Optimising the implementation of Tuberculosis Diagnostics in Kenya

An exercise in mathematical modelling and simulation

submitted in partial fulfillment for the degree of master of science

Alexandra de Nooy
14581728

Master Information Studies
data science
Faculty of Science
University of Amsterdam

Submitted on Fill In The Date In Format DD.MM.YYYY

	UvA Supervisor	External Supervisor
Title, Name	Prof. Debraj Roy	Prof. Brooke Nichols
Affiliation	University of Amsterdam	Amsterdam UMC, Amsterdam Institue for Global Health and Development
Email	d.roy@uva.nl	b.nichols@aighd.org

ABSTRACT

KEYWORDS

Tuberculosis, Mathematical modelling, optimisation, diagnostics

GITHUB REPOSITORY

https://github.com/adenooy2/MSc-Thesis.git

1 INTRODUCTION

Tuberculosis (TB) is an infectious disease with a notable impact on country health systems. In fact, in 2021 the World Health Organization (W.H.O) estimated that 10.6 million cases and 1.6 million deaths were reported globally, with many of these being recorded in Lower Middle-Income Countries (LMICs) [13, 14]. Further, a review of these numbers over time has shown that while TB-related mortality has reduced over the last two decades (from approximately 2.4 million deaths to 1.6 million deaths), the estimated number of annual cases has remained relatively stable [13, 14]. This highlights that although TB treatment and linkage to treatment has improved overall, there is still significant ongoing community transmission.

A notable challenge to reducing this transmission lies within patients being able to access appropriate diagnostics and results. Frequently, this process is complex with patients having to make many (often expensive) visits to facilities to both provide a sample that can be tested as well as to return to receive their diagnosis [19, 20]. Furthermore, collecting sputum-samples for TB testing can be difficult for both the patient and the healthcare provider [20]. These elements both contribute towards individuals falling out of care or not providing a sample for testing and subsequently not receiving a diagnosis (or treatment) and remaining infectious [20]. As such, this has prompted a global call to develop new TB tests, or use available TB tests in a new manners, which: reduce the complexity of the current diagnostic pathway, use more appropriate test samples (e.g non-sputum), bring results closer to patients and overall, increase the number of individuals correctly diagnosed [8, 15].

However, as novel tests begin to be developed according to W.H.O. Target Product Profile guidelines (a document describing the minimum requirements for new TB tests), it becomes necessary to consider how current technologies can be best and most feasibly utilised in countries that have a range of TB diagnostics and infrastructure already in place [12]. This project aims to explore this knowledge gap by developing a framework which can be used to simulate, for the high TB-burden country Kenya, a range of novel diagnostic implementation scenarios to determine which would diagnose the greatest number of individuals as compared to the current standard of care (SoC). Here the SoC is representative of the number of individuals likely to be diagnosed given the current infrastructure and patient journey followed when seeking care for TB symptoms. To explore new diagnostic implementations, several implementation scenarios will be considered and evaluated against the baseline data of an existing TB diagnostic SoC model for Kenya to answer the following research questions (RQ).

Research Question: *To what extent do different implementations of tuberculosis nucleic acid amplification tests have on the number of individuals being correctly diagnosed and how do they impact the TB epidemic over time as compared to the current standard of care for tuberculosis diagnosis in Kenya?*

Further sub-research questions include:

- To what extent do different diagnostic implementations change the percentage of individuals being correctly diagnosed with TB?
- Which implementation scenarios have the greatest impact on increasing the number of individuals being tested for TB?
- Which implementation scenarios have the greatest impact on increasing the number of individuals receiving TB results?
- To what extent do different diagnostic implementations impact the number of new TB cases and TB deaths over time?

Notably, while the developed model can be used to simulate results for this specific use case, a further benefit to the model will be that it can serve as a generic framework for this type of analysis for other countries, further diagnostics and potentially other diseases.

2 RELATED WORK

There are few recent analyses which look to review the optimal combination of TB diagnostics at a country level in Kenya. Further, there is little analysis which has been conducted using the W.H.O's new diagnostic classes, given the recency of the new TB TPP publication (end 2023/early 2024). This work aims to further develop and utilise models centered around TB patient pathway analyses in Kenya, to review the impact these novel diagnostic may have on the number of individuals diagnosed and to use this to determine the optimal implementation for Kenya as compared to the current standard-of-care (SoC).

When reviewing healthcare diagnostic or treatment options, it is useful to have a framework in which to compare the different combinations and their effect on the outcome of interest. In this, the concept of a patient pathway analysis (PPA) becomes useful. These types of analyses attempt to illustrate patient care-seeking behaviour and subsequent service availability (for example options for diagnosis or treatment) by mapping out the journey and healthcare visits required to be made by each patient when attempting to receive care [22]. These analyses are frequently performed in the context of TB and are used to highlight service delivery gaps that should be noted for further intervention. Work by [5, 10] highlights some of the complexities of the TB patient pathway in Kenya and notes several key concepts which should be considered when mapping out the SoC. These include the healthcare sector in which care is initially sought and at which outcomes or treatment are provided, what percentage of facilities have access to diagnostics, the likelihood of a patient accessing a site with diagnostic availability at their first visit as well as what types of diagnostics that are in use and in what proportions [10]. Capturing these concepts

with the most up-to-date data, can then be used to inform a national "average" patient journey from the point of TB symptoms to TB diagnosis and treatment. Further, this journey can be used to track how many visits are required to receive a diagnosis, how this journey may differ between population groups (e.g HIV positive) and highlights key points at which patients are lost from care (for example they do not arrive at subsequent appointments as a result of other barriers to care).

Given a patient pathway representative of Kenya's SoC, it then becomes necessary to consider how the implementation of diagnostics with different attributes and performance may affect a patient's journey. Many of the novel diagnostics and their potential impacts are described in the W.H.O's latest TB diagnostic TPP and consider three main aspects, namely: sample-type (non-sputum vs sputum), the site at which testing is taking place (at the facility or at a centralised lab) and how quickly results can be returned (same visit or at another visit).With this information in focus, other work conducted has developed a baseline stochastic agent-based model for Kenya's patient pathway, with the potential to replace all diagnostics with a single-novel diagnostic at different performance levels [5]. While this model has been used to help define the minimum performance criteria required of novel tests, it could be further adapted to consider alternative implementation scenarios of existing diagnostics. Using models of this type, different scenarios can be simulated, and their key outcome results compared to the SoC.

Utilising and building on these described topics will allow for a methodology to be developed which will provide an initial static analysis, or analysis of a single diagnostic attempt per patient, that can guide on the potential optimal diagnostic combinations. Using the optimal set-up, a dynamic analysis can then be considered. In this analysis, impact is considered over time by looking at the difference in the number of correct diagnoses between the standard of care and the optimal diagnostic implementation. Further, the analysis will be used to consider the potential effect that this has on the underlying incidence and prevalence of TB in the country over time. Frequently, these types of dynamic analyses take the form of transmission models.

There are multiple examples of TB transmission models in the literature [4, 6, 18]. Frequently, developed transmission models have varying levels of complexity, usually centered around the key disease areas under investigation. There are however, often common elements between them. In all three examples, there is a consideration of disease progression - namely moving from uninfected, to fast or slow progressing latent TB followed by active TB. Following an individual having active TB there is a consideration of diagnosis, treatment and recovery. These elements of the transmission model frequently differ somewhat between groups. In the paper by Dodd et al, this process is simplified to individuals being on treatment (based on case detection) and individuals becoming recovered (based on treatment completion rates) [6]. Further, there is the potential for recovered individuals to relapse (or become reinfected) [6]. However, while this aspect of TB transmission is relatively simple in this model, there has been significant focus placed on modelling the complex interactions between HIV and TB co-infection over time, including the incorporation of HIV treatment and the impact this has on TB acquisition, transmission and outcomes [6].

