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Cost-Effectiveness Analysis of Tuberculosis Preventive Strategies among Formerly-Incarcerated Individuals in Brazil

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Abstract

Prisons serve as amplifiers of Tuberculosis (TB) transmission due to overpopulation, lack of hygiene, and bad ventilation [Mabud et al., 2019] [Baussano et al., 2010]. The risk of TB is elevated during and after incarceration, only returning to the general population's risk seven years after liberation. This is an indication that formerly-incarcerated individuals are a high-risk group. By preventing TB among ex-prisoners, the burden and transmission to the general population can remain limited. This study aims to analyze the cost-effectiveness of various preventive measures among formerly-incarcerated individuals in Brazil. With the imprisonment rate growing in the country and the high TB incidence rates, Brazil can benefit greatly from proposed measures.

The research mathematically models the effect of several interventions and quantifies associated health benefits and costs with the use of Disability Adjusted Life Years and Incremental Cost-Effectiveness Ratios. The parameters of the model are estimated with Bayesian statistics, using likelihood functions and prior distributions to calculate a posterior distribution. The results of the research indicate how the different interventions behave and which is most advisable for implementation in the Brazilian health system. Our conclusion is that shorter preventive therapies in combination with the skin test Tuberculin Skin Test perform better than longer therapies and/or the blood test Interferon Gamma Release Assays.

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Contents

Acronyms

CI Confidence Interval. 12, 23

DALY Disability Adjusted Life Years. 1, 4–6, 19–21, 23–28, 30–35, 42, 43

FI Force of Infection. 11, 30

H isoniazid. 4, 5, 15, 16, 18, 24–28, 30, 33, 42

ICER Incremental Cost-Effectiveness Ratio. 1, 4–6, 19, 20, 22–35, 42, 43

IGRA Interferon Gamma Release Assays. 1, 15, 16, 24, 25, 33

LTBI Latent Tuberculosis Infection. 4, 6, 7, 9, 12, 13, 15–17, 21, 22, 24, 27–29, 31, 34

NHB Net Health Benefit. 20

P rifapentine. 4, 5, 15, 16, 18, 24–28, 30, 33, 42

R rifampin. 15, 16, 24, 25

TB Tuberculosis. 1, 4, 6, 7, 9–24, 27, 29–31, 33–35, 41

TPT Tuberculosis Preventive Therapy. 4, 7, 15–18, 21, 22, 25, 26, 28, 29, 33, 34, 40

TST Tuberculin Skin Test. 1, 4, 5, 15, 16, 24–28, 30, 33, 42

WHO World Health Organization. 6, 33

WTP Willingness-To-Pay. 20, 24, 26, 33

YLD Years Lost to Disability. 19

YLL Life Years Lost to due to premature mortality. 19, 20, 27

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1 Introduction

In 2021, an estimated 10.6 million people had Tuberculosis (TB) [World Health Organization, 2023a]. In the same year, 1.6 million people died of the disease, making TB the thirteenth leading cause for mortality globally. It is not strange that the World Health Organization (WHO) wishes to combat the disease. Their goal is to reduce TB incidence by 90% compared 2015 [World Health Organization, 2015]. Despite continuous effort this goals has not yet been achieved, urging further research on the subject.

One of the main characteristics of TB is the split into latent infection and active TB disease. It can take weeks or even years before infected individuals show symptoms [Behr et al., 2018]. This dormant form of the disease is called Latent Tuberculosis Infection (LTBI). Individuals with latent infection cannot transmit the bacteria onto others, but they are at risk of progression to active TB disease. Once progressed the patients might show symptoms, such as coughing up blood, fever and weight loss [Mayo Clinic Staff, 2023], possibly leading to death. However, this long incubation time also provides the opportunity to prevent progression of the disease. Inhibition of the development of active TB is in fact, one of the key pillars in combat of the disease as it can improve the quality of life of those afflicted and of the general population. TB is curable and preventable, and that encourages us in pursuing the WHO's goals.

Researching the most effective strategies plays a central in accomplishing the defined goal. In that regard, the effort is best aimed at geographical areas predominantly afflicted. For that purpose the WHO has listed thirty high-burden countries, among which Brazil [World Health Organization, 2021]. In Brazil alone, 104.000 individuals are estimated to have developed TB in 2021. Even though the TB incidence has slowly been declining, the past COVID-19 pandemic and consequent economic recession reversed this process [World Health Organization, 2022]. Further research might play a significant role in the inverting of the current situation.

The cases are not homogeneously spread within the country. Several cohorts of the population have higher incidence numbers and TB mortality rate, e.g. incarcerated individuals. Prisons display ideal circumstances for transmission of TB due to lack of hygiene, bad ventilation, and overpopulation. The estimated incidence number is twenty-six times higher than in the general population [Baussano et al., 2010]. This transmission is not confined by prison walls, the risk is elevated up to seven years after release from prison [Mabud et al., 2019]. Unfortunately, the individual can then come in contact with the general population, possibly spreading the disease even further.

Research has already been conducted on control strategies during the incarceration period and have shown to be effective [Paião et al., 2016] [Mabud et al., 2019]. However, there has been insufficient research on the strategies aimed at formerly-incarcerated individuals, despite the elevated risk of TB progression. The possible implementation of preventive strategies could not only be beneficial for this specific group, but could also limit the contamination to the general population.

This research performs a cost-effectiveness analysis of different preventive strategies for Brazilian ex-prisoners. We use a Markov model to simulate life outcomes under the different interventions. By applying Disability Adjusted Life Years and Incremental Cost-Effectiveness Ratios, we compare the health benefits and costs of each strategy and come to a conclusion of which intervention is best. This method is frequently used in health economics as seen in [Marx et al., 2021] and [Steffen et al., 2013]. The strategies analyzed in this research differ in diagnosis and preventive therapy and will be explained more thoroughly throughout this thesis.

2 Previous research on the subject

The context of this study is primarily based upon two articles: [Baussano et al., 2010] and [Mabud et al., 2019]. This section briefly describes the content of both articles and their relation to this research.

[Baussano et al., 2010] is a systematic review of the risk of Latent Tuberculosis Infection and Tuberculosis disease in prisons. A study was included in the review if it either mentioned the incidence of Latent Tuberculosis Infection or tuberculosis in prisons, or if it mentioned the number of TB cases and the number of prisoners present at that time. The eligible papers were then independently cross-checked by three reviewers to ensure objectivity. The search resulted in a final twenty-three articles, mostly focused on Brazil and the United States of America. The authors then used these articles to draw overall conclusions concerning the risk of TB and LTBI disease in prisons: They identified a median incidence of tuberculosis in prisons of 1924.8/100.000 persons-year for middle- and low-income countries, and 237.6/100.000 persons-year for high-income countries, showcasing the elevated risk of incarceration.

The incidence rates indicate how big the risk of LTBI and TB disease is for prisoners, but they do not display the effect on the general population. For that reason, the authors calculated the fraction of the cases in the general population that were attributable to prisons and prisoners. They computed this value using the following equation:

$$\text{PAF\%} = \frac{Pe * (\text{IRR} - 1)}{1 + Pe * (\text{IRR} - 1)} * 100$$

where PAF% is the Population Attributable Fraction percent, Pe is the proportion of the population in prisons, and IRR is the incidence rate ratio measured. A rate ratio is a comparison between two rates, in this case the incidence rate in prison as opposed to out of prison. With the use of this equation they estimated a median PAF% for LTBI of 13.1% in high-income countries and 10.4% for middle-income countries. For low-income countries, the authors did not find an appropriate value for the IRR, as a result of which the PAF% for LTBI was not calculated. For TB, the PAF% was 8.5% and 6.3% for high- and middle-income countries respectively. These percentages, along with the high incidence rates illustrate the risk of LTBI and TB among prisoners and consequently, the general population. It leads to the conclusion that incarcerated individuals are a high-risk group and that control strategies among this group could not only be beneficial to them but to the general population as well.

[Mabud et al., 2019] consists of two main parts: the estimation of the incidence in prison and the modeling of various interventions in prison. The authors use individual-level data on active TB cases in prisons in the Brazilian state Mato Grosso do Sul to estimate the incidence in, and after incarceration. They concluded that the peak incidence of TB disease in prison was approximately 1303/100.000 persons-year. After release, it takes seven years before the incidence returns to the level of the general population (42/100.000 persons-year), indicating that prisoners are high-risk, even after liberation.

The second part of the research focuses on the impact of various interventions on the TB incidence in prison. The authors constructed a compartmental model to simulate TB transmission between the prison population and the corresponding local general population. The entire cohort is split into five compartments, each compartment associated with the state of their health. Movement between compartments is calculated with the use of transition parameters, marking the probability of change in health in real-life. The parameters also differ depending on the location of the individual, i.e. depending if the individual is in prison, returning to prison, or has never been in prison. The values of these parameters are either estimated or directly taken from literature.

Using the compartmental model, the authors can implement several strategies and analyze the effects on the incidence. The interventions reviewed are: yearly tests for TB disease, entry and exit screening, the possibility of Tuberculosis Preventive Therapy (TPT), passive diagnosis by improving preexisting testing mechanisms, and a combination of the before-mentioned interventions. Their effect is measured in the amount of decrease in the incidence, in and outside of prison.

The yearly tests are most effective, decreasing the incidence by 47.4% in prisons and 19.4% outside of prison. Entry screening resulted in a decrease of 10.3% in prison, and 3.3% outside,. Exit screening was more effective outside of prison, with a decrease of 27%, as opposed to 14.8% in prison. Providing prisoners with TPT resulted in a decrease of 23.5% in prisons and 16% outside of prison. The improvement of diagnostic tests, also known as passive diagnosis, decreased the incidence by 35% in prison and by 11.5% outside of prison . The combination of all interventions performed the best, with a decrease in the incidence of 79.2% in prison and 40.0% outside of prison.

Both these articles calculate the TB incidence in prisons, but also mention the effect on the general population. Based on their findings, [Mabud et al., 2019] investigate the impact of control

strategies in prison, concluding that implementation is beneficial. Both articles conclude that the risk is not limited to the incarceration period, and that formerly-incarcerated individuals can still be considered high-risk. Yet, both articles omit researching the effect of interventions among this group. This provides the context of the present thesis: the investigation of preventive measures for formerly-incarcerated individuals in Brazil.

3 Simulation of the cohort

To investigate the impact of the different strategies, we simulate the lifetime of a cohort of formerly-incarcerated individuals with a Markov model. This section elaborates on the theory of Markov models and the implementation in this particular research.

3.1 The Markov model: how does it work?

This research aims to compare different TB preventive strategies among formerly-incarcerated individuals. By reviewing lifetime outcomes under various scenarios, we can examine the effects of the different interventions. To accurately simulate life among ex-prisoners, we use a Markov model. This type of model emulates the behavior of a cohort by splitting it into discrete health states. At each point in time, the distribution of the cohort among these states is calculated. For example, it's possible to split an entire population into two states: Healthy and Sick. If at point t, 3% is sick, that fraction of the cohort will be in the state Sick and the rest in Healthy in accordance with their actual health. Assuming that some of the sick individuals recover and thus become healthy once more, they will move to the Healthy state in the following time step. This probability to move from one state to another is called a transition probability. With the distribution of the cohort and the transition probabilities, it's possible to calculate the next time step.

Coming back to the example: if there is a probability of 0.1 to recover each month, you'll have $0.3 - 0.3 * 0.1 = 0.27$ in Sick and $(1 - 0.3) + 0.3 * 0.1 = 0.73$ in Healthy at time $t + 1$. For the following time step $t + 2$, $0.27 - 0.27 * 0.1 = 0.243$ will be in Sick and 0.757 in healthy, and so on. The structure of the calculation remains the same regardless of which time step : the distribution of the previous time step is timed with the transition probabilities resulting in the next distribution of the cohort. That means that future behavior only depends on the present cycle. This independence of the past is called the memory-less property, also known as the Markov property [Grimmet and Welsh, 2014]. This characteristic is what makes Markov models relatively easy to use and quick to calculate, as you only need basic matrix algebra.

Even though the model is memory-less, the transition probabilities do not need to be. The probabilities can differ for each time step and therefore be time-dependent. An example is the probability of dying: An 80-year-old has a much higher chance of passing away than a 20-year-old in the same conditions just because of their age [Sato and Zouain, 2010]. To account for these time-dependent probabilities, the transition probabilities need to be assessed each time step.

Besides the quick and easy calculation, Markov models enable us to compare different interventions. By associating costs and utilities to the health states and transition probabilities, we can evaluate the different life outcomes as well as the economic benefits and drawbacks of each intervention.

3.2 The Markov model: the structure

The structure of the Markov model depends on the focus of the research. In this research, the focus lies on tuberculosis and more specifically, the prevention of tuberculosis. Hence, this model must accurately describe the progression of the disease in its latent and active form. This sections explains the structure of the model as implemented in this research.

We simulate a cohort over their lives, ending at death. We are looking at the effects of LTBI treatment in *ex*-prisoners, so the simulation starts *after* their release from prison. The cohort is divided into nine health states, as denoted in Figure 1. The first state is 'Uninfected', containing all the individuals who have never been infected with mycobacterium tuberculosis or in other words, TB. The next three states in the Figure depict LTBI. After infection, the risk to progress to active TB is highest in the first two years. These individuals are called fast progressors and are represented in the model by 'Latent Fast'. After the first two years the risk decreases enormously, depicted as the 'Latent Slow' state. There is a fraction of the infected that never progress to active TB, portrayed in the model by the 'Latent Cleared' state [Menzies et al., 2018]. The split of latent TB in three states accurately represents the difference in risk of progression over time, without impacting the memory-less property of the model.

If an individual does progress to active TB, they can be in two states: 'Undiagnosed TB disease' and 'Diagnosed TB disease'. This split denotes the lag in diagnosis corresponding to reality. After progression to TB disease, the patient is at risk of dying of TB (TB death). At the same time, the patient can also recover, leading them to the 'Recovered' state. If a patient is diagnosed with active TB, they'll immediately start TB treatment. This treatment increases their chances of recovery, shortening the time of disease to approximately six months, which is the duration of treatment

[Ministério da Saûde, 2019]. At all times individuals can die of non-TB reasons, appropriately called background mortality. This is not shown in Figure 1 in order to make the figure clear and comprehensible. The model runs in a monthly time step. The structure of this model does not yet contain the appropriate framework for the interventions, but that will be explained in section 5.2. The model is programmed in Rstudio [R Core Team, 2021].

