow due to HIV treatment}}} - \underbrace{\mu_{+u} L_{+u}}_{\substack{\text{Outflow due to death}}} \tag{5.6}$$

$$\underbrace{\frac{dL_{+t}}{dt}}_{\substack{\text{Change of number of HIV positive treated and TB latent hosts with time}}} = \underbrace{(1-p_3)\lambda\frac{S_{+t}}{N}}_{\substack{\text{Inflow due to slow progression part of TB infection of susceptibles}}} + \underbrace{\tau_2 L_{+u}}_{\substack{\text{Inflow due to HIV treatment}}} + \underbrace{\rho_3 I_{+t}}_{\substack{\text{Inflow due to TB treatment}}} + \underbrace{a\rho_2 D_{+u}}_{\substack{\text{Inflow due to HIV treatment}}}$$
$$\underbrace{-q_3\lambda\frac{L_{+t}}{N}}_{\substack{\text{Outflow due to TB reinfection}}} - \underbrace{v_3 L_{+t}}_{\substack{\text{Outflow due to latent TB activation}}} - \underbrace{\mu_{+t} L_{+t}}_{\substack{\text{Outflow due to death}}} \tag{5.7}$$

$$\underbrace{\frac{dI_-}{dt}}_{\substack{\text{Change of number of HIV negative and TB infectious hosts with time}}} = \underbrace{p_1\lambda\frac{S_-}{N}}_{\substack{\text{Inflow due to TB infection fast progression}}} + \underbrace{q_1\lambda\frac{L_-}{N}}_{\substack{\text{Inflow due to latent TB reinfection}}}$$
$$\underbrace{+v_1 L_-}_{\substack{\text{Inflow due to latent TB activation}}} - \underbrace{(\alpha_1+\beta_1)I_-}_{\substack{\text{Outflow due to TB case finding}}} - \underbrace{d\frac{H}{N}I_-}_{\substack{\text{Outflow due to HIV infection}}} - \underbrace{(\mu+\delta_-)I_-}_{\substack{\text{Outflow due to death}}} \tag{5.8}$$

$$\underbrace{\frac{dI_{+u}}{dt}}_{\substack{\text{Change of number of HIV positive untreated and TB infectious hosts with time}}} = \underbrace{p_2\lambda\frac{S_{+u}}{N}}_{\text{Inflow due to TB infection fast progression}} + \underbrace{q_2\lambda\frac{L_{+u}}{N}}_{\text{Inflow due to latent TB reinfection}} \underbrace{+v_2L_{+u}}_{\text{Inflow due to latent TB activation}}$$

$$+ \underbrace{d\frac{H}{N}I_-}_{\text{Inflow due to HIV infection}} \underbrace{-(\alpha_2+\beta_2)I_{+u}}_{\text{Outflow due to TB case finding}} - \underbrace{\tau_3 I_{+u}}_{\text{Outflow due to HIV treatment}} \underbrace{-(\mu+\delta_{+u})I_{+u}}_{\text{Outflow due to death}} \tag{5.9}$$

$$\underbrace{\frac{dI_{+t}}{dt}}_{\substack{\text{Change of number of HIV positive treated and TB infectious hosts with time}}} = \underbrace{p_3\lambda\frac{S_{+t}}{N}}_{\text{Inflow due to TB infection fast progression}} + \underbrace{q_3\lambda\frac{L_{+t}}{N}}_{\text{Inflow due to latent TB reinfection}}$$

$$+ \underbrace{v_3 L_{+t}}_{\text{Inflow due to latent TB activation}} + \underbrace{\tau_3 I_{+u}}_{\text{Inflow due to HIV treatment}} - \underbrace{(\alpha_3+\beta_3)I_{+t}}_{\text{Outflow due to TB case finding}} - \underbrace{(\mu+\delta_{+t})I_{+t}}_{\text{Outflow due to death}} \tag{5.10}$$

$$\underbrace{\frac{dD_-}{dt}}_{\substack{\text{Change of number of HIV negative and diagnosed TB infectious hosts with time}}} = \underbrace{(\alpha_1+\beta_1)I_-}_{\text{Inflow due to TB case finding}} - \underbrace{\rho_1 D_-}_{\text{outflow due to treatment of TB patients}} - \underbrace{d\frac{H}{N}D_-}_{\text{Outflow due to HIV infection}} - \underbrace{(\mu+\delta_-)D_-}_{\text{Outflow due to death}} \tag{5.11}$$

$$\underbrace{\frac{dD_{+u}}{dt}}_{\substack{\text{Change of number of HIV positive untreated and diagnosed TB infectious hosts with time}}} = \underbrace{(\alpha_2+\beta_2)I_{+u}}_{\text{Inflow due to TB case finding}} - \underbrace{\rho_2 D_{+u}}_{\text{outflow due to treatment of TB patients}} + \underbrace{d\frac{H}{N}D_-}_{\text{Inflow due to HIV infection}} - \underbrace{\tau_3 D_{+u}}_{\text{Outflow due to HIV treatment}} - \underbrace{(\mu+\delta_{+u})D_-}_{\text{Outflow due to death}} \tag{5.12}$$

$$\underbrace{\frac{dD_{+t}}{dt}}_{\substack{\text{Change of number of HIV positive treated and diagnosed TB infectious hosts with time}}} = \underbrace{(\alpha_3+\beta_3)I_{+t}}_{\text{Inflow due to TB case finding}} + \underbrace{\tau_3 D_{+u}}_{\text{Inflow due to HIV treat-ment}} - \underbrace{\rho_3 D_{+t}}_{\text{outflow due to treatment of TB patients}} - \underbrace{(\mu+\delta_{+t})D_{+t}}_{\text{Outflow due to death}} \tag{5.13}$$

5.3 Results

5.3.1 Model validation

We first validated our model and parameters with field data in Uganda. There is no data about incidences in the rural and urban Uganda areas specifically. We calculated the total incidence and prevalence based on the incidence and prevalence from our model assuming 90% of the Uganda population lives in the rural areas. Table 5.8 shows that our results are approximately in the range of the field data[2].