In terms of HIV consideration, the paper by Cilloni et al differs to this model in that HIV in included as a factor but in a significantly simpler manner [4]. In this paper, the most significant focus has been placed on elements of diagnosis [4]. Here, the diagnostic element is separated into several stages, namely those with disease who have not sought care, those with disease who have sought care but are awaiting diagnosis, those with a diagnosis and on treatment (who either complete or have interrupted treatment) and those who have received an incorrect diagnosis or were lost from care before receiving their results (known as pre-treatment loss-to-follow-up)[4]. This paper is interesting for the context of this project, as different diagnostics have the potential to change the rates at which individuals move between these stages. Potentially the most complex of these three examples is that of Glaziou et al, where they have described the model used for the WHO's TB estimates[18]. Within this model there are simplified key elements like those previously described (infection, latent TB, active TB, TB treatment, Recovery and relapse), however, significant focus has been placed on stratifying each of these compartments and the movement between based on a range of factors [18]. These include time-dependent diagnosis and treatment rates, differences between public and private sectors, HIV status (negative, positive on Art and positive not on ART) and recovery status (long-term recovered, recovered after treatment completion, recovered after treatment interruption or self-cure). Further, all model compartments are considered in terms of age, sex, TB type (pulmonary vs extra-pulmonary) and drug resistance. This model incorporates many complexities which are unlikely to be included in this project, however it is useful to be aware of which factors have been considered in their estimates as this is the data likely to be used for our simplified model's calibration.

Todo: refer back to research gap - add more impact comparators

3 METHODOLOGY

3.1 Patient pathways analysis: Optimising TB Diagnostic implementation

This section presents the methodology used to conduct the static patient pathway analysis, which is used to quantify the impact that different implementations of existing TB diagnostics would have on the number of TB cases being detected and treated as well as on the number of individuals accessing testing and results. A discussion on the baseline model (representative of SoC in Kenya) and the scenarios which are subsequently simulated are provided below. Notably, results from this section are used as input to the second modelling exercise presented in Section 3.2.

3.1.1 ***Patient Pathway Model.*** To determine the impact of new diagnostic implementations, as compared to the current diagnostic SoC in Kenya, a patient pathway analysis is conducted. Here, results are generated through an adapted version of the Kenyan patient pathway model presented in [5] and previously described. The version developed here adapts the model structure in several ways to make it more flexible. Firstly, the structure is modified to present a

more generalised TB patient pathway. The decision tree representing this generalised pathway is presented in Appendix A: Figure 5. An advantage of the generalised pathway is that the structure of the model itself is no longer specific to the country baseline, rather the general model uses different parameter values to represent the country. This is a key contribution to this work as it will allow for multiple countries to be rapidly modelled in the future using one structure with a standardised input and output set. Further, the model it adapted to include several modules representing key stages of TB diagnosis - namely screening, triage testing, confirmatory testing and rif-resistance testing. In each of these modules, there is the ability to include and simulate different tests, tools or diagnostics - making it useful for comparing different diagnostic algorithms. While several of these modules were inherently included in past work, the new format in which these modules have been coded allows for them to be turned on and off at will. This is chosen as it provides significant flexibility for experimentation. Overall, these adaptations will allow for easy analysis and comparison between different countries, diagnostics and diagnostic algorithms. Lastly, this process structurally re-coded the model in R-studio to rapidly speed-up simulation time as compared to the version presented [5] . For the context of this analysis, the developed general model is parameterised to Kenya for the baseline and scenario simulations.

3.1.2 ***Baseline Simulation for Kenya.*** To simulate the baseline results for the Kenyan context, the developed generalised model is parameterised using relevant values sourced from the literature. These have initially been described in [5] but are summarised in Appendix A: Table 5. Notably, these parameters are calibrated to ensure that at baseline, the percentage of individuals with TB correctly diagnosed matched the WHO's TB case detection rate (CDR) for Kenya at that time (57% in 2021) [17]. These parameters represent the specific decision tree values relevant to each combination of HIV and TB status. Notably, in this table, several parameters related to Rifampicin drug resistance have been set to 1 as this component is not relevant to this analysis (as only the point of initial diagnosis is being considered). Using the model with these parameters, several simulations (n=100) of the baseline TB diagnostic pathway in Kenya are run and saved. Multiple iterations are performed to allow for stochasticity in the pathways followed by each individual. In each run, the individual pathways for 10,000 people with TB symptoms (and varied HIV and TB statuses) are simulated.

For each model simulation run an output excel file is generated. Each file follows the naming convention of baseline_run_x_.xlsx where "x" represents the specific run number. Each output file has 10,000 rows, with each row representing an individual from the simulated cohort. There are 35 columns in this output. Here each column represents either a relevant status of an individual (for example HIV and TB status), a note of whether an individual has reached a specific point in the cascade (e.g. have they provided a sample, are they referred to an alternative site, have they received their results), specifics on the test used for each individual and any relevant test results. A full summary of these variables and their description is provided in the appendix Table 6.

Given the model set-up, these output files are always complete, with data available for every simulated individual. Within the output, there are cases where "NA" values are seen, however these are representative of a specific model state as opposed to being a missing result. These occur is columns "screen_result", "tb_triage_result", "conf_sample_result" and "patient_conf_result_receive" and indicate that either the individual or sample did not reach this point in the cascade and hence no result was available. From each output file, summary variables representing the entire cohort are then calculated. For this analysis, key calculated variables are related to the patient care cascade and are used to show the number of individuals with TB who reach key points. This cascade approach is chosen to highlight key-areas of patient loss from care, for example as a result of high numbers of facility visit being required, as well as to indicate the simulated CDR (that is the number of individuals with TB who are diagnosed and treated). For each file, the processing steps to calculate the cascade variables are summarised below:

- Filter data set to only individuals with TB (tb_present==1)
- Select relevant columns: tb_present, tb_seek_care, tb_confirmatory_offered, conf_sample_provided and patient_conf_result_received
- Perform a summation across columns
- Calculate the percentage of individuals who arrive at each point relative to the number of individuals with TB

This process is conducted for all baseline files, following which the average values for each cascade variable are calculated to produce a single set of baseline variables against which new scenarios are compared. In conjunction with the cascade analysis for individuals with TB, a similar approach is followed to analyse the full cohort of individuals to determine the percentage of individuals who receive testing, and of those who receive testing, what percentage receive their results.