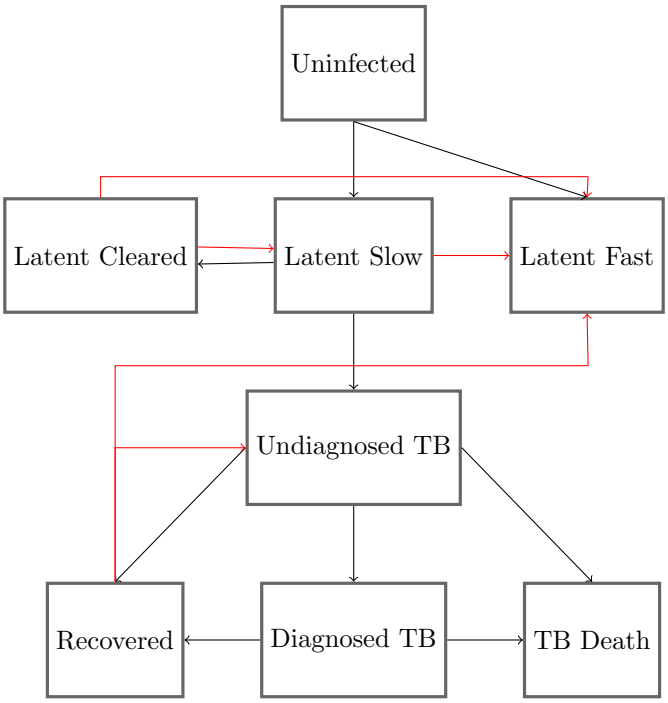


Figure 1: A schematic diagram of the Markov model

The arrows in Figure 1 denote the transition probabilities between states. Once recovered from TB disease, patients are still at risk of recurrent TB, so it's possible to return to the TB disease states. Furthermore, a patient can be re-infected, showed by red arrows in Figure 1. Previous infection has shown to offer some level of immunity [van Crevel et al., 2002], so to depict that the re-infection rate is lower than the force of infection, we time the force of infection with a relative risk (see Table 4). The transition probabilities are either taken from the available literature or estimated using Bayesian methods. The latter will be explained more thoroughly in section 4. The values of the probabilities can be found in Table 4.

4 Estimating parameters using Bayesian methods

The Markov model uses the transition probabilities to calculate the next distribution and therefore, to simulate. Most values of the parameters are found in existing literature, but there are several, mostly epidemiological parameters that cannot be obtained from the literature. For these parameters we use Bayesian statistics to determine their values. This section describes how the estimation works and how it is implemented in this research.

4.1 Theory of Bayesian estimation

As TB infection has a long and varying incubation time, it's difficult to know when and how someone was infected. These epidemiological circumstances are essential to the model, but hard to measure empirically. However, there are other empirical measurements that can be used to 'reverse' estimate the values of the parameters. This 'reverse' estimation is called Bayesian estimation.

Bayesian estimation is based on Bayes' theorem:

$$\mathbb{P}(A|B) = \frac{\mathbb{P}(A) * \mathbb{P}(B|A)}{\mathbb{P}(B)}. \tag{1}$$

where $\mathbb{P}(A|B)$ is the posterior distribution: the probability of event A given the evidence of event B. It depends on the prior distribution $\mathbb{P}(A)$ - the probability of event A - and the likelihood function $\mathbb{P}(B|A)$, a conditional probability of B to A. The $\mathbb{P}(B)$ is a normalizing factor, ensuring that the outcome sums up to one. Using the prior distribution and the likelihood function, we can calculate the posterior distributions, which act as transition parameters in our model. A big advantage to this method is that the results of the estimation are not singular values, but a posterior distribution with uncertainty. It provides the user with an idea of how certain the estimated value is and therefore with more accurate results.

The prior distribution and the likelihood function depend on known information about that specific parameter. Most priors are educated guesses and not definite. To resolve this uncertainty surrounding the priors, we implement a calibration target. This target works as a reality check for the posterior, ensuring that it is realistic and behaves as it should. For example, if we know that around 1000 persons per year die of tuberculosis, we should receive approximately the same value calculating it with the posterior distributions. In conclusion, the prior distribution, the likelihood function, and calibration targets lead to estimated posterior distributions, which are then used in the model as transition probabilities.

4.2 Implementation of Bayesian estimation

We want to estimate the epidemiological parameters, or in other words, the transition probabilities of Figure 1. These include:

1. the Force of Infection, FI,
2. the fraction to latent fast,
3. the progression to TB from latent fast and latent slow,
4. the clearance rate,
5. the diagnosis rate of TB,
6. the TB recovery rates,
7. the TB death rate,
8. the recurrence rate,
9. the relative risk of immunity.

We do need to take into account the effect of incarceration on the cohort [Baussano et al., 2010], as it is shown that ex-prisoners are at higher risk than individuals in the general population. Formerly-incarcerated individuals have a higher force of infection, as the risk of infection is higher in prison. To account for this elevation, we include a rate ratio, a. That means that in prison the force of infection is $FI * a$, and thus a times as high as outside of prison.

As stated in the previous section, Bayesian analysis uses prior distributions and likelihood functions to estimate the posterior distribution. The prior distribution of the parameters can be found in Table 1, which shows the prior mean and standard deviation for each parameter. The choice of the prior depends on the known information and the certainty of that value. The values in Table 1 with a large standard deviation are the values with big uncertainty: there is little to no information on that value. The choice for each prior mean is explained in the next paragraph.

All the parameters are given in yearly rates. A rate describes the number of occurrences of that certain event in the described unit of time [Fleurence and Hollenbeak, 2007]. Rates are relatively easy to work with and manipulate. If you want to go from a yearly rate to a monthly rate, you only need to divide by twelve, whereas a probability is more complex. It is also simple to go from a probability to a rate and vice versa using the following equations.

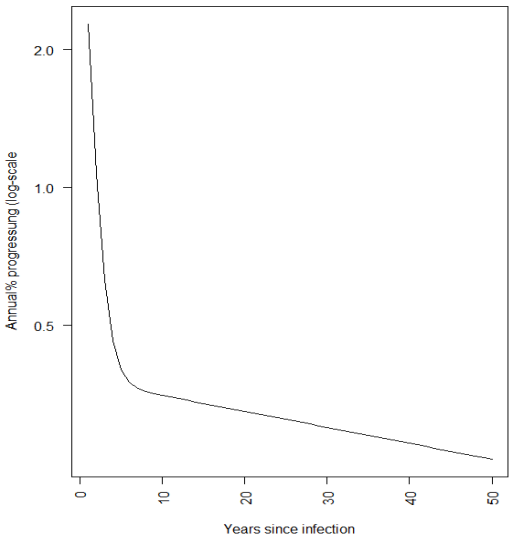


Figure 2: The annual percentage progressing to TB disease using the mean values of the prior distributions

$$p = 1 - \exp(-rt) \tag{2}$$

$$r = -\frac{1}{t}\ln(1-p) \tag{3}$$

where p is the probability of the event, r is the rate of the event and t is the time unit [Fleurence and Hollenbeak, 2007].

For the force of infection, little information is known. Taking a guess, we use 1 as the mean for the rate. For the rate ratio a, [Baussano et al., 2010] tells us that incarceration has an elevated risk of infection of around 27. Since this is specific to their research, we take a mean of 20 and a large standard deviation. This is still close to their value, without restricting the estimation of that value. The parameters 2-4 in the list at the beginning of the paragraph depict the natural history of latent infection. We know that around 5% of new infections progresses to active TB in the first two years [Ferebee, 1970][Sutherland, 1976]. After the first two years, the risk of progression declines. In the following years approximately another 5% progresses to TB [Sutherland, 1968] [Ferebee and Mount, 1962] [Vynnycky and Fine, 1997]. With this information, we construct the mean values of the prior that approximately follow that course, see Figure 2.

Continuing, the diagnosis lag of TB disease is about six months, resulting in a rate of 2. Once progressed, individuals can recover or die of the disease. The process of untreated TB takes approximately three years, ending either in death or self-recovery [Tiemersma et al., 2011]. The rate of dying of TB + self-recovery rate ≈ 0.30, and we assume the probability of either option is equal. That yields a prior mean of 0.15 for both parameters. In case of recovery, the patient is in 'Recovered', where they are still at risk to return to active TB, known as recurrent TB. We assume the recurrence rate to be the same as the progression rate from latent slow. Seeing as these two groups behave in a similar manner - progressing to TB disease after a longer period of time - it seems rational to assume equal distributions. Lastly, an individual can also be re-infected with mycobacterium tuberculosis. Previous infection does provide a level of immunity. This aspect is modeled by multiplying the force of infection with a relative risk, reducing the number to depict the immunity. This relative risk is approximately 0.21, as estimated in [Andrews et al., 2012].

All of these prior values are used to calculate the calibration targets and ultimately the posterior. In the case that the result was way off, the priors were adjusted by widening and narrowing the standard deviation or altering the mean. This method of trial and error resulted in the mean values described in this section and stated in Table 1. All parameters used in this research are notated with a standard deviation. This is a 95% Confidence Interval (CI). This means that of all the random sampling, 95% of that sample is contained within the interval. This ensures that any outliers do not influence the mean, while still taking the uncertainty into account.

To ensure realistic posterior distribution, we utilize calibration targets. The targets used are: TB incidence in prison, the prevalence of LTBI prior to prison, and the prevalence of LTBI in prison.

Parameter	Prior mean (standard deviation)
Force of infection	1 (0.13-1.13)
Rate ratio	20 (0.6-100)
Fraction of latent fast	0.03 (0.01-0.05)
Progression rate to TB disease from latent fast	1 (0.75-1.5)
Progression rate to TB disease from latent slow	0.004 (0.002-0.007)
Clearance rate from latent slow	0.05 (0.03-0.08)
Diagnosis rate of TB disease	2 (1.5-2.5)
Relative risk for reinfection	0.21 (0.15-0.25)
Self-recovery rate	0.15 (0.05-0.25)
TB death rate	0.15 (0.05-0.25)
Recovery rate	2 (1.6-2.3)
Recurrence rate	0.004 (0.002-0.007)

Table 1: Prior distributions of the epidemiological parameters

TB incidence is the fraction of new cases in a time interval proportional to the total person-time in the same time interval, whereas prevalence takes all existing cases into consideration. TB incidence is given in person-time, denoting the number of people in the observed population and the time interval taken.

$$\text{TB incidence} = \frac{\text{number of } \textbf{new} \text{ cases of TB during time interval}}{\text{total person-time}} \tag{4}$$

$$\text{TB prevalence} = \frac{\textbf{all} \text{ cases of TB during time interval}}{\text{total population during time interval}} \tag{5}$$

The three calibration values denote the amount of TB infection before and during prison, which enables us to calculating the effect of incarceration on the spread of the disease. The calibration targets are taken from literature and can be found in Table 2.

Calibration target	Mean value	source
Incidence rate TB disease in prison	1600/100.000prs-yrs (sd: 1500-1700)	[Carbone et al., 2015]
TB prevalence prior to incarceration	0.076 (sample size: 100)	[Navarro et al., 2016]
TB prevalence during incarceration	0.25 (sample size: 100)	[Carbone et al., 2015]

Table 2: Calibration targets for the Bayesian estimation

The only aspect remaining is the likelihood function. The likelihood function of the parameter depends on the certainty we have of that value. Since most values are educated guesses, we take unrestricting likelihood functions. If the parameter is between 0 and 1, the likelihood function is a beta distribution.[1] The beta distribution is defined on the interval $[0, 1]$, making it a good choice for parameters also defined on that interval. It is used for the parameters: fraction to latent fast, pLf and the relative risk, b. For the force of infection and rate ratio a we assume that the likelihood function is normal as we expect the posterior value to be around the prior mean value. In the normal distribution, the further the value is from the mean, the smaller the probability it will be attained.[2] For the rest the likelihood function is a gamma distribution. This distribution is defined on the interval $(0, \infty)$, but is not as restricting as the normal.[3]

To check the accuracy of the posterior distributions, we calculate the TB incidence in prison and the LTBI prevalence before and during prison with the estimated values. We then compare it to the calibration values. This calculation follows the same structure and method as the Markov model in Figure 1, but there are a couple of important differences. Firstly, the model starts at birth. Afterwards, the model runs for 35 years. This ensures the model runs enough time steps to properly calibrate, without taking too much time. Running the model for more cycles does not improve the accuracy and only increases the amount of time it takes. Since this model is solely used for estimation of the parameters, and not modeling of interventions, it is not needed to simulate until death. Secondly, the entire cohort enters prison at 20 years of age. During incarceration,

[1] Beta(α, β): mean $= \frac{\alpha}{\beta+\alpha}$, variance $= \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$

[2] Normal(μ, σ^2): mean $= \mu$, variance $= \sigma^2$

[3] Gamma(α, β): mean $= \frac{\alpha}{\beta}$, variance $= \frac{\alpha}{\beta^2}$

there is an elevated risk of infection. This is the force of infection times the rate ratio a. The cohort enters prison simultaneously but leaves prison according to an exit rate.

The programming of this estimation is done in RStan [Stan Development Team, 2023]. This program uses the calibration targets as well as the prior and the likelihood to calculate the most likely value of the posterior parameters. The model is run 1000 times for accuracy. The posterior distributions are then used in the Markov model as the transition probabilities. The results can be found in Table 4. Table 3 shows the values of the calibration targets using the posterior.

Comparing the values in Tables 2 and 3, we see that both the incidence rate and the prevalence prior to prison are approximately the same. The estimated incidence rate is slightly lower than the target, but this is not problematic. The estimated TB prevalence during incarceration is a lot higher than expected. During the estimation, the model chooses posteriors that fit with our priors and hit our calibration targets as well as possible. If the estimated incidence rate would increase and hit its target, the estimated TB prevalence in prison would increase as well. That value would then be further from our target. The model needs to balance between the two values - either close to the incidence rate and a higher prevalence or closer to the prevalence value and a lower incidence rate. This problem, and a possible solution, is further discussed in Section 9.

Calibration target	Mean value
Incidence rate TB disease in prison	1401/100.000 person-years
TB prevalence prior to incarceration	0.10
TB prevalence during incarceration	0.40

Table 3: Values of the calibration targets calculated with the estimated posterior distributions

Epidemiological parameters	Mean value (95% CI)
Force of infection	0.0043 (0.0026-0.0064)
Rate ratio for infection in prison	103 (64-156)
Fraction to latent fast	0.11 (0.083-0.14)
Progression to active TB from latent fast	1.3 (0.96-1.8)
Progression to active TB from latent slow	0.0049 (0.0022 - 0.0085)
Clearance rate	0.049 (0.028-0.076)
Relative risk for re-infection	0.22 (0.17-0.27)
Diagnosis rate TB disease	2.3 (1.8-2.8)
TB Death rate	0.13 (0.057-0.23)
Self-recovery rate	0.13 (0.060-0.24)
Recovery rate	2.0 (1.7-2.4)
Recurrence rate	0.0049 (0.0022 - 0.0085)

Table 4: The epidemiological parameters of (latent) tuberculosis used in the Markov model estimated with Bayesian statistics

5 The preventive interventions

The Markov model is used to play out different scenarios in the cohort of interest. It is therefore necessary to establish a good definition of those scenarios. This section aims to do precisely that. It describes the different interventions analyzed in this research, and how they are implemented in the structure of the simulation.