Measure	Field data		Model Prediction		
	Value	Range	Urban	Rural	Total
Incidence	193	156-234	334	219	230
Prevalence	183	95-298	144	95	100

Table 5.8: Validation of model prediction with field data. Incidence and prevalence are estimated for a population of 100,000 hosts

5.3.2 Why ACF

Under PCF, TB patients seek health care only when they voluntarily go to hospital. The delay can be several months. During this period, these active TB individuals might still infect other TB un-infected persons. If the number of annual secondary infections by an active TB host is 18, a delay of six months can possibly produce nine new TB infected individuals in the population. Figure 5.2 shows that considering a new TB case, PCF will pick up the TB case on average six months after the onset of disease in the urban area. On the other hand, if ACF is implemented, it can detect the new case as early as two weeks after onset of disease. This suggests that ACF can possibly reduce about six months of infectious duration of a TB patient. As for the rural area, PCF can only pick up the TB cases nine months after the onset of disease. ACF implementation in the rural area can possibly reduce nine

months of infectious duration of a TB patient

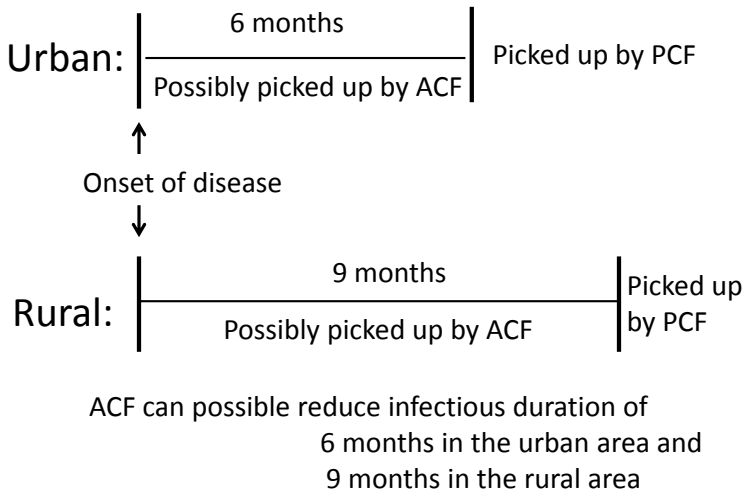
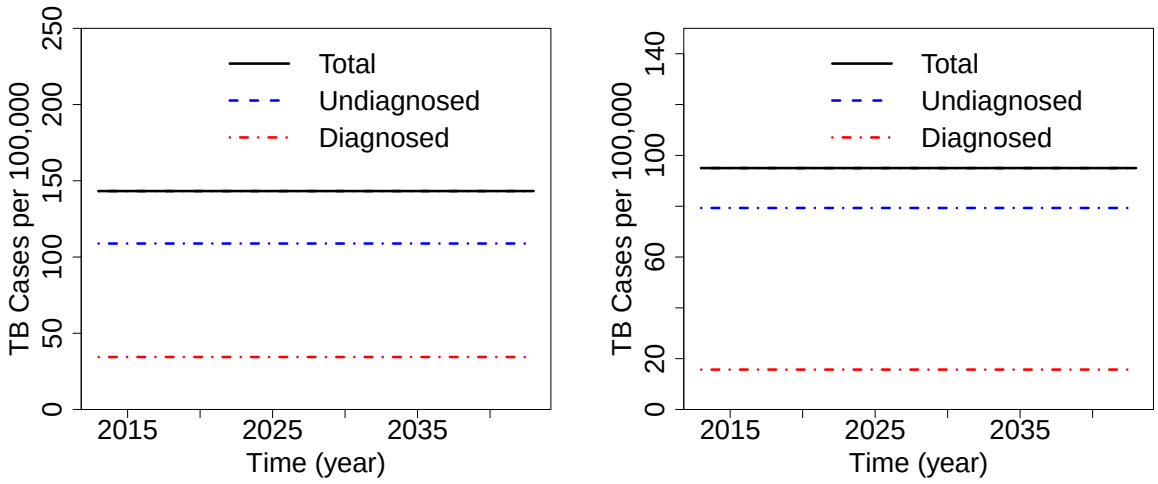


Figure 5.2: Time scale for PCF and ACF case findings.

Figure 5.3 shows only a small fraction (about 20% of active TB cases are detected under PCF. ACF implementation might reduce the total number of TB cases in the population.



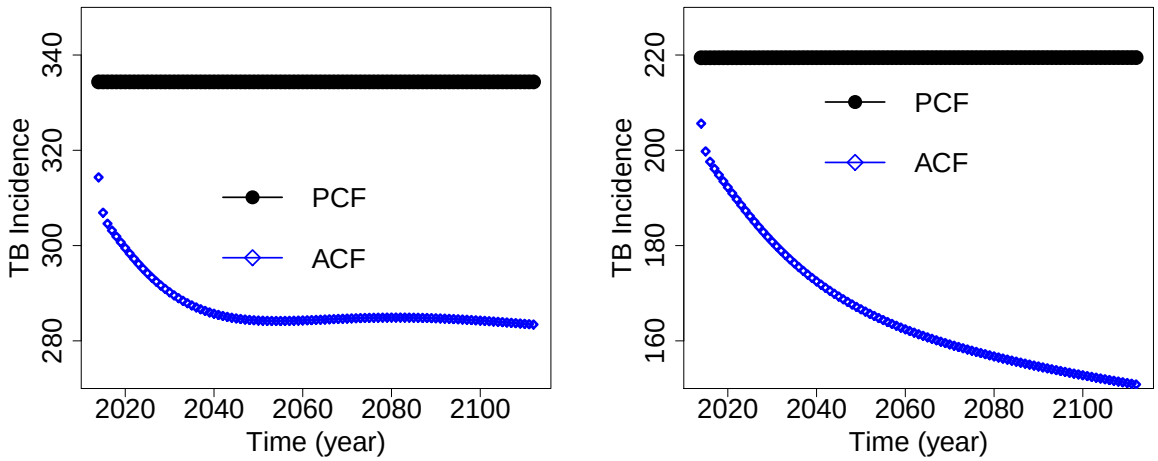
a). Urban b). Rural

Figure 5.3: Detected and undetected TB cases in rural and urban areas under PFC. a). Urban, b). Rural