3.1.3 ***Experimental set-up: Optimal diagnostic implementations.*** While there is significant development of new TB diagnostics occurring, currently, the mostly widely used and available molecular diagnostics are nucleic acid amplification tests (NAATs) like the GeneXpert MTB/RIF test [3]. However, there are multiple ways in which these NAAT tests can be implemented, with each implementation having a different potential CDR as compared to the considered baseline (which uses both NAAT and smear-microscopy). For this analysis, the potential impact of GeneXpert under different usage scenarios is considered. Here, each scenario is defined by four key attributes, namely the test type, where testing is occurring, the turnaround time of results and the sample-type being collected. Changes in each of these are assumed to impact the baseline patient pathway. Firstly, in all scenarios it is assumed that there is 100% GeneXpert coverage. This will improve case detection results over the baseline scenario which uses GeneXpert and the less accurate smear-microscopy. For testing location, in centralised, off-site testing, it is assumed that there will be an element of sample transport, as well as additional patient visits made if patients are referred to an external site. This could result in lost samples, or patient loss-to-follow-up (as each additional visit required could result in a patient not returning to care). Decentralised testing is considered to eliminate these losses by bringing the diagnostics to the initial care seeking sites. With respect to turnaround time of

Table 1: Modelled GeneXpert implementation scenarios

Scenario	Test Type	Testing Location	Return of results	Sample-Type
Baseline	GeneXpert and Smear	Mix of onsite and offsite	Subsequent visit	Sputum
1	GeneXpert	Mix of onsite and off site	Subsequent visit	Sputum
2	GeneXpert	Onsite	Subsequent visit	Sputum
3	GeneXpert	Onsite	At testing visit	Sputum
4	GeneXpert	Mix of onsite and off site	Subsequent visit	Non-sputum
5	GeneXpert	Onsite	Subsequent visit	Non-sputum
6	GeneXpert	Onsite	At testing visit	Non-sputum

results, at baseline individuals are required to return to the facility at a later stage. This additional visit again contributes towards patients being lost-from care. However, this loss is assumed to be eliminated in implementation scenarios which provide results at the initial testing visit. Lastly, sputum and non-sputum sample types are considered. While sputum is the current standard sample type, if its often difficult for individuals (especially those with HIV) to produce. This often results in extra-visits (and loss) being required to conduct more invasive sample collection. Non-sputum sample types, like oral swabs, while less accurate than sputum, are assumed to be much easier to offer for providers and are easily obtained from all individuals.

Given the described assumptions and implementation attributes, six simulation scenarios are developed alongside the baseline (Table 1). These scenarios are simulated using the developed model by changing certain parameters - a list of which is provided in the Appendix (Table 7). With these parameters, the same simulation and analysis process as described for the baseline is then followed. The calculated cascade data for each scenario, along with the CDRs, are then compared against the baseline situation to determine each scenario's relative impact. The determined CDRs for each scenario are also subsequently used as inputs into the long-term impact analysis described in Section 3.2. Lastly, changes to the testing rates and the percentage individuals receiving their test results are also determined.

3.2 Transmission model: Long-term impact of optimal combinations

To consider the long-term impacts of different diagnostics on TB transmission dynamics, it is necessary to have a baseline transmission model to evaluate against. Once calibrated, this model is intended to capture and reflect the historical TB dynamics seen in Kenya. Given an acceptable baseline model, we are then able to use the model to predict future changes in transmission, detection and treatment of TB. These baseline results are then used as a comparator against which new interventions are evaluated. The baseline model development and subsequent experimental set-up is described below.

3.2.1 *Historical TB data in Kenya.*

To develop an appropriate transmission model, it is necessary to have an understanding of available historical TB data. In this case, data from the W.H.O is available for Kenya between 2000 - 2022 [16]. Key data variables include estimates (lower,mean and upper) of incidence for all cases, incidence in the HIV population, number of deaths, CDR and case fatality rates (CFR). These pieces of data will be used for paramaterising and calibrating the baseline transmission model. Notably, for the variables of interest there are no missing data elements that need to be accounted for. Key visualisation of these data are presented in the Appendix - these include a plot of the mean incident cases, cases detected and TB deaths over time as well as a plot of the mean CFR and CDR (Figures 6 and 7).

3.2.2 *Baseline Transmission Model.*

To capture the historic trends in TB in Kenya, a stock-and-flow diagram (SFD) representing the developed baseline transmission model is presented in Figure 1. This SFD represents a simplified TB transmission model utilising key components as described in the literature [4, 6, 18]. The model is developed in Vensim [21], and has five stocks (or compartments) representative of the number of individuals within the population at each stage of the TB disease spectrum per year. These compartments are labelled Susceptible, Latent TB infection, Active, Detected and Treated TB and TB deaths. Two additional stocks are included to track the cumulative number of new cases and total number of TB deaths over time (starting in the year 2000). Further, there are 10 model flows, which represent the yearly number of individuals moving into and out of each compartment. In Vensim, each stock and flow is governed by a set of equations and initial conditions which define the value change of model components per time-step. These have been provided, alongside the relevant component descriptions and units, in Appendix B: Table 8.

3.2.3 *Experimental set-up.*

The model equations also make use of parameters which define various rates (i.e birth, general mortality, case fatality, transmission, progression, case detection , and relapse rate), two stock initial conditions (initial latent and initial incident number of individuals) and one delay time component (progression time). Several of these parameters have been sourced from the literature while others have been defined through a calibration process (Appendix B: Table 9. Calibration is a common transmission modelling tool which works to simulate different combinations of parameter values (within defined ranges), and compare the corresponding results to known reference data [9]. In this case, the flow "Progression" is compared to Kenya's estimated yearly incidence. The process selects the final parameter set by minimising the sum of square differences between the simulation results and the reference data. This process is used to ensure that the model reflects reality as closely as possible and provides confidence in any conclusions drawn from subsequent experiments. The calibration process if performed for the WHO's lower, mean and upper estimates in

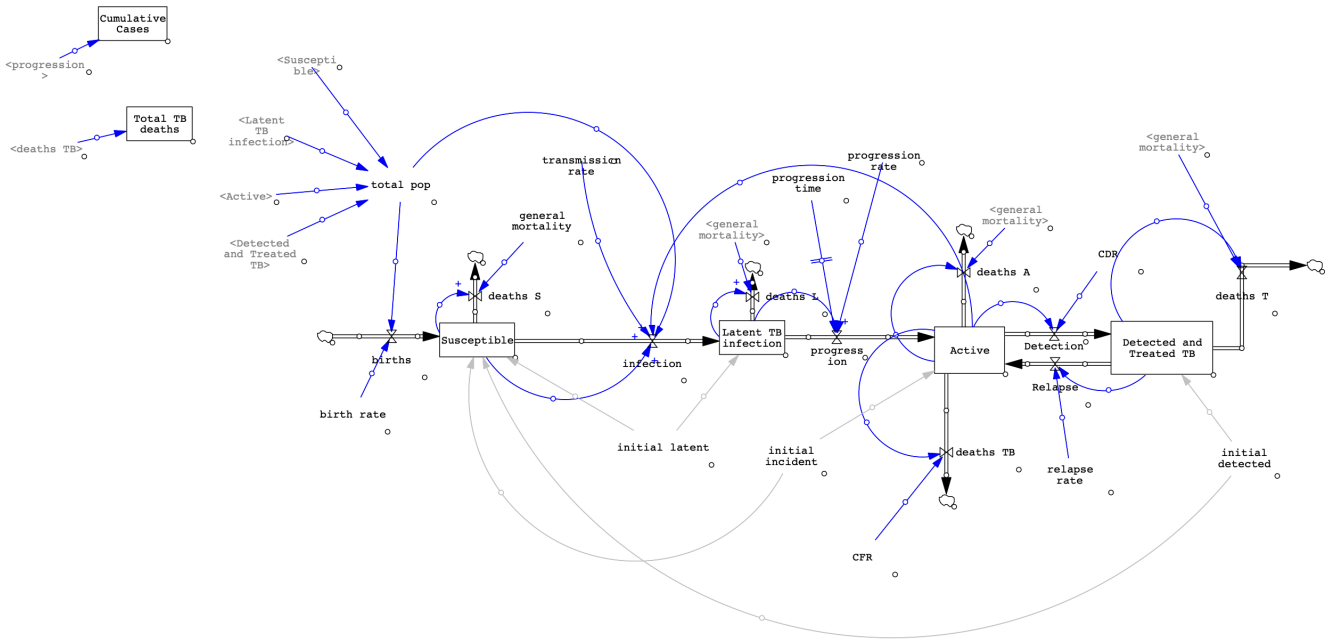

Figure 1: SFD representing the baseline TB transmission model

order to provide an uncertainty range for each calibrated parameter, however, in future experiments the mean calibrated value is used. Further details on the calibration process can be found in the Appendix: Section B.3. Using these calibrated values, the SFD and the corresponding equations, the baseline transmission model can be reproduced in Vensim.