5.1 What are the interventions

As previously described, this research looks at preventive methods in formerly-incarcerated individuals. The structure of the interventions remains the same, the materials used change. The structure is as follows. The cohort is tested for Latent Tuberculosis Infection. These tests cannot differentiate between LTBI and active TB disease. All patients with a positive result, also receive a TB test to distinguish active TB from latent TB. We assume that this TB test has 100% accuracy. That means that it can identify individuals that are sick (true positives) and individuals that are not sick (true negatives). The former is called the sensitivity of the test and the latter is the specificity [Altman and Bland, 1994]. In the case that the result of TB test is also positive, the patient is diagnosed with active TB disease and consequently starts with TB treatment. We assume that 100% of the diagnosed TB patients start treatment. The assumptions of 100% accuracy and 100% start of treatment simplify the structure and calculation of the model. These assumptions do not impact the focus of the research, namely comparing preventive strategies. Returning to the structure of the intervention, if the TB test is negative, the patient is diagnosed with latent TB and is provided the option to start Tuberculosis Preventive Therapy (TPT). This is a drug-intensive regimen which can take up to nine months and completion of the treatment can prevent progression of TB disease. How the process of testing and treatment is implemented in the model, is explained in section 5.2.

The strategies explored in this research differ in two aspects: the Latent Tuberculosis Infection test used and the Tuberculosis Preventive Therapy used. The test used for diagnosis of active TB is the same in each strategy. To properly diagnose TB, a patient undergoes an Chest X-ray examination and a rapid culture test, called Xpert MTB/RIF assay [Nsengiyumva et al., 2022]. Those two examinations determine if a patient has active TB disease or not. This procedure is in accordance with the guidelines of the Brazilian Ministry of Health [Ministério da Saûde, 2019]. As said previously, we do assume a sensitivity and specificity of 100%, not corresponding to real values.

The LTBI tests do differ per strategy. The LTBI tests reviewed in this research are the Tuberculin Skin Test (TST) and the Interferon Gamma Release Assays (IGRA). The former is a skin test, where the patient receives an injection of tuberculin in the arm. The skin reacts by swelling up, which takes between 48 to 72 hours. The diameter of the swelling indicates the results of the test. If the diameter of the induration is equal to or greater than 10mm, the result is positive [Centers for Disease Control and Prevention, 2022], and if the diameter is less than 10mm, the result is negative. For this diagnosis the patient needs to return to the hospital.

The other test, IGRA is a blood test. The patient gives a small amount of blood that is examined for traces of mycobacterium tuberculosis in the lab [NSW TB Program, 2017]. If there is enough proof of those traces, the result is positive. This test is more expensive than the TST, but does not require the patient to return to the hospital for the reading; the results can be shared over the phone.

After a positive LTBI diagnosis, the patient can start TPT. We compare four different regimens, on advice of the Brazilian Ministry of Health. The first therapy is a 9-month regimen of daily isoniazid (9H). The dosage consists of 300mg of isoniazid. The second is a combination of 900 mg isoniazid and 900 mg rifapentine given weekly for 3 months (3HP). It is sometimes referred to as the 12-doses therapy, corresponding to the duration of twelve weeks of the regimen. The third option is a 4-month regimen of a daily dose of 600mg rifampin (4R) [World Health Organization, 2023b]. The fourth and last, is a 1-month regimen, and is essentially a shortened version of 3HP. Instead of a weekly dose, it consists of daily doses of 300 mg isoniazid and 600 mg rifapentine, and is abbreviated by 1HP [World Health Organization, 2023b].

Parameters concerning the different regimens and diagnostic tests can be found in Table 5.

Parameters	Value (range)	Source
Probability of return to TST reading	0.88 (0.65-0.97)	[Steffen et al., 2020]
Probability of starting LTBI treatment	0.82 (0.74-0.97)	[Steffen et al., 2020]
Sensitivity TST $\geq$ 10 mm	0.77 (0.71-0.82)	[Pai et al., 2008]
Specificity TST $\geq$ 10 mm	0.59 (0.59-0.8)	[Pai et al., 2008]
Sensitivity QFT-GIT	0.7 (0.63-0.78)	[Pai et al., 2008]
Specificity QFT-GIT	0.95 (0.94-0.98)	[Pai et al., 2008]
Completion rate 9H	0.70	assumed
Efficacy 9H regimen	0.9 (0.63-0.93)	[Steffen et al., 2020]
Number of outpatient visits	9	internal communication
Number of doses (300mg H)	270	[Sterling et al., 2020]
Completion rate 4R	0.82	assumed
Efficacy 4R regimen	0.9 (0.63-0.93)	[Menzies et al., 2018]
Number of outpatient visits	4	internal communication
Number of doses (600mg R)	120	[Sterling et al., 2020]
Completion rate 3HP	0.84	assumed
Efficacy 3HP regimen	0.9 (0.63-0.93)	[Sterling et al., 2011]
Number of outpatient visits	3	internal communication
Number of doses (900mg H/900mg P)	12	[Sterling et al., 2020]
Completion rate 1HP	0.9	assumed
Efficacy TPT 1HP regimen	0.9 (0.63-0.93)	assumed
Number of outpatient visits	1	internal communication
Number of doses (900mg H/900mg P)	28	[World Health Organization et al., 2003]

Table 5: Latent TB diagnosis and therapy parameters used in the model

The strategies are a combination of the LTBI tests and Tuberculosis Preventive Therapy. In total, we get 8 different strategies.

1. Tuberculin skin test and 9-month regimen of isoniazid, TST + 9H
2. Interferon gamma release assay test and 9-month regimen of isoniazid, IGRA + 9H
3. Tuberculin skin test and 3-month regimen of isoniazid and rifapentine, TST + 3HP
4. Interferon gamma release assay test and 3-month regimen of isoniazid and rifapentine, IGRA + 3HP
5. Tuberculin skin test and 4-month regimen of rifampin, TST + 4R
6. Interferon gamma release assay test and 4-month regimen of rifampin, IGRA + 4R
7. Tuberculin skin test and 1-month regimen of isoniazid and rifapentine, TST + 1HP
8. Interferon gamma release assay test and 1-month regimen of isoniazid and rifapentine, IGRA + 1HP

5.2 Modeling the interventions

The testing is implemented in the model in form of a decision tree prior to the start of the simulation. This decision tree is shown in Figure 3. The tree redistributes the cohort into new initial states, depending on the results of the tests and the decision of the individual. Everyone who is not already diagnosed with TB disease is suitable for LTBI and TB testing. The structure of the decision tree is in accordance with the structure of the interventions as explained in Section 5.1.

If the individual tests positively for TB disease, they move to 'Diagnosed TB disease', independent of their health state prior to testing. In the case that the individual tests negative for LTBI, they stay in the health state they were in prior to the intervention. The biggest change happens if the person tests positive for LTBI, but negative for TB disease. The person is offered the possibility to start Tuberculosis Preventive Therapy. Upon refusal the individual returns to

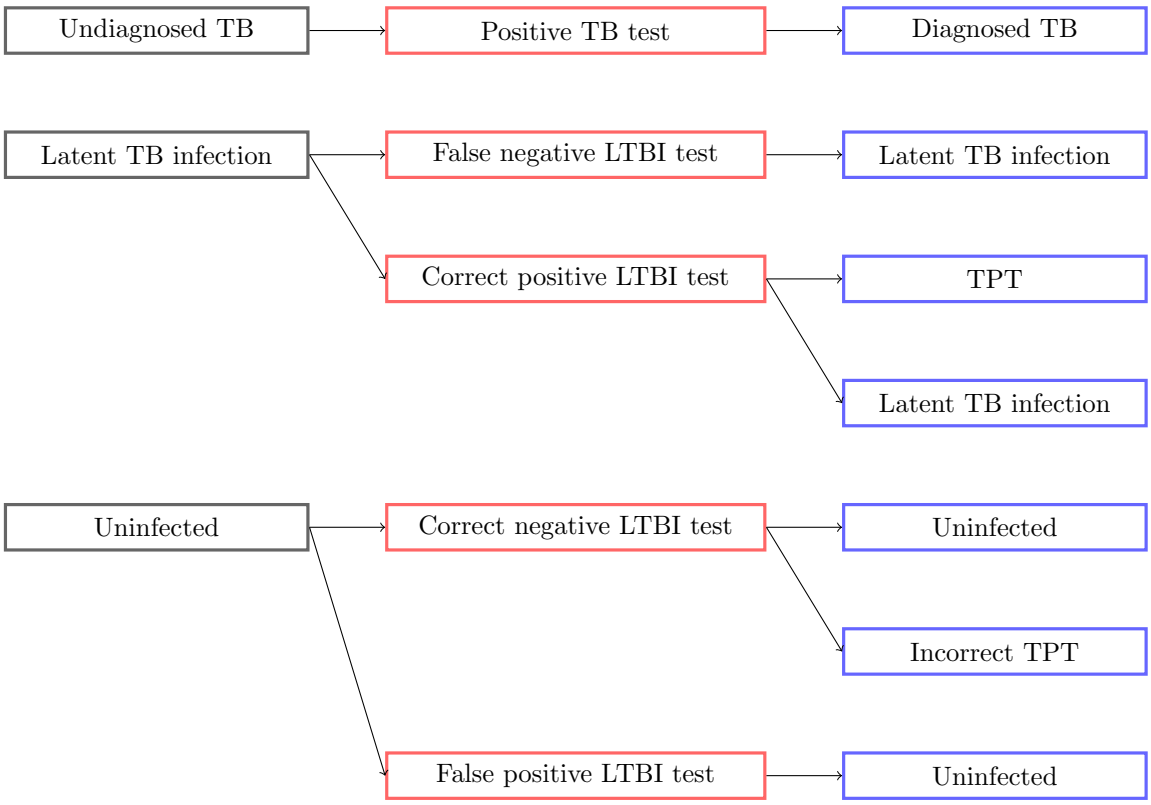


Figure 3: A schematic diagram of the decision tree of the interventions. The blue nodes show the result of the decision tree, and the red nodes indicate diagnosis of LTBI and TB

their health state, in the same way as one would with a negative LTBI test. However, if the patient does commence treatment, they move to a new state: TPT.

This TPT-state was not included in the first version of the Markov model (Section 3.2) and is therefore added to the model. An important aspect of TPT is that the progression of the disease continues while in treatment. If the patient was in Latent Fast and they start TPT, they go to the state: 'TPT while Latent Fast'. In the same way, if the test was a false positive, but the patient does start TPT, they enter 'TPT while Uninfected'. If the individual would have progressed to 'Latent Cleared' in the model without TPT, they will do so in the model with TPT by moving to 'TPT while Latent Cleared'. This ensures that at the moment TPT ends, everyone returns to the correct health state. Not including the progression during TPT would mean that it holds onto infection. For example, if you were in 'Latent Slow' and were going to progress to 'Latent Cleared', you would never progress to TB disease. But imagine that you receive a positive result for latent TB and you start TPT. You complete TPT, but it was not successful: you then return to the state 'Latent Slow', your state prior to TPT, where you are still at risk for TB disease. In that case it would have been beneficial to **not** start TPT; TPT even *increased* your probability to progress to TB disease. For those cases it is necessary to keep track of the disease progression. It does not make a difference for the amount of people cured due to the preventive treatment, but it does make a difference for the behavior of individuals in the cohort.

The TPT states are slightly different than the rest of the health states. Since TPT takes a fixed amount of time, we need to know how long someone is in treatment for. There is a difference between a patient in the fourth month of TPT and a patient in the first month of the therapy. The first one has had more doses of drugs, so the probability of cure is higher, but so are the costs. Unfortunately, the Markov property impedes us to keep track of past states. To solve this problem, we create tunnel states. These states are unique due to their following property: you cannot remain in them for more than one time-step. So after one time-step in a tunnel state, you **must** progress to a new state; the probability of staying is 0. This is why they are called tunnel states, you pass through them just as you would in a tunnel. For the 3-month regimen, we have 3 tunnel states: month 1, month 2 and month 3. So after being in month 1, the patient **must** proceed to month 2, and so on.

The tunnel states also enable us to model how many individuals stop with TPT each month. As the therapies take quite a long time, a fraction will not complete their treatment. Quitting

the regimen can be due to a varying array of reasons, ranging from financial, medical, or personal. Most people quit in their first month, so we concentrate the loss-to-follow up in the first tunnel state of the regimen. We assume a loss of around 10% in the first month and 3% for each following month. For the 9-month therapy this accumulates to approximately 70% completing treatment, for the 4-month regimen to 82%, for the 3-month regimen to 84%, and for the 1-month treatment to 90%. These numbers correspond to empirical evidence [Belknap et al., 2017], [Doan et al., 2018].

Another reason why it is important to keep track when a patient quits their treatment, is that partial treatment still has a curing effect. We model this by assuming that if individuals are halfway through their treatment, they have 50% chance of cure. In the case of the 9-month regimen, if a patient has already reached month 6 of the treatment and decides to stop, they have a 50% to be cured even without completing the treatment.

See Figure 4 for a simplified diagram of the tunnel states. The blue arrows denote the fraction lost-to-follow-up. The appendix contains Figures for the TPT tunnel states and the continued progression of the disease, and the new model containing TPT.

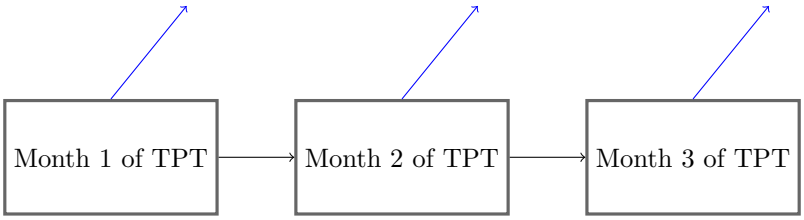


Figure 4: Schematic diagram of TPT tunnel states for 3HP

The last change to the model structure is the state 'Cured'. If TPT was successful, the individual moves to that new state. The group in this state behaves similarly to 'Latent Cleared': there is no probability of progressing to active TB but does contain the immunity of prior infection. Figure 18 in the appendix contains the new version of the Markov model.

6 How to compare the results

We need to compare the different interventions to be able to decide which is the 'best'. To accurately quantify the burden of tuberculosis and the effect of preventive strategies, we calculate the Disability Adjusted Life Years (DALY). This section describes the theory of DALYs and how we connect it to their respective costs with the Incremental Cost-Effectiveness Ratio (ICER). We end with the implementation of DALY and ICER in this research.

6.1 Disability Adjusted Life Years

To compare the different strategies, we asses the various lifetime outcomes and the health benefits of each strategy. The question arises how to measure health benefits. The convention in health economics is to calculate the burden of the disease and to analyze how a certain strategy alleviates this burden. A metric often used for this burden are the Disability Adjusted Life Years (DALY). It provides a single number quantifying the health burden of the disease and aids us in the choice of the 'best' strategy.

DALYs consist of two parts: the morbidity and the mortality of the disease. The morbidity is the diminished quality of life due to the disease. It is expressed in the Years Lost to Disability (YLD). In comparison with a healthy person, a TB patient does not live life to its fullest extent. This health gap is precisely what YLD depict. YLDs run between 0 and 1, where 0 denotes perfect health and 1 is equivalent to death [Murray and Acharya, 1997], i.e. the worst health someone can be in. Depending on the burden of the disease, the quality of one life year is diminished with a certain weight, appropriately called disability weight. Two years with a disability weight of $\frac{1}{2}$ is equivalent to one year in full health. For active tuberculosis the disability weight is 0.333 [Center for Evaluation of Value and Risk in Health (CEVR), 2019]. The disability weights are constructed with evaluations of patients and health-care professionals. These measurements are published in the Global Burden of Disease paper [Salomon et al., 2015] and provide a number to be consistently used across all research. The number is then used to calculate the YLDs for an entire population. We use the following equation:

$$YLD = \sum_i \sum_t N_{i,t} * w_i \tag{6}$$

where $N_{i,t}$ is the number of life-years for health state i and year t and w_i is the disability weight for health state i.