5.3.3 How ACF

ACF can be implemented with various approaches. One common approach is to sample a fraction of the total population and conduct door to door visit to find individuals that have un-diagnosed active TB. Health worker will generally recommend individuals that have been coughing for two weeks for TB tests. With this approach, health workers would be able to identify almost all active TB individuals that are infectious. Of course, only a fraction of individuals will follow the recommendation for TB tests. In our model, we assume that every individual who is recommended for TB test will follow the guidance to take the test. In our model, we use ACF efficiency to define the level of ACF implementation. ACF efficiency of 10 % implies that 10% of the population is sampled, and it ideally leads to detection of 10% of the undiagnosed TB cases in the population. Figure 5.4 shows that ACF implementation can reduce about 50 TB cases annually in both urban and rural Uganda areas after 30 years. Figure 5.4 also implies that after ACF implementation, the system reaches steady state in a

shorter time in the urban area. This might be caused by the fact that the delay from onset of disease to treatment is longer in the rural area.



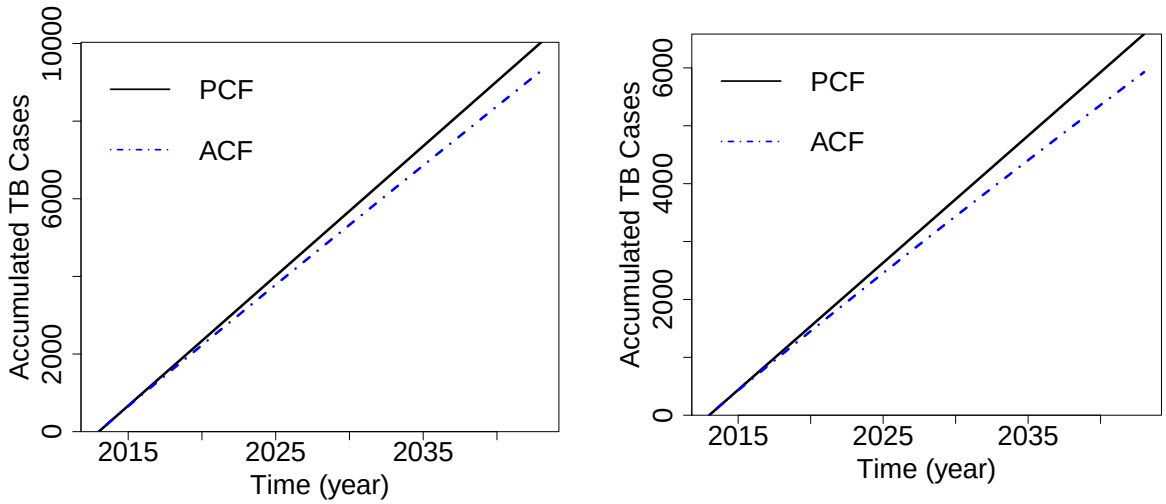
a). Urban b). Rural

Figure 5.4: Annual TB incidence after ACF implementation in urban and rural Uganda. ACF is conducted once a year and the efficiency is 50%

5.3.4 ACF Effectiveness Measures

The goal of ACF implementation is to reduce TB transmission. Various measures are used to define the effectiveness of ACF implementation. The most common measures are the number of TB cases averted and the number of deaths due to TB averted.

ACF can pick up TB patients earlier compared with PCF. Under ACF, TB patients will have shorter periods of being infectious, and thus infect fewer individuals before being treated. To measure the number of TB cases averted, we first calculate the total number of TB case with or without ACF over a period of time, and then subtract the number of case with ACF from that without ACF. The number of deaths due to TB is calculated similarly. Figure 5.5 shows the accumulated cases with or without ACF for urban rural areas in over 30 years.

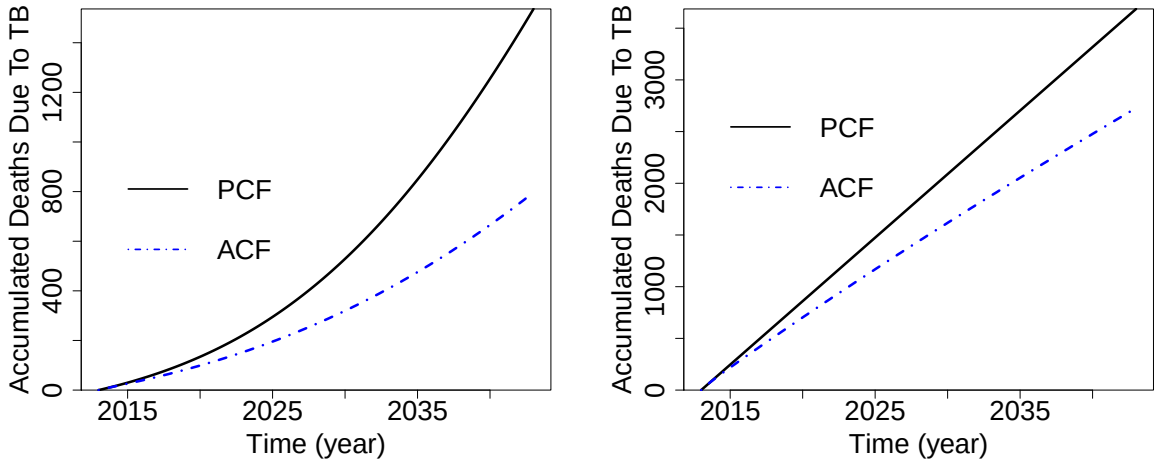


a). Urban b). Rural

Figure 5.5: Accumulated cases for PCF and ACF in rural and urban areas. ACF is conducted once a year with an efficiency of 30 %. a). Urban, b). Rural