Using the developed baseline transmission model, a sensitivity analysis is conducted. This analysis is used to review which parameters have the greatest impact on model results. Given that the number of year new cases (*progression*) is used during calibration, this flow has been chosen as the key variable considered. In this case, two common sensitivity-analysis methodologies are used, namely Tornado plots (produced in Vensim) and Sobel indices (conducted in Python) [11, 23]. The first-order and total Sobel indices have been considered at two time points, namely 2005 (when TB incidence peaks) and 10 years later in 2015 (when TB incidence is on the decline). This is done to quantitatively explore the impact that different parameters have on the epidemic and how this might shift with time. Lastly, a stability analysis is conducted on the transmission model to review the relevant equilibrium points for each stock. To do this, each stock is written as a differential equation (see Appendix: Section B.4). . Equilibrium is also explored visually using the Vensim model. In this case the simulation time-frame is extended to the year 3000 and the values of the Susceptible, Latent Tb Infection, Active and Detected and Treated Tb stocks are examined. If at any time-point, one of these stocks remains at a constant or zero-value (where in-flows = outflows or inflows=outflows=0), it will be considered to be at equilibrium [7].

stability

This section describes two experiments conducted in Vensim using the calibrated model. In each case, the simulation timeline is expanded until 2041 (20 years past the calibration point) to provide time for the impact of any changes in model parameters to be seen. The model is then used to predict the cumulative number of TB cases and deaths and their relative difference from baseline under different model conditions. In both sets of experiments, the impact of different CDRs is explored. Here it is assumed that between 2022-2041 a new constant CDR is modelled.

For **Experiment 1**, the CDR is increased at regular intervals, starting from the 57% value seen in 2021, up until 100% case detection is reached. This experiment looks to explore the impact of different CDRs over time, without considering a specific diagnostic or diagnostic implementation. Here, the CDR values simulated are: 57%, 62% , 67%, 77%, 87%, 97% and 100% (corresponding to relevant increases from the baseline CDR of 0%, 5%, 10%, 20%, 30%, 40% and 43%). Each of these CDRs are simulated, the relevant model outputs are plotted over time and key end-point values are extracted from Vensim for comparison. For **Experiment 2** a similar approach is followed, however, the CDRs which are simulated are taken from the results of the static model scenarios described in Table 1, the results of which are provided in the following Section (Section 4.1: Table 2). The intention of this experiment is to explore the long-term impact that could be made on the TB epidemic, given different implementations of currently available diagnostic tools.

4 RESULTS

4.1 Patient Pathway Analysis

Using the developed model, the baseline diagnostic journey for Kenya is simulated. The baseline data is analysed, with a focus on individuals with TB, to produce the relevant cascade variables. These variables are visualised in Figure 2. Here it is highlighted that the baseline case detection rate, or the percentage of individuals

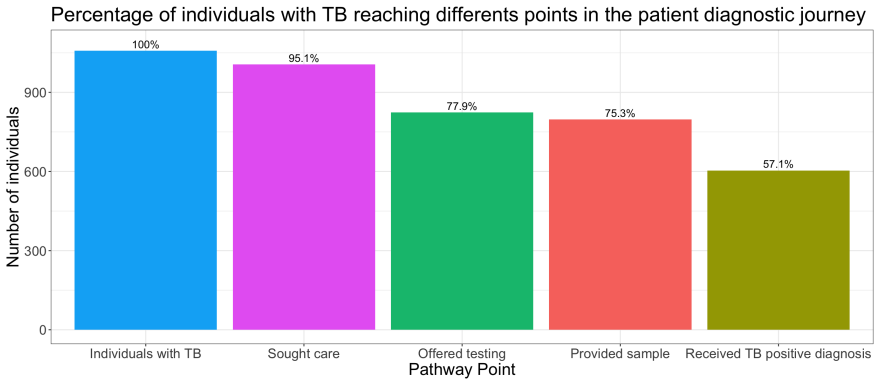

Figure 2: Visualisation of the number of individuals with TB reaching key points in the baseline TB diagnostic pathway

with TB who receive a TB positive result, is 57.1%. This matches the W.H.O's treatment coverage value for 2021 (57%) which was used to calibrate the model parameters [17]. The figure also highlights a notable drop in the number of individuals moving through the cascade at two points - namely between individuals seeking care and being offered confirmatory testing (a loss of approximately 17.2% of individuals), and again between samples being provided for testing and results being received (where 18.2% of the cohort is lost from care).

Given these baseline results, the analysis is repeated for the six described scenarios. Of interest, is the CDR and the relevant change in this value, as compared to baseline, for each scenario (Table 2). Here it is seen each that each scenario improves on the baseline, with Scenario 6 having the largest improvement in CDR (an increase of 26.4%). These improvements in CDR correspond to a greater number of individuals being correctly diagnosed on average with TB. Generally, it can be seen that as scenarios increase the access to accurate testing and results (and hence decrease the number of individuals lost from care) the CDR increases. These results also highlight two trends in CDR. That is, within each class of sample-type (sputum vs non-sputum) there is a notable increase in CDR for scenarios 3 and 6, which ensure that results are returned to individuals at their testing encounter. Further, the non-sputum scenarios (scenarios 4,5,6) also have increased CDR relative to their corresponding sputum-scenarios.

Table 2: Case detection rates for simulated scenarios

Scenario	Case Detection Rate	Change in Case Detection rate from baseline
Baseline	57.09%	-
1	63.36%	6.27%
2	64.35%	7.26%
3	71.77%	14.68%
4	73.73%	16.64%
5	74.84%	17.75%
6	83.49%	26.4%

The final output for the patient pathway analysis looks at the full cohort of individuals tested (those with and without TB) and calculates the relevant rates of testing and return of results per scenario (Table 3). Within this table, the final two columns represent the rates of interest. It can be seen that for the sputum scenarios (scenario 1,2 and 3), the percentage of individuals being tested for TB does not change significantly from baseline. Of these three, scenario 3 has the largest change with a 3.1% increase. Conversely, the non-sputum sample scenarios (scenarios 4,5 and 6)have a larger impact on testing rates with increase from baseline of 12.11%, 13.58% and 15.64% respectively. These results highlight that moving from testing with sputum samples to testing with non-sputum samples improves on the number of individuals being offered testing and decreases loss from the TB diagnostic cascade. Finally, the percentage of individuals tested who received their TB results is considered. Overall, these percentages were high, with >91% seen for all scenarios. Notably, there is little to no difference compared to baseline for Scenarios 1,2,4 and 5 - highlighting that GeneXpert usage and decentralisation has little effect on how many individuals receive results. However, it is seen that with Scenario 3 and 6, where results are received at the initial testing encounter, the percentage of those test who receive results is 100% as expected. This is an increase of 8% from the baseline scenario.