The mortality is expressed in Life Years Lost to due to premature mortality, YLL for short. The YLL are the number of years that someone was expected to live, when they prematurely died of the disease. This is calculated in the following way:

$$YLL = \sum_x \sum_t D_{x,t} e_x \tag{7}$$

where $D_{x,t}$ is the numbers of deaths at age x and year t and e_x is the life expectancy at age x. If a 20-year old is expected to live 60 more years but dies prematurely of tuberculosis, the YLL $= 1 * 60 = 60$. The YLL and YLD together are the DALY:

$$DALY = YLL + YLD \tag{8}$$

[Center for Evaluation of Value and Risk in Health (CEVR), 2019]

The DALYs are a fairly straightforward calculation, which makes it easy to work with. However, it is a simplified version of reality, and critics have scrutinized this simplification. One of the biggest criticisms surrounds the calculation of YLL. The underlying assumption of YLLs is that all life years are worth the same, whereas critics say they are not. The idea behind this is that life years spent as a young adult are more valuable (to society) than life years spent as a 60-year old. This problem can be solved by applying age-weighting, or in other words, discounting for future life years lost. Some criticize this by saying it is not ethical to value life in productivity to society, but it is general practice in health economics. Another practice is the discounting of health benefits. It is assumed that future health benefits are lower than present gains. The discount rate used for DALYs is 3% [Homedes, 1996]. Taking both forms of discounting into account gives us the following equations for double-discounted DALYs.

$$YLD = \sum_i \sum_t N_{i,t} w_i * (1+d)^{1-t} \tag{9}$$

$$YLL = \sum_x \sum_t D_{x,t} * \frac{(1-(1+d)^{-e_x})}{d} * (1+d)^{1-t} \tag{10}$$

where d is the discount weight of 0.03. The DALYs calculated with equations (9) and (10) are appropriately called discounted DALYs. The DALYs using equations (6) and (7) are called undiscounted DALYs. In this research we show both forms of DALYs.

Using the DALYs we can compare different health benefits of the strategies. By calculating how many DALYs a strategy has prevented in comparison to doing nothing shows how effective this particular strategy is. Important to note is that we are looking at the effect of prevention of TB. To correctly analyze the interventions on that effect, we need to only look at TB DALYs. In a general population without TB people will still die prematurely due to other reasons. However, the formula for YLLs does not make a distinction between premature death due to TB or to other reasons. To avoid incorrect YLLs, we calculate the YLLs in a cohort without any TB. We then subtract those YLLs from the YLL in a cohort with TB. What rests are the DALYs attributed to TB, which is what we want to investigate. But, effectiveness is not the only factor for choice of strategy. We need to take costs into account. For that we look at the Incremental Cost-Effectiveness Ratio (ICER).

6.2 Incremental Cost Effectiveness Ratios

The Incremental Cost-Effectiveness Ratio is the ratio of incremental costs and the difference in health benefits.

$$\text{ICER} = \frac{\text{Cost of strategy A} - \text{Cost of strategy B}}{\text{Effect of strategy A} - \text{Effect of strategy B}} \tag{11}$$

It shows the ratio of cost per health benefit between two strategies [Barnsbee et al., 2018]. Using the ICER we can see which strategy is the most cost-effective and therefore the most advisable.

The best strategy would provide more health benefits for less money than the base case. In that case the ICER would be negative: the numerator would be negative as the costs of strategy B are greater than those of A. But note that not all negative ICERs are good - if the strategy is more expensive but less effective the ratio will also be negative. The same concept is true for positive ICERs. Either the strategy is more expensive and *more* effective, or it is less expensive and provides *less* health benefits. It is therefore always important to know what the exact values are to avoid any mistakes of interpretation.

It is unfortunate that the numerical value of the ratio does not tell the user all the necessary information. One must be aware of the prior information used to make the correct assessment of the ICER. In order to avoid this problem, Stinnett and Mullahy established a new method for cost-effectiveness analysis. This new method is based on the concept of Net Health Benefit (NHB), which is defined as:

$$\mu_{Ei} - \mu_{Ci}/\lambda \tag{12}$$

where μ_{Ei} is the average health effect associated with intervention i, μ_{Ci} is the average cost associated with intervention i, and λ is the threshold that a society is willing to pay for a marginally cost-effective strategy. The first part of equation (12) denotes the health effect of the intervention analyzed. The second part shows the minimum health effect a society or organization requires for that investment. This is also called the Willingness-To-Pay (WTP) threshold. So the net health benefit looks at the health effect of an intervention compared to what society would minimally expect for the resources. To compare different interventions to each other, in other words, incremental NHB, the following equation is used:

$$(\mu_{E1} - \mu_{E0}) - (\mu_{C1} - \mu_{C0})/\lambda. \tag{13}$$

This is similar to equation (12), the only difference is that now the effect and cost are substituted for the incremental effect and incremental cost associated with the intervention [Stinnet and Mullahy, 1998].

This method omits the problem of ICERs: a negative NHB means that the intervention is not advisable. However, this method does have a downside. By using the WTP in the calculation of the cost-effectiveness it becomes an integral part of the results. In the case that the threshold changes, the NHB needs to be calculated again. The ICER on the other hand is independent of the budget and can therefore still be used in decision making when the budget alters. The advice formulated with the use of ICERs can still include the WTP threshold. The threshold only denotes the maximum amount of costs per health benefit. So as long as the ICER $\leq$ WTP the intervention is worth the expenses made. Seeing as ICERs do not include the budget in the calculation, but can still be included in the overall health decision-making process, we have decided to use this measure of cost-effectiveness as opposed to the Net Health Benefit method.

6.3 Incremental Effectiveness Ratio and Disability Adjusted Life Years in this research

In this research we use the scenario where no preventive strategies are implemented as the base case. This is how the Brazilian health system works already, which makes it a good comparison point. In equation 11, the base case would be 'Strategy B'. For each of the strategies described in section 5 we calculate their respective costs and DALYs. This section explains what those costs are and how we calculate it.

There are several costs each strategy makes during the simulation: the costs of TB diagnosis, and costs for the consequent treatment. This is calculated in the following way. Every month a fraction of the cohort goes from 'Undiagnosed TB disease' to 'Diagnosed TB disease'. That fraction is multiplied with the cost for diagnosis. Then, for the treatment costs, we time the fraction of the cohort in 'Diagnosed TB disease' with the monthly cost of treatment. This way we get the total cost due to TB diagnosis and treatment during simulation. However, with the preventive strategies the costs change due to the LTBI testing and TPT. Everyone in the cohort except for 'diagnosed TB' is offered a LTBI test, so we time that group with the costs associated with the test. Everyone who receives a positive result also does a TB test. Based on the results of the tests a patient starts with TPT. In the same way as TB treatment, the amount of people with TPT is timed with the monthly cost of the respective treatment. The costs used can be found in Table 6.

Parameter	Cost in USD (range)	Source
Diagnostic cost TB	54,34 (27,1-108,68)	[Nsengiyumva et al., 2022]
Montly TB treatment costs	144 (108-180)	[Nsengiyumva et al., 2022]
Costs IGRA	37,88 (30,41- 45,95)	[Loureiro et al., 2019]
Costs TST	10,48 (5,22-20,88)	[Steffen et al., 2013]
Costs outpatient visit	3,80 (3,42-5,02)	[Bastos et al., 2022]
Costs rifampin dose 300mg	0,087	[Sistema Integrado de Administração de Material, 2023]
Costs rifapentine dose 150mg	0,31	[Sistema Integrado de Administração de Material, 2023]
Costs isoniazid dose 300mg	0,037	[Sistema Integrado de Administração de Material, 2023]
Monthly cost 9H	4,91 (4,53-6,13)	calculated
Monthly cost 3HP	11,68 (11,30-12,90)	calculated
Monthly cost 4R	9,02 (11,30-12,90)	calculated
Monthly cost 1HP	58,99 (58,61-60,21)	calculated

Table 6: The costs of the diagnosis and treatment of TB and LTBI

7 Results of the model

After reviewing the model and its structure, we can simulate to get the results. We first compare the different interventions in the main analysis. After reviewing this main analysis, we look at one intervention in different circumstances. We alter the age of testing, the time spent in prison, and the time since liberation. In all cases, we analyze the health benefits, costs spent and ICERs.

7.1 Base case of the model

Using the Markov model and the estimated parameters described in the previous sections, we can simulate the behavior of the cohort. We want to ultimately compare preventive strategies with the base case (no preventive efforts) and then compare the different strategies with each other. So first, we simulate the cohort with no preventive intervention.

This base case simulation runs from age 30 until age 101, assuming that no individuals live beyond that age. In reality there might be someone that lives to 101 or even further, but including those individuals would have a very small effect on the results in comparison to the time and effort of adding them. We run the simulation a 1000 times for accuracy.

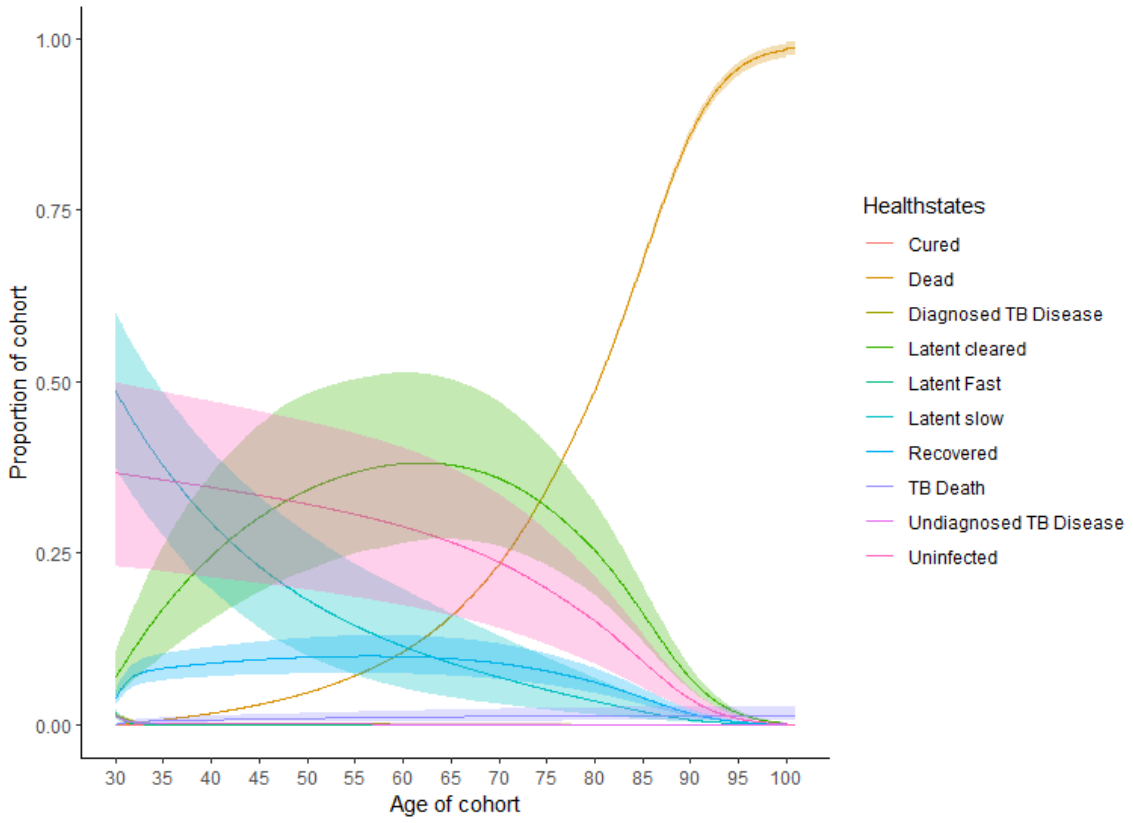


Figure 5: Plot of simulation of cohort formerly-incarcerated individuals from age 30 until death, with 95% uncertainty

Figure 5 shows how the cohort moves between states over time. There is no Tuberculosis Preventive Therapy or Latent Tuberculosis Infection testing, but there is treatment for active TB. It is important to review this scenario for two reasons. It reflects the system for TB testing and treatment in Brazil right now. By comparing to this scenario, we know if it is useful to implement any preventive strategy. It is possible that the most cost-effective strategy is implement no strategy. The other reason to analyze this situation is to check if the model is behaving correctly. There are empirical measurements for the (cumulative) incidence and mortality, which the model should abide by. These benchmarks ensure that the model is correct and thus that the results are true.

The benchmarks reviewed are, as described in [C.F.McQuaid et al., 2021]:

1. the cumulative incidence over the first five years of infection
2. Annual incidence of active TB after five years since infection
3. Case fatality in the absence of treatment

4. Mean duration of active TB in absence of treatment

5. Reduction in the risk of TB afforded by prior infection

The cumulative incidence is the percentage of predicted new active TB cases, a_t, in year t divided by the size of the cohort, b_t at year t.

$$\text{Cumulative incidence over first five years} = \frac{(a_0 + a_1 + a_2 + a_3 + a_4)}{b_0} * 100 \tag{14}$$

This does not include any re-infection. This value should be between $4 - 15\%$. Indeed, using equation (14), we get an average cumulative incidence over all 1000 runs of 12.81%.

For the annual incidence after five years since infection, the value should be less than 0.2%. This can be calculated in a similar manner as the cumulative incidence:

$$\frac{a_{t>5}}{b_{t>5}} * 100 \tag{15}$$

where a_t and b_t are the same as defined in equation (14). To review this, we plot it in Figure 6. We see a slightly higher value then the benchmark entails, but this is not necessarily problematic. A cohort of formerly-incarcerated individuals are a high-risk group and are in general more prone to progression to TB. For that reason, a higher annual incidence after five years of infection is not unexpected. Most cases arise from the first five years of infection and seeing as the cumulative incidence does satisfy the benchmark-value, the higher annual incidence after five years is not worrisome.

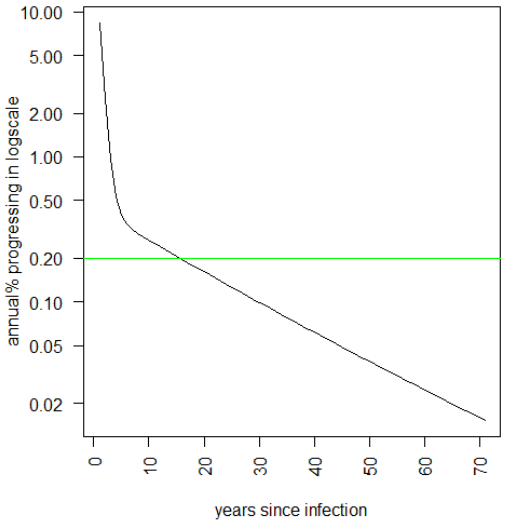


Figure 6: Annual TB incidence without re-infection in logscale over time since infection for a cohort of formerly-incarcerated individuals

The case fatality in absence of treatment is the percentage of individuals dying d in relation to the number of people in the initial cohort with active TB, s. This value should be between $40 - 70\%$. In our case, the case fatality is 50.35%. This is expected, as we set the values for case fatality and self-recovery equal (see Section 4.2), automatically leading to approximately 50% case fatality.