TB disease leads to higher human mortality. ACF can reduce the number of deaths due to TB in two ways. ACF detects TB patients earlier so TB patients are less likely to die without proper treatment. Secondly, ACF reduces the number of TB cases, which who

might die due to TB. To estimate the number of deaths due to TB averted, we calculate the number of deaths due to TB with and without ACF implementation over a period of time and the number averted would be the difference between the two. Figure 5.6 shows numbers of deaths due to TB under PCF and ACF in urban and rural areas. The number of deaths due to TB is smaller in the urban area regardless of ACF implementation. We will add uncertainty analysis in the next section.



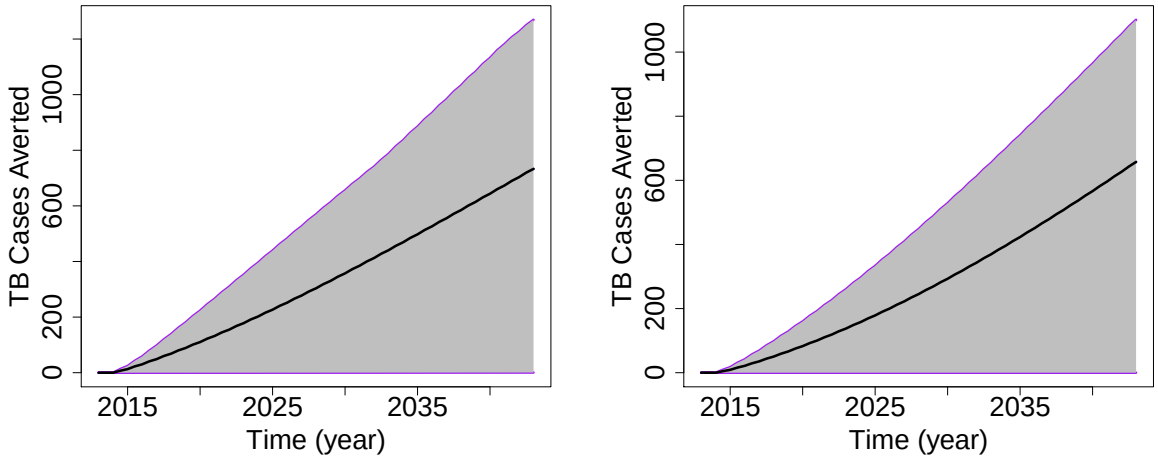
a). Urban b). Rural

Figure 5.6: Accumulated cases for PCF and ACF in rural and urban areas. ACF is conducted once a year with an efficiency of 30 %. a). Urban, b). Rural

5.3.5 Uncertainty Analysis

There are many parameters in our model. Some parameter values are not from previous field studies, but from educational guess. For most of these parameters, we also estimated ranges for their values. Uncertainty analysis are conducted to explore the full impact for parameters in their ranges. Figure 5.7 shows the confidence interval lines for the number of TB averted with 100 simulations for both urban and rural areas. The confidence interval

covers a wide range. At the lower bound of the confidence interval line, there is almost no case or death averted. This corresponds to the scenario that the treatment and diagnosis time is very short, such that ACF does not do much to avert the number of TB cases or deaths due to TB.



a). Urban b). Rural

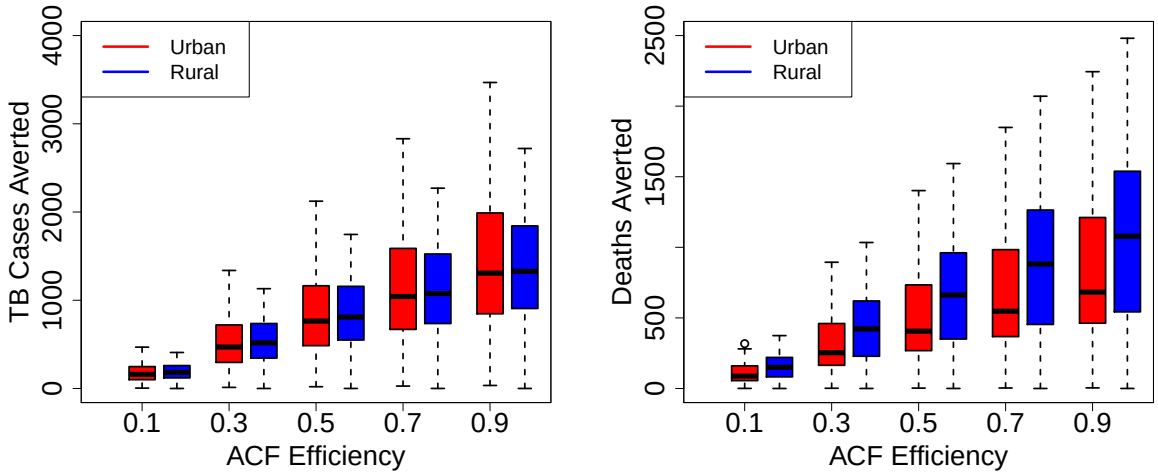
Figure 5.7: Accumulated cases for PCF and ACF in rural and urban areas. ACF is conducted once a year with an efficiency of 30 %. a). Urban, b). Rural

5.3.6 ACF Implementation in Urban and Rural Areas

What would be the difference that ACF implementation causes between rural and urban areas? Here we assume the same ACF strategy over a period of time. Figure 5.8 (a) shows that for various ACF efficiencies, the number of TB cases reverted is approximately the same between the urban area and the rural area. The TB prevalence is higher in urban than in rural. ACF implementation of 10% efficiency will detect a larger number of undetected cases in the urban area than in the rural area. On the other hand, the delay for TB diagnosis is longer in rural areas than in urban areas. So ACF implementation might have larger impact on the number of cases reverted in rural areas than in urban areas. The mixed impact of all

these factors might lead to the result that there is not much difference in the number of TB cases reverted between urban and rural areas.