4.2 Transmission model: Long-term impact Analysis

This section presents the results of the long-term analysis conducted using the developed TB transmission model. To draw conclusions from the model, it is necessary to understand how well it reflects reality. For this, the model has been calibrated to the WHO's three incidence estimates. The resulting model output for each calibration set is presented below (Figure 3), with the determined calibration parameter values given in Appendix: Table 10. Within Figure 3, the calculated sum of square errors between the calibrated models and the WHO's lower, mean and upper estimates of incidence are 555 888 429, 823 510 209, 75 542 338 440. These values highlight that the model outputs have significantly lower error values when calibrated to the lower and mean estimates as compared to the upper estimates. This indicates that conclusions can be drawn, with relative confidence, for the mean-estimate calibrated model calibrated which is used for the remaining analyses and experiments.

Table 3: Patient pathway analysis - scenario cascade variable results, testing rates and rates of results received

Scenario	Number of symptomatic individuals	Sought Care	Offered Testing	Reach testing site	Provide Sample	Sample Tested	Received Results	Percentage Individuals Tested for TB	Percentage of individuals tested who receive results
Baseline	10000	9503	7792	7609	7581	7456	6860	74.56%	92.01%
1	10000	9500	7789	7605	7578	7453	6858	74.53%	92.02%
2	10000	9499	7788	7606	7578	7578	6968	75.78%	91.95%
3	10000	9500	7796	7796	7766	7766	7766	77.66%	100.00%
4	10000	9504	9029	8819	8813	8667	7969	86.67%	91.95%
5	10000	9506	9032	8819	8814	8814	8112	88.14%	92.04%
6	10000	9500	9026	9026	9020	9020	9020	90.20%	100.00%

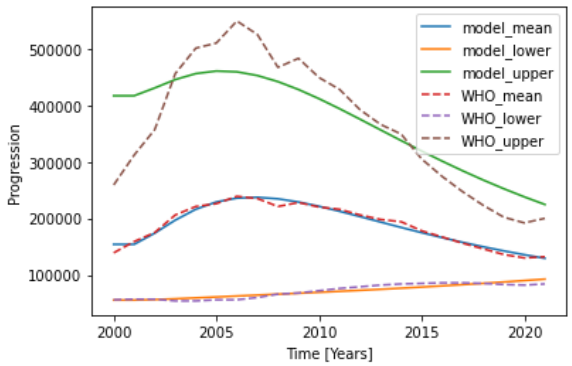

Figure 3: Calibration output for the model's *progression* variable when calibrated against the World Health Organization's lower, mean and upper estimates for incidence between 2000-2021

In conjunction with the calibration results, stability and sensitivity analyses are also conducted. These are performed for the model calibrated to the mean WHO incidence estimates. In terms of system stability and equilibrium, the outputs of each stock are considered up to the year 5000 (Appendix: Figure 8). The plots highlight that the Susceptible stock continues to increase exponentially with time and hence does to reach or tend to an equilibrium point. For the remaining three stock an exponential decay can be seen, although the rates of decay are different for each stock. With time, all three stocks tend towards zero, highlighting that zero is the only likely equilibrium point for each stock. Although time has been extended to the year 3000, none of the stocks have yet reached a constant zero value (Appendix: Table 11).

For the sensitivity analysis, the *progression* flow is the focal variable and the resulting tornado plot, and Sobel incides' plots are presented in Appendix: Section B.5. The tornado plot (Figure 9 indicates that the transmission rate, progression rate and the initial latent number of individuals have the largest impact on the *progression* flow at the end time point (mean absolute deviations of at least 8300 individuals per year). Conversely, the initial detected, birth rate and relapse rate variables have a minimal impact on *progression* (a deviation <500 individuals per year). Figure 10 highlights the Sobel indices for 4 rate variables at two time points. In 2005, the peak of TB incidence, it is seen that progression time has the largest effect on the *progression* flow with Sobel index values greater than 0.65. This is followed by the transmission rate variable (Sobel indices 0.3). Of the other two, progression time has a small impact, represented by total and first order Sobel indices <0.1, and relapse rate has with zero impact. In 2015, where the incidence of TB is declining, the transmission rate variable has the largest effect on incidence (Sobel index values >0.9) with progression rate, relapse rate and progression time all having a minimal or zero effect on *progression*. The differences in the Sobel indices between the two time points highlight the differential effects of certain TB dynamic properties at different points in the TB epidemic. That is, at an early time point (2005) where the pool of latently infected individuals is large, the number of individuals moving from latent to active TB has the greatest effect on *progression*. However in 2015, when the epidemic is on the decline, the *progression* flow is most affected by the transmission rate which results in additional individuals moving into the latently infected group.

For Experiment 1, where case-detection rate was increased at regular intervals from baseline, the long-term impact on the total deaths and cumulative and new TB cases is presented in Appendix: Table 12. These results highlight that as CDR increases, the total number of TB deaths and cumulative cases in 2041 decrease relative to the baseline scenario. Here it can be seen that at 100% CDR, 31 111 deaths and 335 300 could be averted as compared to baseline. Notably, the number of new cases and deaths in 2041 for this scenario (where all individuals with active TB are detected and treated), while reduced by by 70.5% and 72.9% respectively are not zero. This highlights that TB interventions with perfect performance focused only on diagnosing active TB cases would not be sufficient to eliminate TB over the next two decades.

In Experiment 2, the CDRs determined for Scenarios 1-6 of the patient pathway analysis (see Table 2) are applied over two decades and the long-term impact on the TB cases and deaths, relative to the baseline scenario, are determined (Table 4). Figure 4 visualises these results for the *progression* flow (which represents the number of new active cases each year), as well as for the cumulative number of cases and TB deaths. In each case, the plots for each variable over between 2000-2041 are shown. Further, a close-up plot between 2030-2041 is included to better see the difference in values between scenarios. As seen in Experiment 1, scenarios which increase the CDR result in a decreased number of total cases and TB related deaths by 2041. Overall, the non-sputum scenarios (scenarios 4-6) decrease TB cases and deaths to a greater degree than the sputum-scenarios (scenarios

Table 4: Experiment 2 - Simulated TB deaths, deaths averted, cumulative cases, cased averted and the percentage change in deaths and cases in the final year of simulation for the CDR results determined from the patient pathway analysis

Scenario	Case Detection Rate (%)	Increase in CDR from baseline	Total TB Deaths	TB deaths averted	TB deaths 2041 (% change from baseline)	Cumulative Cases	Cases Averted	New Cases in 2041 (% change from baseline)
Baseline	57.1	-	463 512	-	2 190 (0%)	5 583 870	-	43 965 (0%)
1	63.4	6.3	456 026	7 486	1 745 (-20.3%)	5 509 020	74 850	35 923 (-18.3%)
2	64.3	7.2	455 085	8 427	1 693 (-22.7%)	5 499 390	84 480	34 923 (-20.6%)
3	71.8	14.7	448 253	15 259	1 330 (-39.3%)	5 427 800	156 070	27 753 (-36.9%)
4	73.7	16.6	446 744	16 768	1 256 (-42.7%)	5 411 570	172 300	26 193 (-40.4%)
5	74.8	17.7	445 918	17 594	1 216 (-44.5%)	5 402 610	181 260	25 342 (-42.4%)
6	83.5	26.4	440 231	23 281	956 (-56.3%)	5 339 620	244 250	19 572 (-55.5%)