For the next two benchmarks we can look at the values of the estimated parameters. The mean duration of active TB stands in direct contact with the value of the self-recovery rate and TB-mortality rate. As denoted in Table 4, the self-recovery rate and TB-mortality rate together are $0.13 + 0.13 = 0.26$. The rates in this model are denoted in for a yearly unit of time, so the duration of TB disease in absence of treatment is approximately 3.8 years ($\frac{1}{0.26} \approx 3.8$), which is in accordance with the values of the benchmark of $1.5 - 4.0$ years. Lastly, we look at the reduction in the risk of TB afforded by prior infection, which should be between $40\% - 85\%$. This is implemented with the relative risk for re-infection in the model. The value of that parameter is 0.22 ($95\% CI 0.17 - 0.27$), or in other words, the reduction of the risk is 78%. All values of the benchmarks are taken from [C.F.McQuaid et al., 2021]. In conclusion, the model is behaving as it should and we can continue with the analysis of the different strategies.

7.2 Analysis of different preventive strategies

In this section we analyze the different strategies. We compare the respective health benefits in DALYs, the costs, and finally combining the two with the ICERs. To accurately compare the different strategies we keep the circumstances of the model equal in all cases: the cohort is tested at age 30, 3 months after liberation of prison, and was in prison for 2 consecutive years.

The first aspect we look at, are the health benefits of each strategy. This is calculated using the theory described in Section 6.1. Table 7 shows the different DALYs of each strategy. It includes both the undiscounted and the discounted version of DALYs.

Strategy	Undiscounted DALY/person-year	Discounted DALY/person-year
No strategy	0.428 (0.188-0.751)	0.218 (0.0997-0.377)
IGRA and 1HP	0.290 (0.128-0.528)	0.147 (0.0672-0.257)
TST and 1HP	**0.279 (0.124-0.508)**	**0.142 (0.0649-0.248)**
IGRA and 3HP	0.294 (0.129-0.533)	0.149 (0.0679-0.260)
TST and 3HP	0.283 (0.125-0.513)	0.143 (0.0658-0.250)
IGRA and 4R	0.295 (0.130-0.535)	0.149 (0.0682-0.261)
TST and 4R	0.284 (0.126-0.515)	0.144 (0.0660 - 0.251)
IGRA and 9H	0.305 (0.134-0.539)	0.154 (0.0706-0.267)
TST and 9 H	0.295 (0.130-0.522)	0.149 (0.0685-0.258)

Table 7: The mean (un)discounted TB DALYs per person-year for various interventions with the 95% uncertainty

The less DALYs, the better, as they describe the burden of disease in the cohort. All preventive strategies avert DALYs in comparison to the base case, meaning that they all are effective. Furthermore, we see that the strategies with TST as LTBI test have less DALYs than those with IGRA. Seeing that TST has a higher sensitivity than IGRA, 0.77 and 0.7 respectively, this is not strange. As the sensitivity is higher, more infected people are tested positively and therefore starting preventive treatment. This has a positive effect on the burden of disease and thus the DALYs. However, it is important to note that the specificity of the tests is not included yet. Since there is no burden associated to preventive treatment, the effect of unnecessary treatment is not taken into account. This is included in the costs of the strategy, which can have a big effect on the overall policy advice.

For the treatments, it is clear that shorter treatments are preferred. The most effective treatment is 1HP and then, in descending order 3HP, 4R, and 9H. Shorter treatment have a higher rate of completion, leading them to be more effective. In conclusion, the most effective test is TST and the most effective treatment option is 1HP, displayed in bold in Table 7.

However, efficiency is not the only aspect of importance in health decision. It is vital to take the costs into account.

Intervention	Cost in USD (range)
No TPT	100,40 (74,06-129,52)
9H +IGRA	161,23 (116,20-228,24)
9H + TST	139,79 (95,57-212,96)
4R + IGRA	157,57 (113,63-222,39)
4R +TST	**135,40 (92,51-205,72)**
3HP +IGRA	157,18 (113,42-221,58)
3HP + TST	**134,95 (92,29-204,72)**
1HP +IGRA	164,90 (121,54-228,40)
1HP +TST	145,92 (103,76-214,50)

Table 8: Total costs per intervention per person in the simulation

Table 8 shows the costs associated with each strategy. We see that no preventive treatment, also known as the base case, is the least expensive. This strategy does not include any LTBI testing or treatment, the only costs made are those of TB diagnosis and TB treatment. For that reason it is the least expensive. The interventions containing TST are less expensive than those including IGRA, seeing that IGRA is more expensive. For the treatments, we see that 1HP is the most expensive, followed by 9H, 4R and 3HP. The last two differ by very little. So looking solely at the costs the interventions with TST are better and either 4R or 3HP is a good choice for treatment, both in bold in Table 8.

After having reviewed both the costs and the health benefits, we can now combine the two by analyzing the Incremental Cost-Effectiveness Ratios, see Table 9.

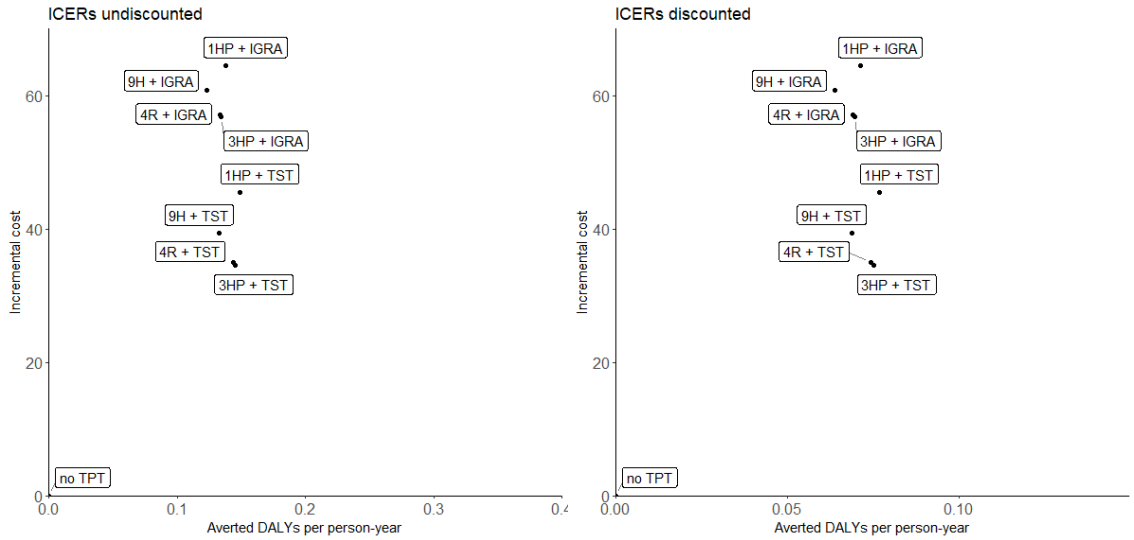
The ICERs tells us how much it costs to avert one DALY. It shows how cost-effective a certain intervention is. To implement a strategy, we need to make sure it stays under the WTP threshold. The suggested WTP threshold in Brazil is a maximum value of USD 8,397/DALY, which is

Strategy	Undiscounted ICER	Discounted ICER
9H +IGRA	495,1	951,86
9H + TST	296,8	571,99
4R + IGRA	429,4	828,36
4R +TST	243,2	470,27
3HP +IGRA	422,2	814,88
3HP + TST	**237,7**	**459,82**
1HP +IGRA	468,6	905,3
1HP +TST	**305,9**	**592,40**

Table 9: Incremental cost-effectiveness ratio in USD per (un)discounted DALYs averted for each intervention in comparison to the base case

approximately 98% of the gross domestic product per capita [Ochalek et al., 2018]. We see that all the interventions in comparison to no intervention fall below that threshold, and are thus cost-effective.

Figure 7 is a plot of the incremental cost over the averted DALYs for each intervention, both the undiscounted and the discounted version. The intercept is the base case to which all strategies are compared. That means that the figure shows how cost-effective the interventions are compared to doing nothing.



(a) Undiscounted DALYs

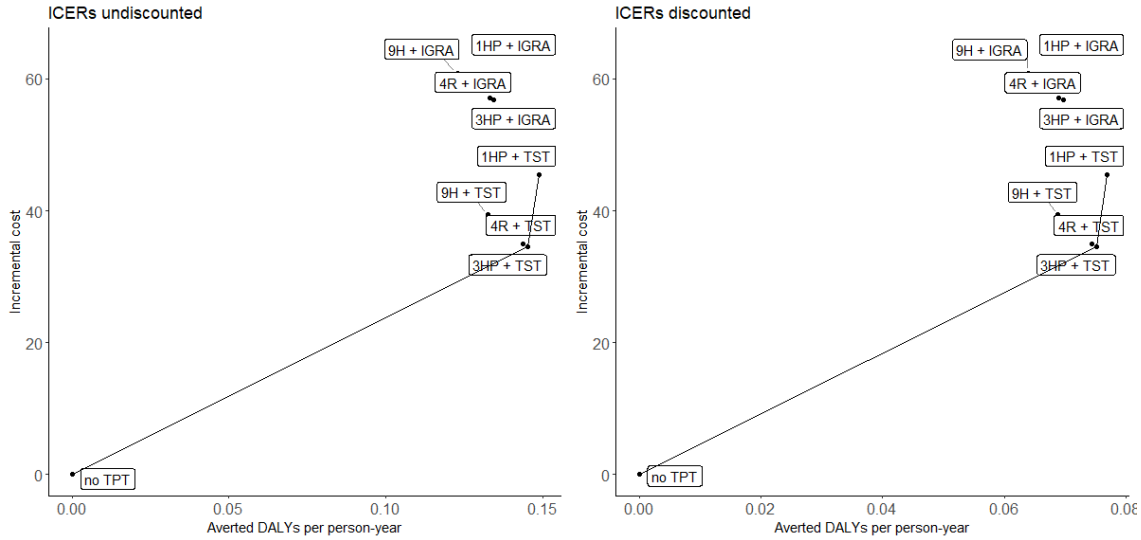
(b) Discounted DALYs

Figure 7: Incremental Cost-Effectiveness Ratio plane for the preventive strategies

The ICER shows how expensive a strategy is in relation to how effective it is. In Section 6.3 describes that a positive ICER does not necessarily mean that the incremental cost and incremental effectiveness are positive; they could both also be negative. Plotting it in a plane ensures that this mistake in interpretation is not made. If the ICER is positive due to negative incremental costs and negative incremental effectiveness, it would be plotted in the third quadrant of the plane. In this analysis all strategies are more effective and more expensive than the base case, so they are all plotted in the first quadrant.

Using the ICER-plane we can decide which strategy is the most cost-effective. We want the strategy to be effective without costing a lot. Those strategies will be closer to the bottom right corner of the quadrant. The more to the left upper corner, the worse the strategy is; those are relatively expensive for the health benefit gained. These strategies are dominated by the strategies more to the right and are therefore taken out of consideration. In this research, the dominated strategies are those including IGRA, 9H+TST, and 4R + TST. They are more expensive and offer less health benefits than the left-over two. This way of ruling-out strategies is called the dominance principle [Bambha and Kim, 2004]. This is easy to visualize by drawing a line between the most effective strategies, see Figure 8. This line is called the efficient frontier.

There are now three possible interventions to choose from: no TPT, 3HP+TST, and 1HP + TST. To choose between the three, we need to inspect the values of the ICERs, not only in



(a) Undiscounted DALYs

(b) Discounted DALYs

Figure 8: Incremental Cost-Effectiveness Ratio plane with efficient frontier

comparison to the base case, but also compared to each other. The goal is to maximize the life-years gained given the budget constraint. It is not the goal to choose the cheapest intervention - but the best within the budget.

We first order the remaining interventions in order of ICER compared to the base case (see Table 9):

- 3HP +TST = 237,70/DALY averted
- 1HP +TST = 305,9/DALY averted

Here we see that 3HP + TST has the lowest ICER, and that they both stay under the threshold. However, since we want to maximize the life-years gained, or DALYs averted, it is vital to compare the interventions to each other. This is done by calculating the ICER between 3HP +TST and 1HP +TST, in other words the slope of the line in Figure 8 between the two interventions. The value of that ICER is USD $3204,46$/DALY averted. This value is still less than the WTP threshold, indicating that 1HP +TST is the preferred strategy. Even though it is more expensive per DALY averted than other strategies, it is also more effective. The goal is not to limit the amount of money spent, but to help the population the best under budget constraints.

1HP is a fairly new form of preventive therapy. Information about the clinical efficacy of the therapy is still limited, and the regimen has not been implemented on a greater scale. Though recommended in several countries [Regional Office for South-East Asia, 2020], not all health systems have the appropriate framework for the regimen and are willing to implement the treatment as of yet. For that reason, it is important to keep the second-best regimen in mind: 3HP+TST.

In conclusion, comparing the strategies to each other results in the following advice: The most effective strategy staying under budget is that of Tuberculin Skin Test (TST) and 1-month TPT consisting of daily doses isoniazid (H) and rifapentine (P) is most advisable for implementation.

7.3 Results per age of testing

In the cost-effectiveness analysis of the different strategies we kept the circumstances of the model consistent. However, to properly understand the model and its results, it is important to investigate the effect of those circumstances on the results. For that reason, in the following three sections, we look at the effect of the age at testing, time spent in prison, and the time since prison.

In this first section, we analyze the effect the age of testing has on the efficacy and cost of a certain intervention. We keep all circumstances consistent except for the age at testing. In the base case the age at testing was thirty years. Since in the population there will be several different ages, it is interesting to look how the interventions affect the cohort at different times in their lives. For that reason, we look at the following ages: 25, 30, 35, 45, 65. The ages chosen are mostly on the younger side, because 92% of the incarcerated population is under 45

Age	Total cost	Incremental cost
25	138,78 (95,09-209,66)	**33,23 (17,25-73,50)**
30	134,91 (92,25-204,66)	34,50 (18,19-75,14)
35	130,74 (89,19-199,26)	35,69 (19,08-76,67)
45	122,44 (83,10-188,53)	38,64 (21,28-80,49)
65	105,46 (70,63-166,59)	46,02 (26,75090,04)

Table 10: (Incremental) costs in USD of the intervention for various ages at testing

[Monteiro and Cardoso, 2013]. It is therefore useful to inspect those ages more thoroughly than the older ones.