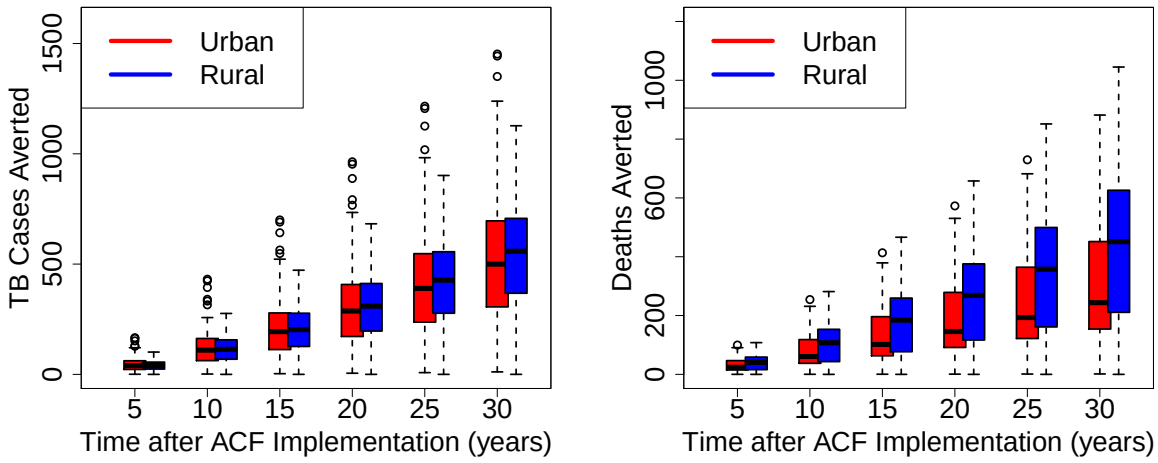
The number of deaths due to TB averted is another measure for ACF implementation. Figure 5.8 (b) shows that there are a larger number of deaths averted in the rural areas than in the urban areas. The main reason is that we assume that the life expectancy of TB patients is shorter in rural areas than in urban areas.



a). TB Case Averted b). Deaths averted

Figure 5.8: ACF implementation in urban and rural areas over 30 years. ACF is implemented once a year. Efficiency of 10% means 10% of the population is sampled and 10% of the undetected cases are found, a)Case averted, b). Deaths due to TB averted.

Previous ACF studies focused on exploring the impact of ACF implementation in a fixed time period. It would be interesting to explore the impact of ACF over various time duration. Figure 5.9 a) shows that at the first 15 years, there is not much difference in the number of TB cases averted between urban and rural areas. However, the number of TB cases averted is higher in the rural areas than in the urban areas. This is very likely due to the fact that ACF implementation is of slower dynamics in rural areas compared with that in the urban areas as shown in Figure 5.4. On the other hand, the number of deaths reverted is higher in rural areas all the time.



a). TB Case Averted b). Deaths averted

Figure 5.9: ACF implementation in urban and rural areas over 30 years. ACF is implemented once a year. ACF efficiency: 30%. a)Case averted, b). Deaths due to TB averted.

5.3.7 ACF Cost

ACF implementation involves additional costs. To implement ACF for TB case detection, economic cost is one important factor needed to be considered, especially in Africa countries where resources are limited. The additional cost for ACF implementation includes costs for surveys, door to door visits, TB tests, and TB treatments.

The first part of cost involves the cost for health care personnel to detect suspected persons for TB test. This part of the cost may include the labor cost for conducting surveys, transportation cost, and cost for data collection. The cost will be different for ACF implementation in urban and rural areas. The labor cost might be higher in the urban areas. However, the cost for transportation is much higher in the rural area where the health worker might travel a long distance to conduct surveys. It is estimated that the ACF cost is \$2.86 to detect a TB case in an ACF practice with 10% of efficiency in urban Uganda [32, 131]. We assume that the cost will remain the same for ACF implementation of higher

efficiency. But it will be different for various TB prevalence. For example, for TB prevalence of 200/100,000, the cost is $2.86, then the cost would be higher if the prevalence is reduced to 100/100,000. The reason is that a large sample needs to be surveyed to detect an active TB case for population with lower TB prevalence. Results in the previous section imply that the TB prevalence is not significantly reduced. We therefore assume a constant ACF cost for detecting an active TB case, i.e. we assume a constant cost of $2.86 for urban areas and twice of $2.86 for rural ACF implementation.

The second part of the additional cost is the cost of TB tests for all suspected individuals. ACF normally recommends individuals that cough for a certain period for TB tests. Obviously not all recommended individuals have active TB disease. The number of additional TB tests needed to detect an active TB patient is different for various ACF strategies. It is estimated that one of five individuals tested for TB have active TB in an ACF study in Kampala, an urban area in Uganda [7]. There is no direct ACF studies in rural Uganda. But it would be reasonable to assume that a larger number of individuals need to be tested to detect an active case in rural areas as the TB prevalence is lower there. A TB surveillance project surveyed hosts that went to hospitals for any reasons in six rural Uganda regions. They recommended patients that have coughed for two weeks or longer for TB tests. About one out of seven patients recommended was found to have active TB [105]. In this project, TB patients were not detected by ACF, however, it gave a rough estimate about the fraction of active TB patients among individuals coughing for more than two weeks. We shall use this number as the number of patients needed to be tested to detect an active TB patient in rural Uganda. There are various techniques for TB test. In Uganda, the practice for TB test is a simple sputum smear test with microscopy. A small fraction of individuals might be tested with chest X-ray if they can not produce smears. In our model, we will assume that the TB test cost is simply the cost for sputum smear test and there is no cost difference for a single sputum smear test between rural and urban Uganda($2.99 for the test [31, 32]).