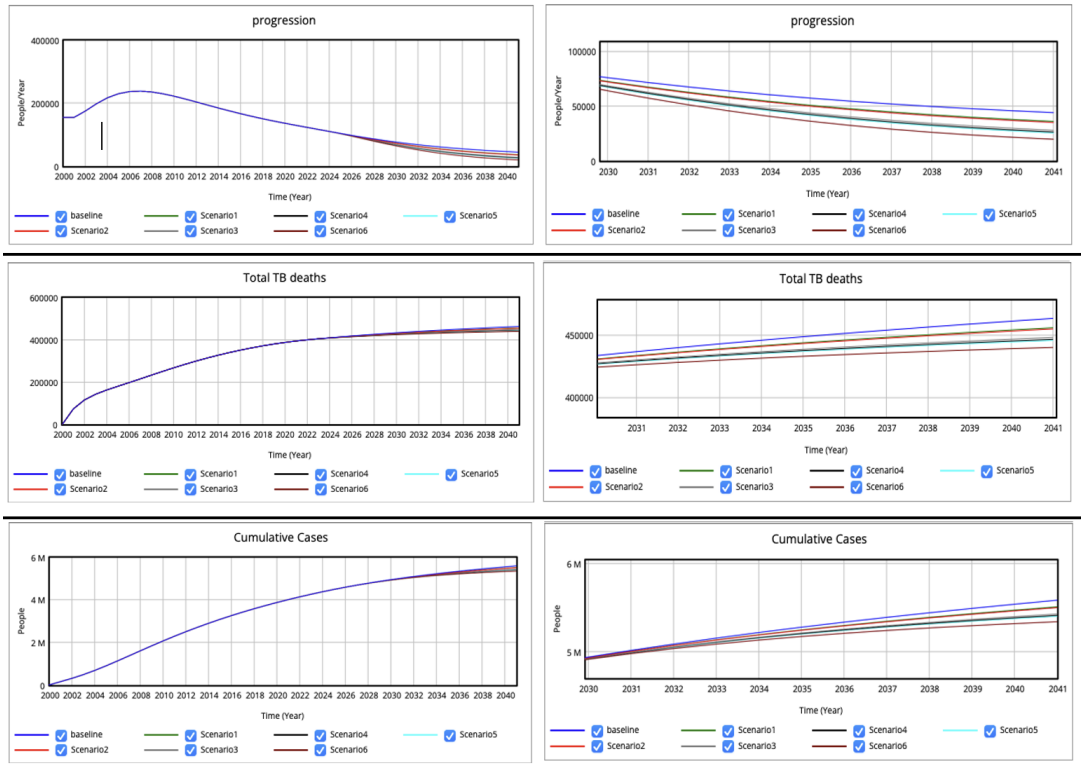

Figure 4: Plots of progression, cumulative cases and total TB deaths for each diagnostic implementation scenario for the simulated period 2000-2041, and in close-up for 2030-2041

1-3). Further, Scenario 6 (the decentralised non-sputum scenario) had the highest estimated CDR in the patient pathway analysis (83.5%), and corresponding saw the largest number of TB cases and deaths averted as compared to baseline at 23 281 and 244 250 respectively. The results in Table 4 and Figure 4 further highlight that regardless of the particular implementation of GeneXpert, 100% CDR cannot be reached. Further, while the number of new cases (19 572) and deaths (956) in 2041 represent >55% reduction as compared to the basdline values, they are still greater than zero. This highlights that regardless of diagnostic implementation, it would not be possible to eliminate TB with GeneXpert diagnosis alone.

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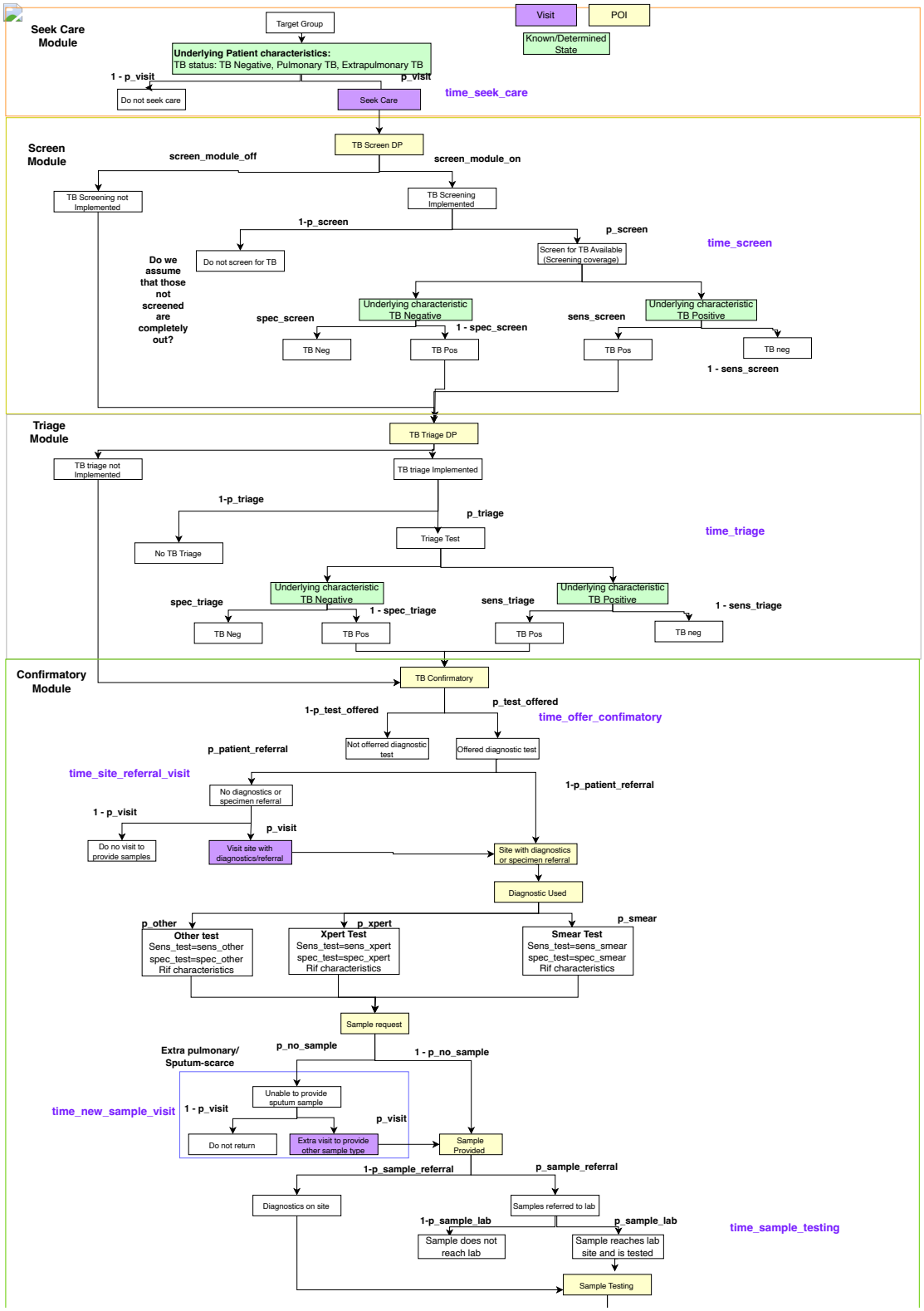
Appendix A STATIC ANALYSIS: OPTIMAL IMPLEMENTATION OF TB DIAGNOSTICS

This appendix provides relevant parameters and outputs for the patient pathway analysis which explores the impact of different diagnostic implementations. Figure 5 presents the decision tree representing the baseline patient pathway. The baseline parameter values are provided in Table 5, with relevant values sourced from the original model [5]. Model output variables used for analysis are detailed in Table 6 and Table 7 describes how baseline parameters are changed for each scenario.