For all ages, the cohort was in prison for two years and tested three months after liberation. We did not include ages for which the individual should have been a minor while entering in prison. For example, testing at age 20 means that the individuals entered prison two years and three months prior, at age seventeen and nine months. For that reason the youngest age is twenty-five. Besides the length of the stay in prison and the time since liberation, also the intervention is kept consistent throughout the analysis. We chose one strategy, namely 3HP + TST. We chose this regimen as opposed to 1HP + TST, as there is more certainty concerning the parameters of that regimen.

Lastly, we only included the undiscounted DALYs for the sake of comprehensibility, but the discounted version is included in the appendix in Table 16. The conclusion of the results does not change if looking at discounted versus undiscounted, so this decision will not impact the research.

After running the model with the details described above, we receive the following amount of DALYs averted per age at testing. For each of the ages, the results are compared to the same model without the preventive intervention, in order to accurately depict the effect of age. Figure 9 shows the averted DALYs per age, including the 95% uncertainty. We see that for older cohorts, less DALYs are averted.

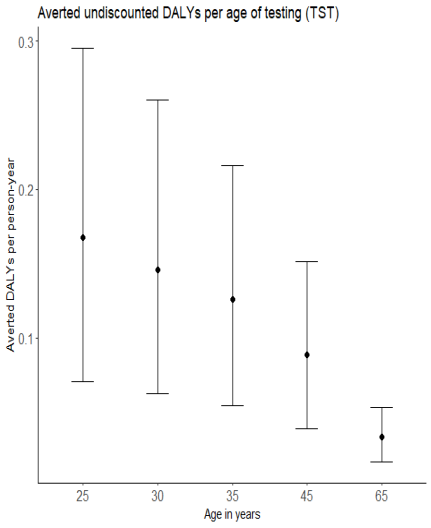


Figure 9: The averted DALYs for 3HP+TST for various ages at testing

A big fraction of the value of DALYs comes from the YLL. If a 20-year-old dies prematurely due to TB, a relatively big number of life years are lost. Hence the DALYs will be bigger as well. That also means that implementing a preventive strategy has the biggest effect on a younger cohort. The rule applies: the younger the cohort, the more effective the preventive intervention. This is clearly visible in Figure 9.

After reviewing the health benefits for the different ages, we now inspect the incremental costs. Just as with the DALYs, we only show the difference between the costs at a certain age with the preventive intervention and the costs at the same age without the intervention. This is plotted in Figure 10. Interestingly, the incremental costs grow with the age of testing. An explanation is the relatively large contribution of costs associated with the intervention in older cohorts. Most costs are attributed to TB diagnosis and treatment during the simulation. Since treatment and diagnosis are relatively expensive and are not a singular event, they are a big fraction of the costs. However, older cohorts will receive less TB treatment than younger ones due to non-TB mortality. Less people will have recurrent TB, simply because they have already died. That means that testing the cohort for LTBI at age sixty-five will comparatively cost a lot. This is what Figure 10 depicts. Thus, the older the cohort the more relatively expensive an intervention is.

The last step is to analyze the ICER per age at testing. We included both a figure of the ICERs over age (Figure 11 and a table with all information in this section (Tables 10 and 11). We see in Figure 11 that the value ICER increases with age. Seeing that we already know that the health benefits declined with age, but the costs increased, it is expected that the ICER increases with age. So we can draw the conclusion that testing at a younger age of the cohort is more cost-effective than at an older age.

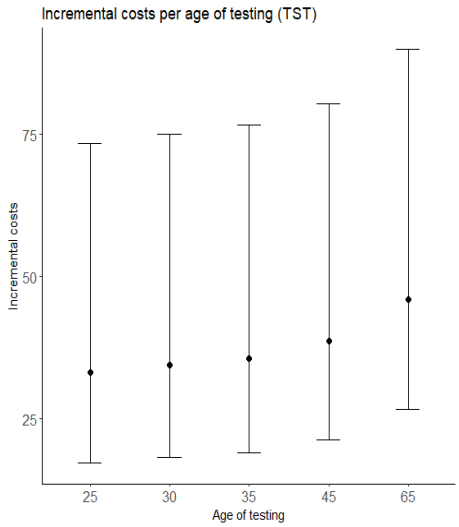


Figure 10: Incremental costs in comparison to the base case for various ages at testing

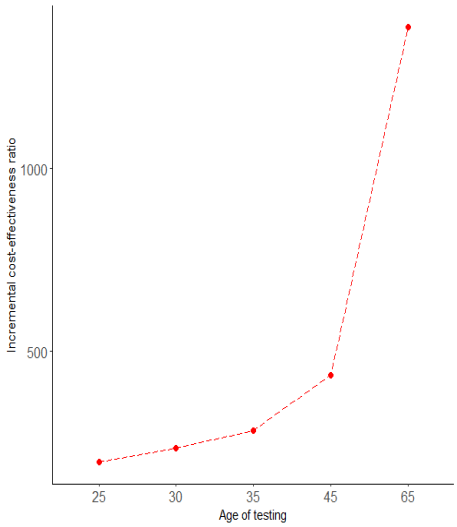


Figure 11: The Incremental Cost-Effectiveness Ratio in comparison to the base case for various ages at testing

Age	DALY/person-year	averted DALY/person-year	ICER
25	**0.33 (0.14-0.58)**	**0.17 (0.071-0.30)**	**198,28**
30	0.28 (0.13-0.49)	0.15 (0.063-0.26)	236,87
35	0.23 (0.11-0.42)	0.13 (0.055-0.22)	283,69
45	0.17 (0.077-0.29)	0.089 (0.039-0.15)	435,52
65	0.060 (0.031-0.10)	0.033 (0.017-0.054)	1385,03

Table 11: (Averted) DALYs per person-year and the ICER of the intervention for various ages at testing in comparison to the base case

7.4 Results for different times spent in prison

This section looks at the effect of the length of incarceration on the results of the intervention. The age at testing stays the same across all simulations, at thirty years. Testing is still done 3 months after liberation, but we differ the amount of time spent incarcerated. In the previous sections the incarceration-time was consistently two years. Now we look at incarceration periods of one month, three months, six months, one year, two years, five years, and lastly, ten years. The intervention implemented is still 3HP and TST. The structure of this section is similar to that of Section 7.3: we start with the DALYs, the costs, and finally the ICERs.

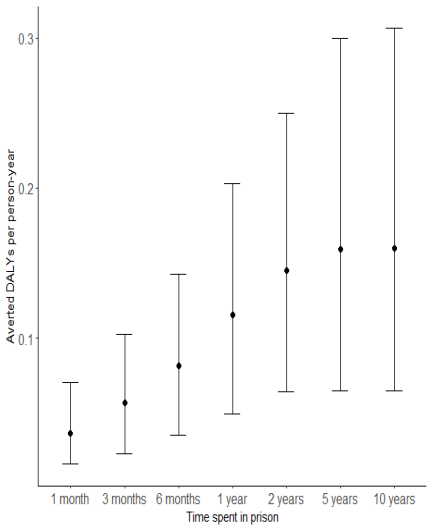


Figure 12: Averted DALYs for different amount of time spent incarcerated in comparison the base case

Figure 12 shows the averted DALYs for different incarceration periods. The DALYs are compared to the same cohort without TPT and LTBI testing. We see that the intervention in a cohort with shorter incarceration periods provides less health benefits than in a cohort with longer incarceration. The force of infection is a hundred times as high in prison, so for longer periods of incarceration it means that more people will be infected. Consequently, an intervention will have a large effect, as it prevents more cases. This trend does not continue linearly for different incarceration periods: the health benefits plateau around two years in prison. For an incarceration period of ten years the average averted DALY are even slightly lower than for five years.

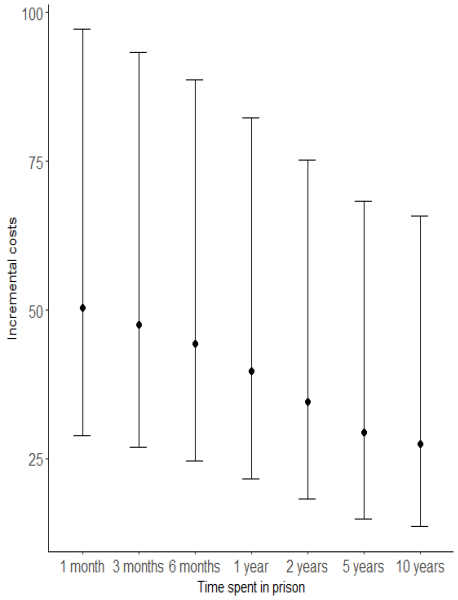


Figure 13: Incremental costs for different times spent in prison in comparison to the base case

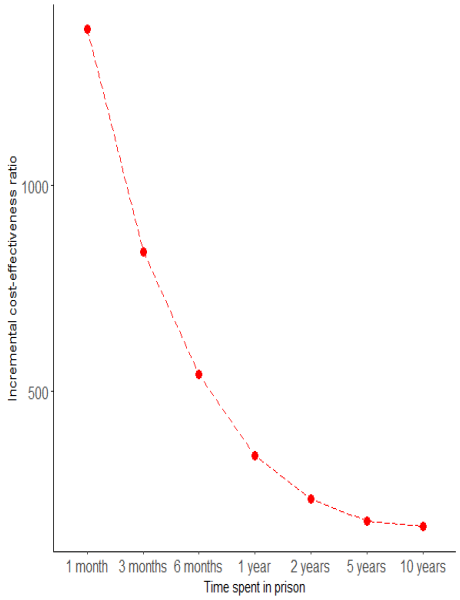


Figure 14: The ICERs for different times spent in prison in comparison to the base case

There are several possible explanations for this plateauing effect. First, we know that prior infection provides immunity to a certain level. The cohort that is in prison for ten years is almost all infected - they were exposed to a high force of infection for quite a long time. That means that a lot of these individuals are already infected once and recovered while in prison. Indeed, only 2% of the cohort is uninfected, opposed to 16% who has already recovered from active TB disease. So the immunity protects them from re-infection, so a preventive measure will have less effect. Secondly, the burden of the disease is mostly concentrated during incarceration. Since so many people are infected while incarcerated, a lot of people are sick while still in prison. So a preventive intervention after prison will not have that much added value. In conclusion, even though it is true that cohorts with longer periods in prison benefit more from preventive measures, it is not true that this increases with directly with the increase in time spent in prison. The health benefits plateau.

Now we look at the costs for different amount of times spent in prison, see Figure 13. Here we see a gradual decline in incremental costs with the increase of the time spent in prison. As less people are uninfected in cohorts in a longer prison stay, less people will start TPT due to a false positive LTBI test. This saves on unnecessary costs. Secondly, more people will be infected if the cohort remains longer in prison due to the high-infection rate. Around 5-10% of those individuals progress to active TB and receive treatment. This is a big portion of the costs, due to the costs associated with that treatment. Seeing as TPT prevents those individuals who would otherwise progress, it 'saves' on those TB treatment costs. The simple conclusion follows: the more people prevented from TB disease, the less the incremental costs. The opposite is also true. After one month in prison, a relatively small amount of people are infected with LTBI and thus an even smaller fraction would ever progress to TB disease. Then the costs of TPT and LTBI testing will be relatively high, in comparison to the costs you're 'saving' by preventing TB disease. For those reasons, we see a decline in the incremental costs.

The last thing that remains are the ICERs. In Figure 14 we see a decline in the value of the ratio. Seeing as the incremental costs decline for the longer incarceration periods, but their health benefits increase, it is logical that the ICERs would decline as well. We can draw the conclusion that for cohorts with longer periods of incarceration, preventive intervention will be most cost-effective. Again, we see a small plateauing effect after two years. The difference between the ratios is comparatively small compared to the difference in time spent incarcerated. This corresponds to the plateauing of the health benefits and the incremental costs. Tables 12 and 13 contain all the information discussed in this section in numerical values.

Time in prison	Total cost	Incremental costs
1 month	92,98 (60,22-152,27)	50,41 (28,87-97,17)
3 months	99.18 (64.92-160,09)	47,60 (26,93-93,35)
6 months	107,89 (71,53-171,04)	44,26 (24,66-88,77)
1 year	121,73 (82,08-188,32)	39,66 (21,56-82,34)
2 years	134,98 (92,31-204,76)	34,58 (18,25-75,24))
5 years	135,65 (93,22-205,50)	29,39 (14,88-68,31)
10 years	133,09 (91,44-202,31)	**27,51 (13,64-65,89)**

Table 12: (Incremental) costs in USD of the strategy for different times spent in prison in comparison to the base case

Time in prison	DALY/person-year	averted DALYs	ICER
1 month	0.12 (0.054-0.22)	0.037 (0.016-0.070)	1378,37
3 months	0.15(0.066-0.27)	0.057 (0.023-0.10)	838,66
6 months	0.18 (0.081-0.33)	0.082 (0.035-0.14)	542,02
1 year	0.24 (0.10-0.42)	0.12 (0.050-0.20)	343,68
2 years	0.28 (0.12-0.50)	0.15 (0.064-0.25)	238,09
5 years	0.28 (0.12-0.52)	0.16 (0.065-0.30)	184,32
10 years	**0.26 (0.10-0.51)**	**0.16 (0.65-0.31)**	**172,27**

Table 13: (Averted) DALYs per person-years and ICERs for different times spent in prison in comparison to the base case

7.5 Results for different times since prison

In our main analysis, testing happens three months after liberation of prison. In reality, a cohort of ex-prisoners has left prison at a number of different times. For that reason, we investigate the effect of time between liberation of prison and the moment of testing on the cost-effectiveness of the intervention. The age at testing remains at thirty, and the group was still in prison for two years. The intervention used is, in the same way as for the two previous sections, 3HP + TST. The only thing we adjust is the time since prison. We look at the following 'times since prison': no time (so immediate testing), one month, three months, six months, one year, two years, five years, and lastly, ten years. The structure of the section is the same as of those previously: we start with the health benefits, followed by the costs, and ending with the ICERs and a small conclusion.

Figure 15 shows the averted DALYs for different amount of time since prison. We see quite clearly that the longer time since prison, the less DALYs are averted. As the time since prison increases, the effect of the higher force of infection dies down.

Immediately after prison, a lot of the infection will be due to prison and those will be quite recent. Since recent infections have a higher probability of progressing to active TB, the effect of preventive therapy is relatively big. In a cohort that was in prison five or ten years ago, only a small fraction of the infections can be traced back to prison. That means that those who were infected in prison, will either already have progressed to TB or not progress anymore. For that reason, the intervention will have less effect on that cohort.