The third part of the additional cost is the cost for treatment of the TB patients detected by ACF. Treatment cost varies for treatments of different kinds of TB. The cheapest treatment is the first line treatment for new TB cases. If the first treatment fails, the second line or drug resistant TB treatment might be initiated. Generally only a small fraction of TB patients would need second line and drug resistant TB treatment. In our model, we will only consider the cost for first line TB treatment for new TB cases ($15 for first line treatment [32, 132]).

Description	Urban	Rural
Number of TB tests to detect an active TB case	5	7
PCF cost for detecting an active TB cost ($/person)	0.92	0.92
ACF cost for detecting an active TB cost ($/person)	2.86	2.86×2
Cost for TB test (Sputum smear,$/person)	2.99	2.99
Cost for TB treatment (First line,$/person)	15	15

Table 5.9: Cost for TB detection, diagnosis, and treatment. See text for discussion of parameter value selections.

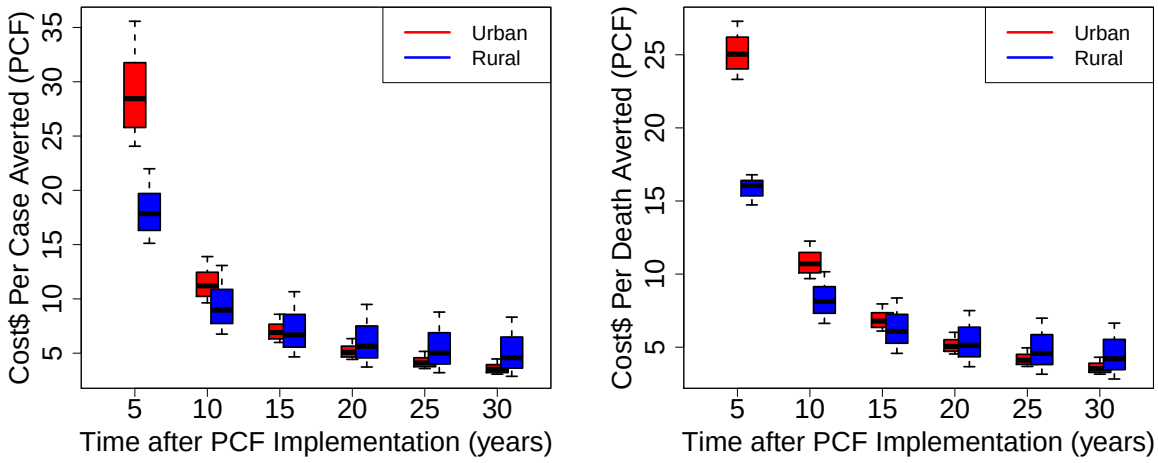
5.3.8 PCF Cost Effectiveness for Urban and Rural Areas

Before studying the additional cost to avert a TB case with ACF implementation, we take a look at the cost to avert a case under PCF. To calculate this value, we compare the scenario that there is no TB treatment with the scenario with passive case finding and TB treatment. Although it is very unlikely for the scenario that there is no TB detection and treatment to occur in modern world, it is worth exploring the cost to avert a TB case under PCF. The cost per TB case and per averted is calculated as,

$$\frac{\text{Total cost under PCF}}{\text{Number of TB cases (deaths) averted by PCF}}$$

Figure 5.10 shows the cost to avert a TB case and death due to TB under PCF and treatment. The cost is about $30 to avert a case in the urban area and about $20 in the rural area in the

first five years of PCF implementation. The cost drops to about $5 per case 20 years after PCF implementation. The cost reaches a certain stabilized level after 20 years. The cost is higher in the urban area at the beginning of PCF implementation but lower in the urban area at the stabilized level after 20 years. The cost per death averted under PCF follows the same pattern as the cost per case averted. This is not surprised as the TB cases will die in a couple of years if they are not detected by PCF and placed for treatment. So every case averted is basically a life saved.



a). Cost per TB Case Averted b). Cost per Death Averted

Figure 5.10: Cost per TB case averted and per death averted under PCF. No ACF.

5.3.9 ACF Cost Effectiveness for Urban and Rural Areas

Additional cost for ACF implementation increases every year. Figure 5.11 shows that the addition cost for ACF implementation is higher in the rural area than in the urban area. The lines for the medians of the costs are becoming "flatter" after ACF implementation. This suggests that the increase in additional cost is getting slower with time.

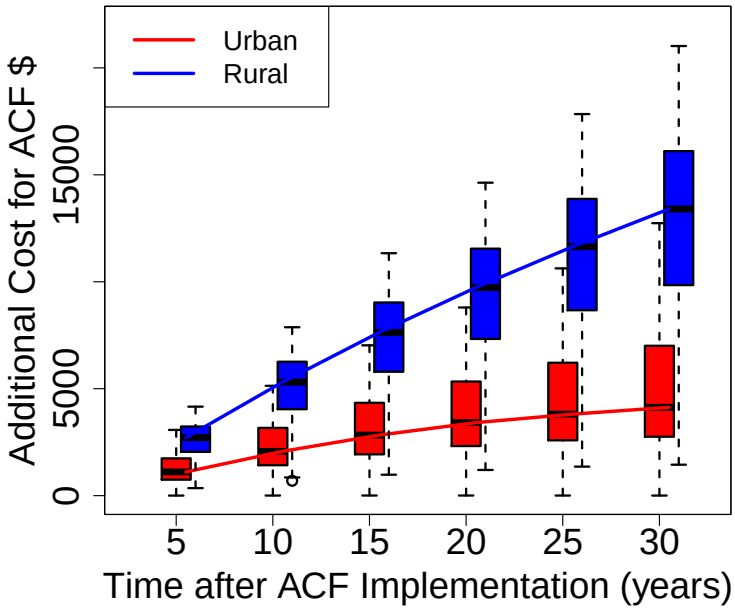


Figure 5.11: Accumulated cost for ACF implementation. ACF is implemented with an efficiency of 30%