Table 5: Kenya Baseline Input parameters

variable	value_hiv_neg	value_hiv_pos	value_hiv_neg_eptb	value_hiv_pos_eptb
prev	0.07904442	0.25093201	0.00999891	0.03733721
propHIV	0.086	0.086	0.086	0.086
propEPTB	0.13	0.13	0.13	0.13
propRifRes	0.1	0.1	0.1	0.1
p_visit	0.95	0.95	0.95	0.95
time_seek_care	1	1	1	1
p_screen	0	0	0	0
sens_screen	1	1	1	1
spec_screen	1	1	1	1
time_screen	0	0	0	0
p_triage	0	0	0	0
sens_triage	1	1	1	1
spec_triage	1	1	1	1
p_test_offered	0.82	0.82	0.82	0.82
time_offer_confirmatory	2	2	2	2
p_patient_referral	0.47	0.47	0.47	0.47
time_site_referral_visit	2	2	2	2
p_xpert	0.531	0.531	0.531	0.531
sens_xpert	0.91	0.9	0.82	0.82
spec_xpert	0.96	0.96	0.89	0.89
p_smear	0.469	0.469	0.469	0.469
sens_smear	0.68	0.52	0.4	0.4
spec_smear	0.9	0.9	0.7	0.7
p_other	0	0	0	0
sens_other	1	1	1	1
spec_other	1	1	1	1
p_no_sample	0.05	0.19	1	1
time_new_sample_visit	2	2	2	2
p_sample_referral	0.33	0.33	0.33	0.33
p_sample_lab	0.95	0.95	0.95	0.95
p_encounter_res	0	0	0	0
p_return_results	0.92	0.92	0.92	0.92
time_collect_result	2	2	2	2
p_emp	0.31	0.31	0.31	0.31
p_rif_included	1	1	1	1
p_rif_onsite	1	1	1	1
p_visit_rif	1	1	1	1
time_rif_visit	1	1	1	1
sens_rif_xpert	1	1	1	1
spec_rif_xpert	1	1	1	1
sens_rif_external	1	1	1	1
spec_rif_external	1	1	1	1
p_encounter_res_rif	1	1	1	1
p_return_rif_res	1	1	1	1
time_collect_rif_results	1	1	1	1
time_sample_testing	1	1	1	1


Seek Care Module
Target Group
Visit
POI
Known/Determined State
Underlying Patient characteristics:
TB status: TB Negative, Pulmonary TB, Extrapulmonary TB
1 - p_visit
p_visit
Do not seek care
Seek Care
time_seek_care
Screen Module
TB Screen DP
screen_module_off
screen_module_on
TB Screening not Implemented
TB Screening Implemented
1-p_screen
p_screen
time_screen
Do we assume that those not screened are completely out?
Do not screen for TB
Screen for TB Available (Screening coverage)
Underlying characteristic TB Negative
Underlying characteristic TB Positive
spec_screen
1 - spec_screen
sens_screen
TB Neg
TB Pos
TB Pos
TB neg
1 - sens_screen
Triage Module
TB Triage DP
TB triage not Implemented
TB triage Implemented
1-p_triage
p_triage
time_triage
No TB Triage
Triage Test
Underlying characteristic TB Negative
Underlying characteristic TB Positive
spec_triage
1 - spec_triage
sens_triage
1 - sens_triage
TB Neg
TB Pos
TB Pos
TB neg
Confirmatory Module
TB Confirmatory
1-p_test_offered
p_test_offered
time_offer_confimatory
p_patient_referral
Not offerred diagnostic test
Offered diagnostic test
time_site_referral_visit
No diagnostics or specimen referral
1-p_patient_referral
1 - p_visit
p_visit
Do no visit to provide samples
Visit site with diagnostics/referral
Site with diagnostics or specimen referral
Diagnostic Used
p_other
p_xpert
p_smear
Other test
Sens_test=sens_other
spec_test=spec_other
Rif characteristics
Xpert Test
Sens_test=sens_xpert
spec_test=spec_xpert
Rif characteristics
Smear Test
Sens_test=sens_smear
spec_test=spec_smear
Rif characteristics
Sample request
Extra pulmonary/ Sputum-scarce
p_no_sample
1 - p_no_sample
time_new_sample_visit
Unable to provide sputum sample
1 - p_visit
p_visit
Do not return
Extra visit to provide other sample type
Sample Provided
1-p_sample_referral
p_sample_referral
Diagnostics on site
Samples referred to lab
1-p_sample_lab
p_sample_lab
time_sample_testing
Sample does not reach lab
Sample reaches lab site and is tested
Sample Testing