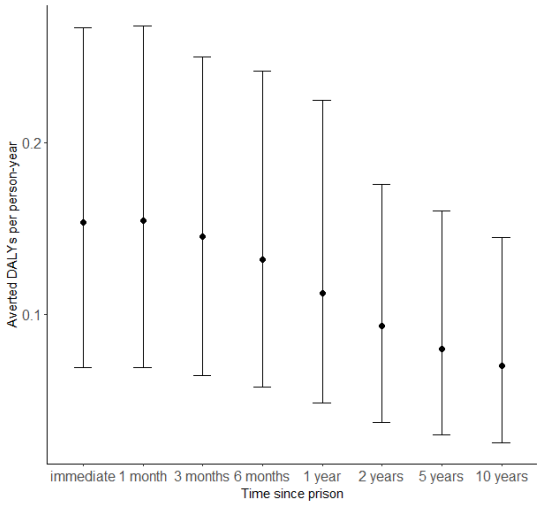


Figure 15: Averted DALY per time since prison in comparison to the base case

We do see that the health benefits for time period of one month are slightly higher than for immediate testing. This goes against the idea that the longer since prison the less effect the interventions have. An explanation is the lag between infection and progression. An individual can be infected in prison but only progress after liberation. The fraction of people infected with (latent) TB is bigger than the fraction of people recovered of the disease in the same time step, due to the high Force of Infection and lower recovery rate. Indeed, in the cohort of immediate testing 2.3% is diagnosed with TB disease and

in the cohort testing after one month 2.4% has TB disease. The effect of recovery becomes visible in the following cohorts, as we see the averted DALYs decline. Thus in general, the longer since prison, the less effect the intervention has.

The costs are calculated as described in Section 6.3. Since we are interested in the incremental costs, the absolute costs are subtracted with the costs of no preventive strategy in the same cohort. This results in the values seen in Table 14 and Figure 16. In the figure, we see that the longer since prison, the more expensive intervening is. This has the same explanation as the difference in DALYs. A preventive measure is relatively cheap in comparison to TB diagnosis and treatment. Thus, if the cohort has a lot of cases that are prevented because of the intervention, the incremental costs will be lower. It means that the costs of LTBI testing and treatment are a smaller fraction of the total costs in those cohorts than in a cohort with few cases. For the absolute costs we see that immediate testing is more expensive than ten years later (see Table 14), but the fraction attributed to the intervention is relatively lower.

Combining the incremental costs and the DALYs leads to Figure 17, where we see that the longer since prison the more cost-effective the strategy is. Interesting is the small dip in the line: it is more cost-effective to intervene in a cohort that was liberated one month prior than directly after prison. Before this research, the focus lied mostly on entry- and exit-strategies in prison. The fact that the ICER is lower one month after incarceration than immediately after, indicates that it is beneficial to also keep track of formerly-incarcerated individuals. However, the difference in ICER is quite small and could also be attributed to the rounding of values in the calculations.

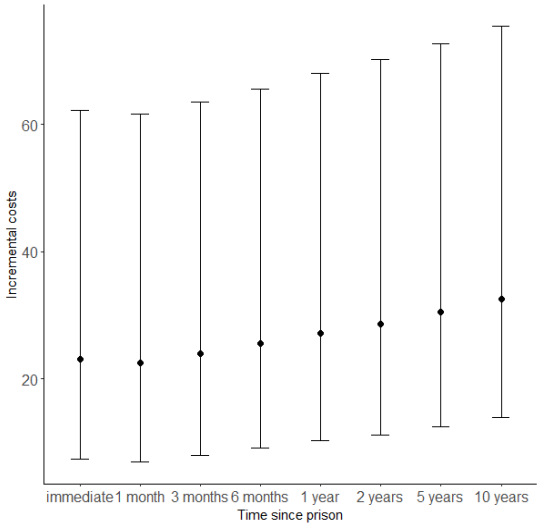


Figure 16: Incremental costs for different times since prison in comparison to the base case

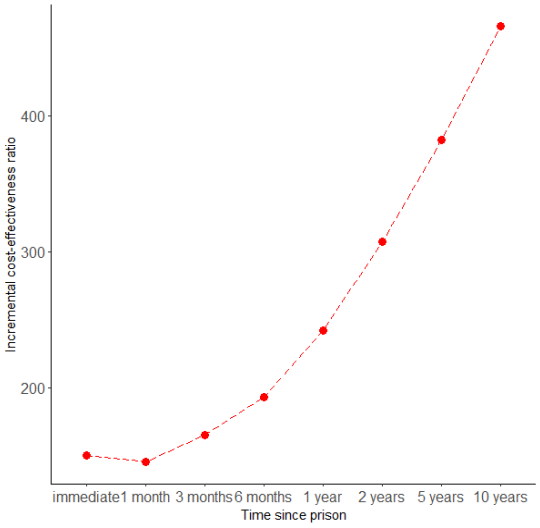


Figure 17: ICER for different time since prison in comparison to the base case

Time since prison	Costs	Incremental costs
no time	125,78 (83,10-194.88)	23,01 (7,3-62,27)
1 month	126,20 (83,39-195,41)	**22,50 (6,91-61,62)**
3 months	124,36 (82,03-193,02)	23,95 (7,97-63,50)
6 months	120,78 (79,37-188,45)	25,47 (9,07-65,54)
1 year	112,84 (73,43-178,44)	27,20 (10,26-67,98)
2 years	101,38 (64,82-164,15)	28,64 (11,20-70,18)
5 years	92,96 (58,50-153,62)	30,42 (12,44-72,70)
10 years	86,68 (56,07-149,39)	32,49 (13,96-75,38)

Table 14: (Incremental) costs in USD of the intervention for different testing moments since prison in comparison to the base case

Time since prison	DALY/person-year	Averted DALY/person-year	ICER
no time	0.29 (0.13-0.52)	0.15 (0.069-0.027)	150,03
1 month	**0.29 (0.13-0.52)**	**0.15 (0.069-0.27)**	**145,42**
3 months	0.28 (0.12-0.50)	0.15 (0.064-0.25)	164,92
6 months	0.26 (0.11-0.48)	0.13 (0.057-0.24)	192,93
1 year	0.23 (0.098-0.42)	0.11 (0.048-0.22)	242,20
2 years	0.19 (0.076-0.36)	0.09 (0.037-0.18)	307,36
5 years	0.15 (0.059-0.31)	0.080 (0.030-0.16)	382,39
10 years	0.14 (0.053-0.28)	0.070 (0.025-0.14)	465,57

Table 15: (Averted) DALYs per person-years and ICER of the intervention for different testing moments since prison in comparison to the base case

8 Synopsis and conclusion

In Section 7 we reviewed different preventive interventions in a cohort of formerly-incarcerated individuals. All of the interventions fall under the WTP threshold and are therefore cost-effective. Any of them can be implemented in the Brazilian health-system. However, the most advisable is TST in combination with one month of isoniazid and rifapentine, compared to the base case, but also compared to other strategies. This regimen is still relatively new, and for that reason there is not a lot of information known about the therapy. The second-best option is TST in combination with three months of weekly isoniazid and rifapentine. Independently of the choice of TPT, TST performs better than IGRA. We reviewed the results for undiscounted and discounted DALYs which did not affect the conclusion - it merely changed the numerical values.

The main analysis was performed for a fixed age, incarceration period and time since prison. To inspect how the intervention works in reality, we analyzed the results for a variable age, incarceration period and time since prison. First, we look at the age at testing. The averted DALYs tell us that younger cohorts profit more from a preventive strategy. As there are more life-years to be 'saved', the intervention contributes more to the overall quality of life in that cohort. The incremental costs behaved exactly opposite, increasing over age. It is therefore logical that the ICERs also increase over time and hence, the intervention is most cost-effective in younger cohort.

Second, we investigate the effect of the amount of time spent incarcerated. The expected result is true: cohorts with shorter time in prison benefit less from the intervention. However, for periods longer than two years in prison the health benefits gained plateau. This could be because of the immunity provided by previous infection or because a lot of individuals will already have progressed prior to release. It means that the health benefits do not increase linearly with the amount of time spent incarcerated. The incremental costs decrease for longer prison-sentences, meaning that the ICERs also decrease. Figure 14 shows quite clearly that the ICERs do not decrease proportional to the time spent in prison. It does become slightly more cost-effective the longer in prison, but the difference also becomes increasingly smaller.

Third, we analyzed the effect of the time between liberation and testing. There we see that a longer waiting time will negatively impact the health benefits of the intervention. This does, just as for time spent in prison, not decrease linearly. Interestingly, the health benefits slightly increase after one month since prison. The possible explanation is that more people have progressed to TB disease due to the high force of infection, whereas only a small fraction have already recovered. The difference after one month is also visible in the incremental costs, where the costs are slightly lower in that cohort than in the cohort eligible for immediate testing. Therefore, the ICER is the lowest after one month, indicating that it is more beneficial to wait one month with testing than to immediately test at release.

In conclusion, this research shows that is advisable to implement preventive strategies for formerly-incarcerated individuals in the Brazilian health system. The measures reviewed are all cost-effective and quite cheap in comparison to the WTP threshold. Though 1HP + TST is the best option while staying in the budget, and has therefore our preference, any strategy is a step forward. The strategies alleviate the burden of tuberculosis in this particular group, but also reduce the amount of TB cases in the general population. Ex-prisoners return to society and can then spread the disease among the population. Implementing these strategies can stop that spread and impact the national TB incidence and prevalence. This is one of many steps that the Brazilian government can take to achieve the WHO end TB goals. The research shows that focusing on high-risk groups, even after they left high-risk environments, has a positive effect on the overall quality of life and could decrease the national incidence of the disease.

9 Discussion

This research explores the cost-effectiveness of preventive strategies among formerly-incarcerated individuals in Brazil. The aim is to provide the Brazilian Ministry of Health with advice if such a strategy would be useful and how to do this most cost-effectively. To answer those questions, the lifetime outcomes of the cohort are simulated under several possible scenarios. We constructed a Markov model, distributing the cohort into health-states. The model has the ability to predict the future behavior of the cohort depending on their present state using transition parameters to calculate the next possible distribution of the cohort. The value of these parameters are either taken from literature or estimated using Bayesian statistics. The model allows for the implementation of testing for LTBI and preventive therapy. The former is included in the form of a decision tree, altering the initial distribution of the cohort. The latter is added to the model as (tunnel) states depending on the TPT chosen. The lifetime outcomes of the simulation are then used to calculate the burden of the disease in DALYs and the costs of each scenario. These two values combine into the ICERs, which tells us how cost-effective a particular strategy is.

The use of Markov models, DALYs and ICERs in health economics is conventional, as seen in [Mabud et al., 2019] [Steffen et al., 2020] and [Nsengiyumva et al., 2022]. The math behind the model is simple and allows the user to quickly and clearly predict the behavior of the cohort. The DALYs and ICERs provide us with numerical value with a straightforward interpretation. It makes decision-making for health systems easier. However, there are some pitfalls to be aware of. These are discussed in this section.

One of the possible mistakes lies in the Bayesian estimation of the epidemiological parameters. Since there is little known about the exact epidemiology of tuberculosis, specifically latent tuberculosis, we need to guess the values. Bayesian statistics allows us to estimate the necessary values. The method uses prior distributions and likelihood functions, and calibrating targets to estimate the posterior distribution. This always remains an estimation and there is never 100% certainty of the correctness of the values. We used a version of the Markov model to estimate the posterior distributions. Since we calibrate to values in prison, the cohort needs to enter prison as well. This means that the entire cohort enters prison at the same time, which is unrealistic of itself. Then to achieve the high incidence in prison, the force of infection is upped a lot: a hundred times. In reality, the cohort does not enter prison and then create the high incidence: they enter prison where there is already a high incidence. The difference is that in the second scenario the cohort enters a high-incidence environment where they are at risk for TB, and in the scenario in this research they form that high-incidence. This can affect the rate ratio estimated and possibly other values as well. This simplification is most visible in the values of the calibration targets: the TB prevalence in prison is a lot higher than expected (see Table 3). A lot of people need to be infected in a short period of time to achieve the calibration target of the incidence rate, and that increases the prevalence by a lot.

The modeled group has once been in prison for a fixed time and then never re-enters. Seeing as the recidivism rate in Brazil is quite high, this aspect of the model does not depict reality. However, this entering and re-entering in prison is difficult to model. A possible method is to have two parallel models: one in prison and one out of prison. Individuals can then hop between the two models, while still keeping count of their epidemiological progression. The only difference between the two models are the transition probabilities, i.e. the force of infection, re-infection rate, but also treatment completion. This does make the model a lot more complicated and was therefore omitted in this research. Seeing as multiple incarceration periods only increase the risk of infection, the results of this research still hold true. Yet it might be interesting to further research the impact of recidivism on the fulfillment of preventive strategies and the efficacy of the proposed intervention.

The model can also be improved in regards to TB treatment. First, we assume that 100% of those diagnosed with TB disease start treatment, where in reality a fraction will default before they start the regimen. Secondly, we do not take into account adverse events due to treatment. The drugs used in the both latent and active TB treatment are linked to several adverse events, such as hepatotoxicity, nausea, and skin reactions [Ramappa and Aithal, 2013]. In the model there is no burden associated with TPT, and no extra burden due to adverse events associated with diagnosed TB disease. By including a state in the model for individuals suffering from adverse events, we can properly depict the effect of the drug-intensive treatments. Another solution is to implement this with the disability weight for TPT. The reason we did not yet include this is that there is no peer-reviewed value for that weight as there is for active TB.

The last assumption that can be improved is that of the TPT-efficiency. We assume that all the preventive strategies have the same efficacy. Across all simulations (for the different strategies)

the efficacy parameters stay the same. Though the assumption that the efficacy is approximately the same, is valid (see [Menzies et al., 2018], [Steffen et al., 2020], [Sterling et al., 2011]), we can still variate across the iterations. We would still use the same mean value and uncertainty for the efficacy parameters across the simulation, but then randomly draw the value of that iteration per simulation. More clearly, if we assume that the efficacy is 0.9 $(0.63 - 0.93)$, for each preventive therapy we randomly draw a value from that distribution. This ensures that the different simulation do not correlate. This is not yet included due to time constraints. We also assume that if a patient defaults halfway through treatment, they can still be cured. This assumption is true - receiving partial treatment is associated with some of form of cure - but the details are not widely researched as of yet and could be improved upon.

The final part of the research focuses on the cost-effectiveness of the reviewed strategies. DALYs and ICERs add numerical values to the health benefits and cost-effectiveness of the intervention, which makes the results simple to interpret. Some shortcomings of the method are already discussed in Sections 6.1 and 6.2. Besides the drawbacks in interpretation, there are some possible improvements in the implementation. We included costs for diagnosis and treatment of both latent and active TB infection. Those costs are mostly viewed from the perspective of the caregiver, in this case the Brazilian Ministry of Health. To accurately depict the burden of the disease, it might be interesting to research the costs associated to those who receiving treatment. While in treatment a patient might not be able to work or have to spend more on insurance or medicines. As mentioned before, this research is performed from the perspective of the Brazilian government and therefore those costs/burdens are not integral. Further research could inspect the costs and effects from the perspective of the patient.

The model is a simplified, estimated version of reality. That means that the results always come with some degree of uncertainty. A lot of values need to be rounded off which affects the uncertainty as well. It is important to always reflect upon the model, and validate it. In this research we check the model with some known benchmarks, but that does not mean there is a 100% certainty it is still correct. Further research can improve the model, e.g. implementing re-incarceration, and add more benchmarks, based on empirical evidence. Lastly, to effectively reduce the TB incidence in Brazil it is important to research more possible interventions among other high-risk groups, such as HIV-positive individuals, children, and homeless people [Ministério da Saûde, 2019].