Cost effectiveness measure the cost to achieve "effectiveness". For the ACF cost effectiveness, it is calculated as the number of additional cost for ACF implementation divided by the number of cases averted by ACF,

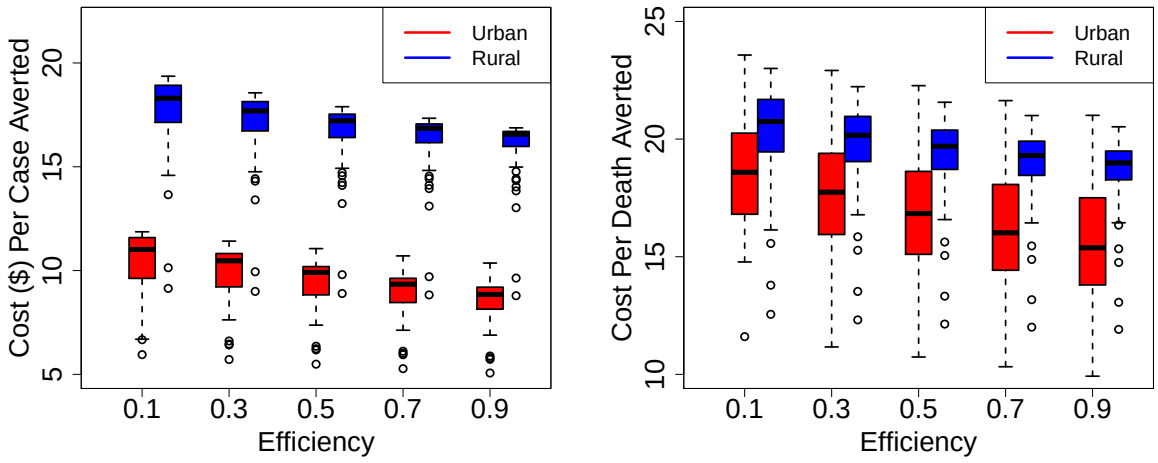
$$\frac{\text{Total cost under ACF - Total cost under PCF}}{\text{Number of TB cases averted by ACF}}$$

Similarly, the ACF cost per death averted is calculated as,

$$\frac{\text{Total cost under ACF - Total cost under PCF}}{\text{Number of deaths averted by ACF}}$$

Results from previous section suggest that ACF implementation can reduce more TB cases in urban areas than in rural areas. However, there are more deaths averted in rural areas than in urban areas. ACF cost to detect an active case is higher in rural areas. Not surprisingly, the cost to revert a TB case is higher in rural areas than in urban areas as shown in Figure 5.12 a). Figure 5.12 a) also suggests that the cost to avert a TB case is becoming a little smaller with higher ACF efficiency. But the change is not much as shown. This implies that level of ACF efficiency does not have much impact on the cost per TB averted.

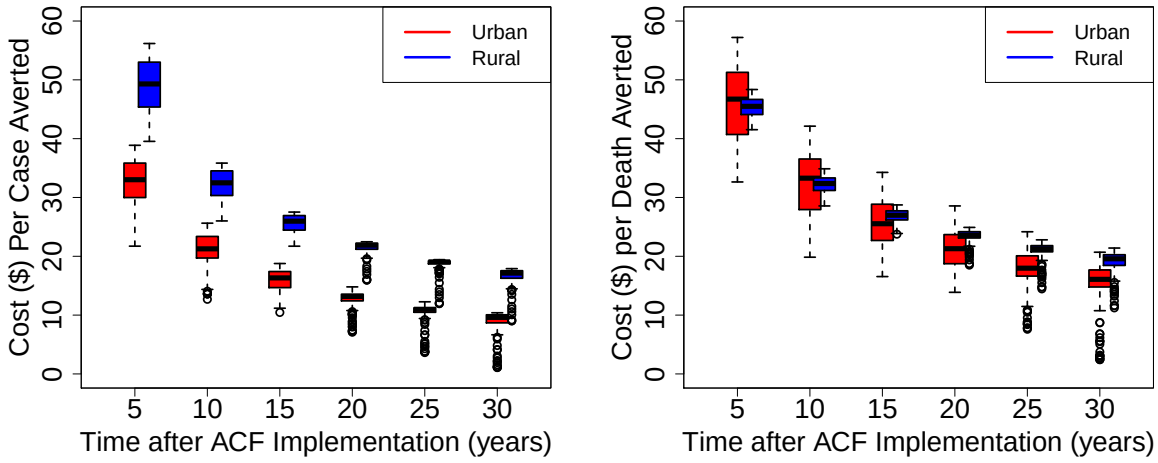
Figure 5.12 b) shows that the cost per death averted is higher in the rural area. It also suggests that the cost per death averted is getting smaller with higher efficiency. This implies that ACF implementation with higher efficiency in the urban area is more cost effective.



a). Cost per TB Case Averted b). Cost per Deaths Averted

Figure 5.12: ACF implementation in urban and rural areas over 30 years. ACF is implemented once a year. a)Cost per case averted, b). Cost per death due to TB averted.

Figure 5.13 shows the change of cost per case and cost per death over 30 years. It shows that the cost per case averted and the cost per death averted are higher at the beginning of ACF implementation. The costs are significantly reduced if ACF is implementation for a longer time. The cost somehow stabilizes after about 20 years. Figure 5.13 a) shows that the cost per TB case averted is higher in the rural area at the plotted time points after ACF implemented. Figure 5.13 b), on the other hand, shows that the cost per death averted is lower in the rural area 5 and 10 years after ACF implementation. After 15 years, the cost per death averted is higher in the rural area.



a). Cost per TB Case Averted

b). Cost per Deaths Averted

Figure 5.13: ACF implementation in urban and rural areas over 30 years. ACF is implemented once a year. ACF efficiency: 30%. a)Cost per case averted, b). Cost per death due to TB averted.

5.4 Discussion

Our results show that ACF implementation with efficiency of 30% can avert about 30 cases/100,000 persons in 5 years and about 500 cases/100,000 persons in 30 years in both urban and rural areas. If we scale the population to the national population of about 36 million in Uganda, ACF implementation can avert about 10,000 TB cases in 5 years and about 180,000 cases in 30 years. In terms of deaths averted, ACF implementation can avert about 8,000 deaths in 5 years and about 150,000 deaths in 30 years.

It first looks strange that under ACF implementation with efficiency of 30%, ACF can detect about 150 additional TB cases in a 100,000 population in the urban area, however, the number of TB cases averted is only about 30 cases. This is due to the fact that these TB patients will be picked up by PCF in six months if they are not screened by ACF.

ACF implementation is more cost effective in the urban area than in the rural area in terms of cost per case averted. In terms of cost per death averted, it is about as effective to implement ACF in the urban area and in the rural area.

Previous studies generally focused on cost effectiveness of ACF implementation in several years. This might overlook the slow dynamic of TB transmission. ACF implementation does not only avert the current active case (fast progressors), but also reduce the number of latent hosts, who might become a TB patient in the future (slow progressor). In other words, ACF implementation at the present time can still avert TB cases in the future. Figure 5.14 shows that the incidence averted is mainly from fast progression and reinfection at the beginning of ACF implementation. The fraction of incidence averted from slow progression of latent hosts is getting larger. Earlier rounds of ACF implementation might contribute to the aversion of slow progression part of incidence in the later time. This might be the reason that cost per case averted becomes smaller with longer time of ACF implementation.

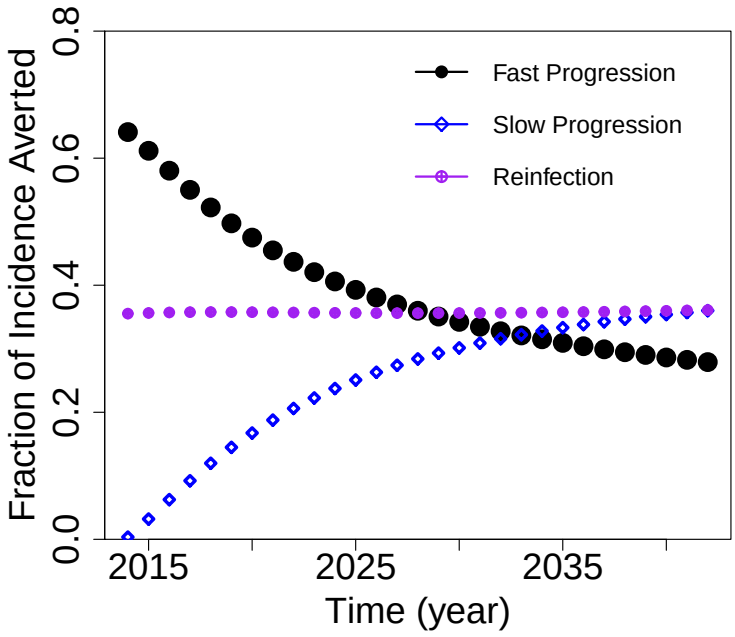


Figure 5.14: Fraction of incidence averted from fast progression, slow progression, and reinfection as a function of time. ACF is implemented once a year with efficiency of 30% in the urban area

When calculating the costs for ACF implementation, we only assume simple smear test and first line treatment for new TB cases. To include more complex TB tests such as chest X-ray and GeneXpert and second line and drug resistant TB costs, the cost to avert TB cases and deaths due to TB is going to be higher. However, our finding that ACF implementation is more cost effective in the urban area in averting TB cases than in the rural area will likely still stand.

Chapter 6

Summary

In this thesis, I presented three projects of mathematical studies of TB transmission and controls.

In the first project, we used a mathematical model to investigate the role of activation rate and latency duration on the ability of MTB to persist in a host population. Our results suggest that an intermediate level of activation from latency to disease is optimal for MTB persistence, that the optimal level depends on the detailed pathogen, host and environment characteristics, and that it tends to be higher than the observed value, suggesting an important role for the immune response to keep MTB in check. While increasing activation rates beyond the optimum to reduce MTB persistence is not a suitable goal from a public health perspective, a reduction in activation rate is much more promising. This would lower the number of hosts with disease, and thereby reduce incidence and prevalence for TB cases and at the same time reduce persistence potential. Potential TB vaccines currently under consideration might help us to achieve such a shift in activation rate. If this shift is strong enough, eradication of MTB might become a possibility.

The second project studied the impact of HIV prevalence on TB epidemic. Simulation results

show that the majority of TB cases are HIV negative when the HIV prevalence is below 25%. The number of HIV positive TB cases outnumbers the number of HIV negative TB cases when the HIV prevalence is over 25%. This result suggests that in the current world, TB controls should also emphasize controls for HIV- TB patients.

The third project analyzed the cost effectiveness of active case finding (ACF) in urban and rural Uganda areas. Results suggest that ACF implementation is more cost effective in the urban area than in the rural in terms of cost per TB case averted and ACF is more cost effective if implemented for a longer period.

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