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10 Appendix

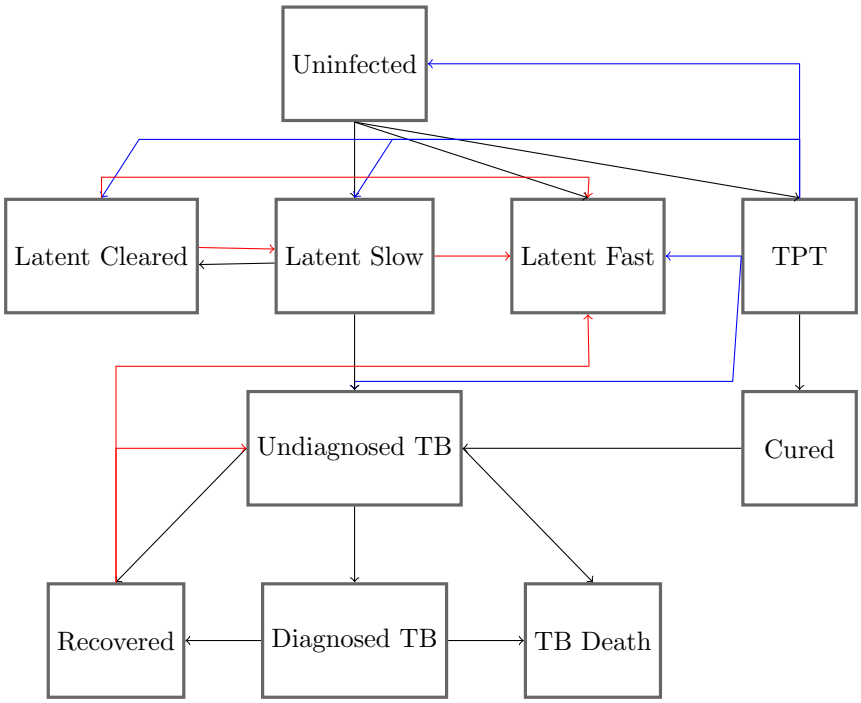

Figure 18: A schematic diagram of the Markov model including preventive treatment. Red arrows denote reinfection and blue arrows denote the fraction not cured by TPT

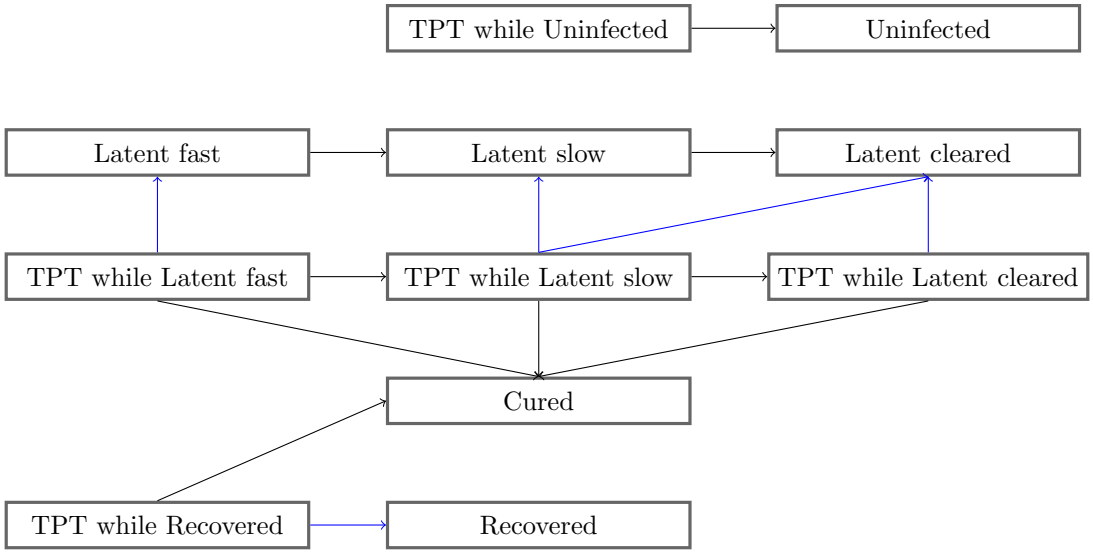

Figure 19: Schematic diagram of the TPT states and the ongoing progression during treatment in the Markov model in Figure 18. Blue arrows are due to loss-to-follow up during treatment or failure to cure.

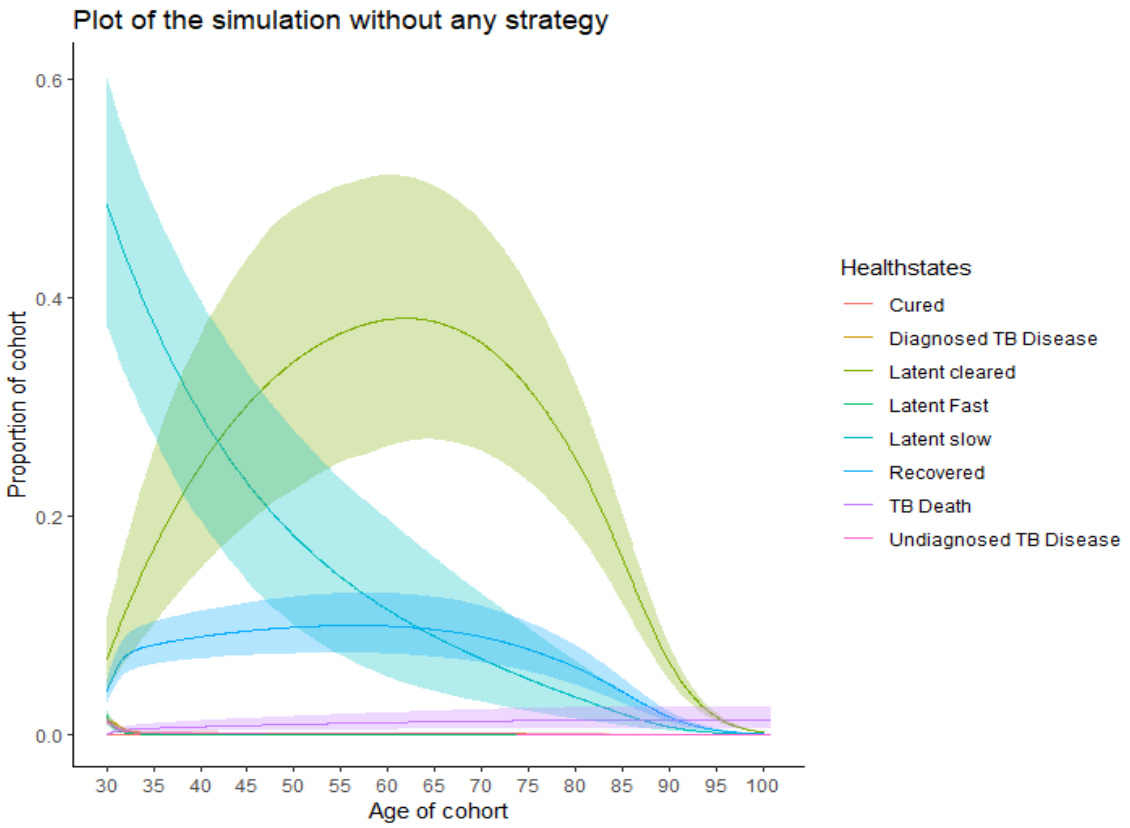

Figure 20: Zoom of simulation plot of the base case. This plot contains the states Cured, Latent fast, cleared and slow, Recovered, (un)diagnosed TB disease, and TB death

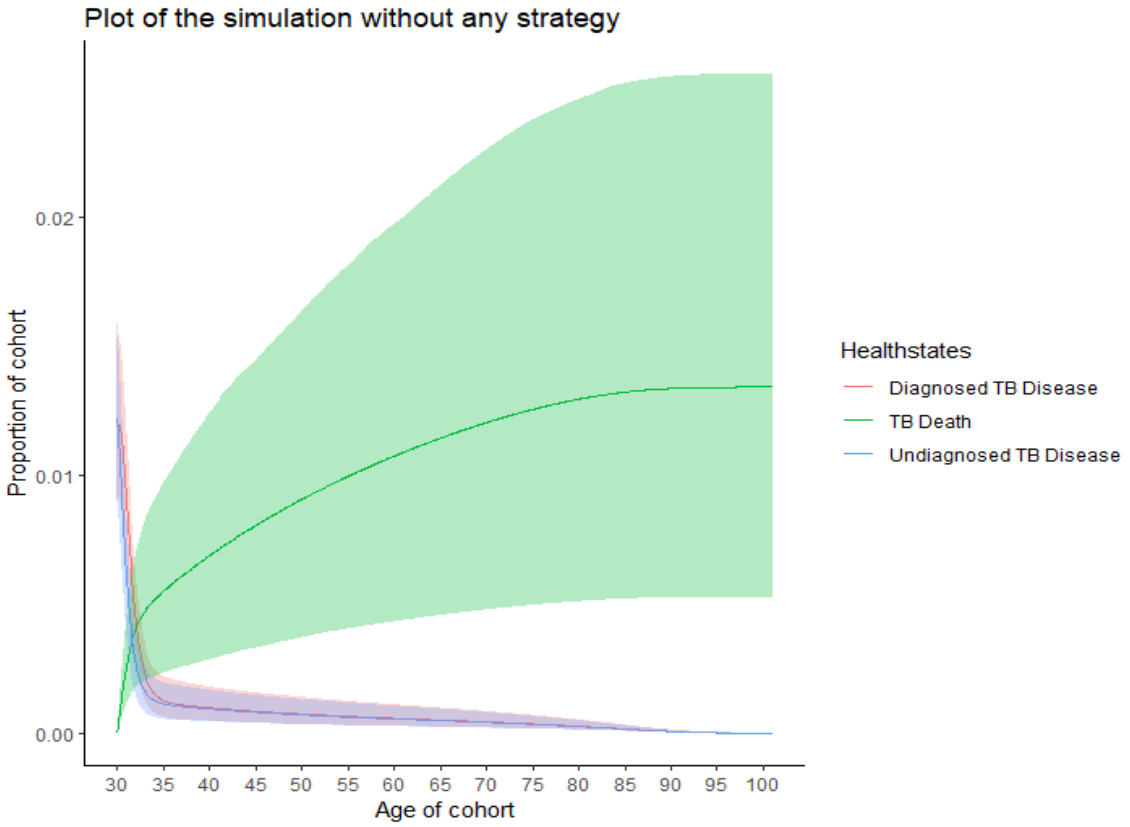

Figure 21: Zoom of the simulation plot of the base case. This plot contains the states (un)diagnosed TB disease and TB death

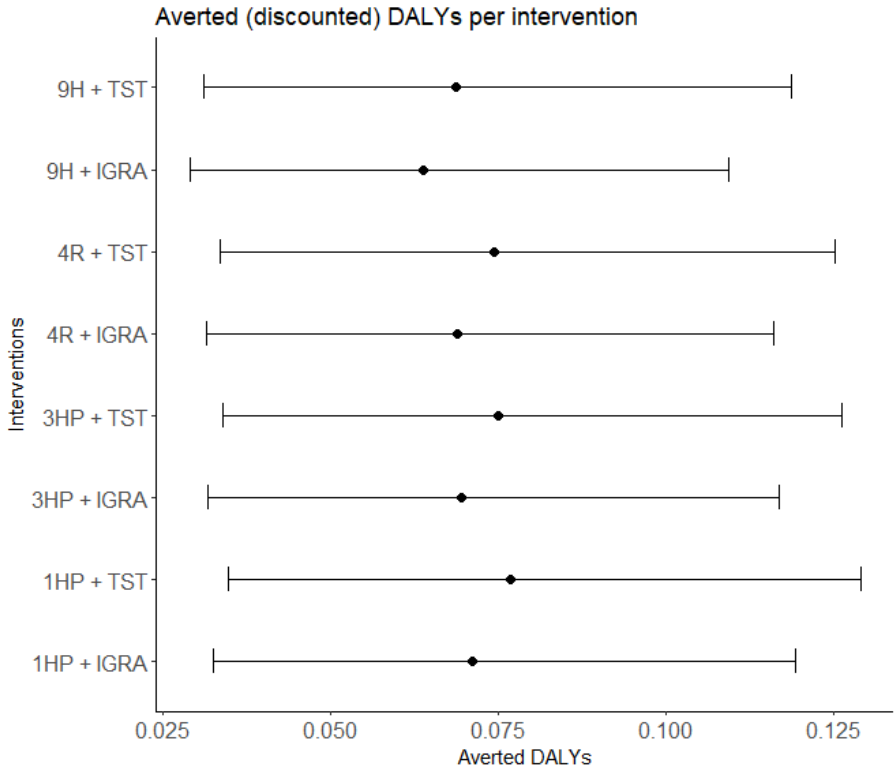

Figure 22: Averted discounted DALYs per intervention for two years in prison, testing at age thirty and three months after liberation

Age	DALY/person-year	Averted DALY/person-year	ICER
25	**0.15 (0.07-0.27)**	**0.081 (0.036-0.14)**	**408,8**
30	0.14 (0.066-0.25)	0.075 (0.034 - 0.13)	458,3
35	0.13 (0.061-0.22)	0.069 (0.030-0.12)	514,6
45	0.10 (0.050-0.18)	0.056 (0.026-0.094)	692,6
65	0.049 (0.026-0.80)	0.027 (0.014-0.043)	1697,6

Table 16: (Averted) discounted DALYs per person-year and the discounted ICER of the intervention for various ages at testing with 3HP+TST

Time spent in prison	DALY/person-year	Averted DALY/person-year	ICER
1 month	0.056 (0.025-0.98)	0.019 (0.0085-0.035)	2679,08
3 months	0.070 (0.032-0.12)	0.030 (0.014-0.051)	1605,75
6 months	0.090 (0.041-0.16)	0.043 (0.019-0.073)	1030,86
1 year	0.12 (0.054-0.21)	0.061 (0.028-0.10)	654,35
2 years	0.14 (0.065-0.25)	0.075 (0.035-0.13)	460,57
5 years	0.14 (0.059-0.25)	0.079 (0.034-0.15)	371,90
10 years	**0.13 (0.053-0.25)**	**0.077 (0.033-0.14)**	**355,87**

Table 17: (Averted) discounted DALYs per person-years and discounted ICER of the intervention for different testing moments since prison)

Time since prison	DALY/person-year	Averted DALY/person-year	ICER
no time	0.15 (0.068-0.26)	0.080 (0.037-0.13)	288,0
1 month	**0.15 (0.068-0.26)**	**0.80 (0.037-0.14)**	**280,0**
3 months	0.14 (0.065-0.25)	0.075 (0.035-0.13)	319,0
6 months	0.13 (0.060-0.23)	0.067 (0.031-0.12)	377,5
1 year	0.11 (0.051-0.21)	0.056 (0.025-0.10)	485,6
2 years	0.088 (0.037-0.17)	0.045 (0.019-0.087)	638,4
5 years	0.070 (0.028-0.14)	0.037 (0.014-0.075)	813,4
10 years	0.063 (0.025-0.13)	0.032 (0.012-0.066)	997,0

Table 18: (Averted) discounted DALYs per person-years and discounted ICER of the intervention for different testing moments since prison)