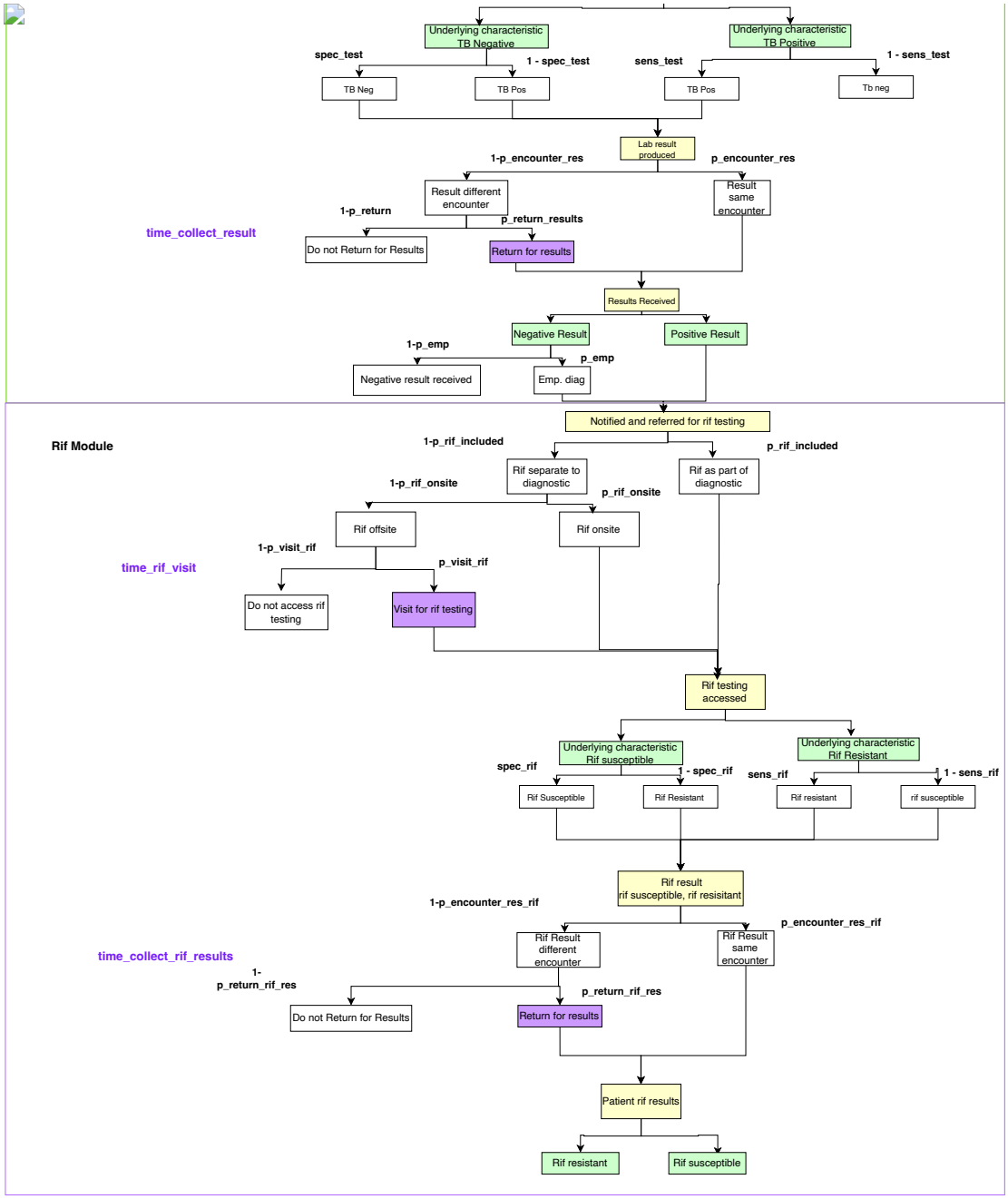


Figure 5: Generalised Patient Pathway Model

Table 6: Description of patient pathway model output variables

Variable	Description	Data Type	Data Notes/Options
hiv	Indication of individual HIV status.	Binary	0=HIV- , 1=HIV+
rnum	Random number generated to determine individual pathway followed	Float	-
tb_status	Indicates whether individual has extra-pulmonary TB, pulmonary TB or no TB	Text	eptb, tb_negative, ptb
tb_present	Binary indication of whether TB is present	Binary	0=TB Negative, 1= TB positive
rif_status	Indicates individual's resistance to Rifampicin drug	Binary	0=Rifampicin susceptible, 1 = Rifampicin resistant
num_visits	The total number of visits the individual has to make to receive diagnosis	Numeric	-
patient_time	The total number of days required from seeking care to receiving diagnosis	Numeric	-
tb_seek_care	Indicates whether individual sought care for TB symptoms	Binary	0= Did not seek care, 1= Sought Care
do_triage	A model indicator determining whether the triage module is on or off	Binary	0=on, 1 = off
tb_screened	Indicates whether individual is screened for TB	Binary	0=not screened, 1 =screened
sens_screen	Sensitivity of the screening test individual is screened with	Float	-
spec_screen	Specificity of the screening test individual is screened with	Float	-
screen_result	Result of screening test. Either TB positive, TB negative or no results	Binary	0=TB Negative, 1= TB positive, NA = no screening result
do_confirmatory	Indicates whether individual should receive a confirmatory tests	Binary	0=No confirmatory test, 1 = confirmatory test
tb_triaged	Indicates whether individual receives a triage test	Binary	0=no triage, 1 = Triage test received
sens_triage	Sensitivity of the triage test individual is screened with	Float	-
spec_triage	Specificity of the triage test individual is screened with	Float	-
tb_triage_result	Result of triage test. Either TB positive, TB negative or no results	Binary	0=TB Negative, 1= TB positive, NA = no screening result
tb_confirmatory _offered	Indicates whether individual is offered TB testing by provider	Binary	0=No, 1 =yes
patient_referred _for_sample	Indicates whether individual is referred for sample provision at another site	Binary	0=no referral, 1 = referral
patient_reached _sample_site	Indicates whether individual reaches sample provision site	Binary	0=Does not reach site, 1 = Reaches site where sample can be collected
conf_test	Indicates the type of confirmatory test used to test individual	Text	None, xpert, smear, other
spec_conf	Specificity of the confirmatory diagnostic individual is tested with	Float	-
sens_conf	Sensitivity of the confirmatory diagnostic individual is tested with	Float	-
rif_sens	Sensitivity of the rifampicin drug resistance test	Float	-
rif_spec	Specificity of the rifampicin drug resistance test	Float	-
conf_sample _provided	Indicates whether individual provides a sample for testing	Binary	0=No sample, 1 = sample provided
conf_initial_ sample_provided	Indicates whether individual is able to provide a sample at first sample collection attempt	Binary	0=No, 1=Yes
conf_sample_status	Indicates whether sample is provided and how many attempts were needed to acquire it	Numeric	0=No sample, 1 = initial collection attempt, 2 = second collection attempt
conf_sample_tested	Indicates whether sample arrives as lab and is tested	Binary	0=Not test, 1 = tested
conf_sample_referred	Indicates whether the sample is referred to another site for testing	Binary	0=Not referred, 1 = referred
conf_sample_result	Result of confirmatory test test. Either TB positive, TB negative or no results	Binary	0=TB Negative, 1= TB positive, NA = no screening result
patient_conf_ result_received	Result which the individual receives. Either TB positive, TB Negative or no results	Binary	0=TB Negative, 1= TB positive, NA = no screening result
conf_res_same_ encounter	Indicates whether the result was received in the initial testing visit	Binary	0=No, 1=Yes
emp_notification	Indicates whether individual received an empiric TB notification (i.e test result is negative but clinically it is decided that TB is present)	Binary	0=No, 1=Yes

When simulating each new diagnostic scenario, different model input parameters need to be altered to so as to impact the diagnostic algorithm. Table 7 below highlights which parameters are changes and to what value for each scenario. Notably, within this table, any parameter written as "baseline" remains unchanged. Further, these parameter values are applied across HIV and TB groups.

Table 7: Parameter value changes per scenario

Parameter	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
p_patient_referral	baseline	baseline	0	baseline	baseline	0
p_xpert	1	1	1	1	1	1
p_smear	0	0	0	0	0	0
p_sample_referral	baseline	0	0	baseline	0	0
p_test_offered	baseline	baseline	baseline	0.95	0.95	0.95
p_no_sample *	baseline	baseline	baseline	0	0	0
xpert accuracy **	sputum	sputum	sputum	swab	swab	swab
* The use of swab only affects those without extrapulmonary TB as more invasive samples are required for this diagnosis in all cases						
** Swabs only affect Xpert accuracy in cases which are not extrapulmonary TB						

Appendix B BASELINE TRANSMISSION MODEL

This appendix provides extra information and results related to the dynamic analysis. This includes further detail and visualisation on the World Health Organisation's (W.H.O) TB estimate data, specific details of the baseline transmission model (including parameter values and model equations), information on the calibration process and results from the sensitivity analysis.

B.1 World Heath Organization TB estimates

Figures 6 and 7 visualise key components from the W.H.O's TB estimate data which have been used to provide additional information during the transmission model development. Figure 6 provides the mean estimates over time for the number of new cases (incident cases), the calculated estimates of the number of detected cases (as a product of case detection rate and incident cases) and the total number of TB related deaths. Figure 7 highlights the estimated percentage of case fatality and case detection rates over time. Notably, the mean estimate of incidence is used as the calibration data for the baseline model (Section B.3).

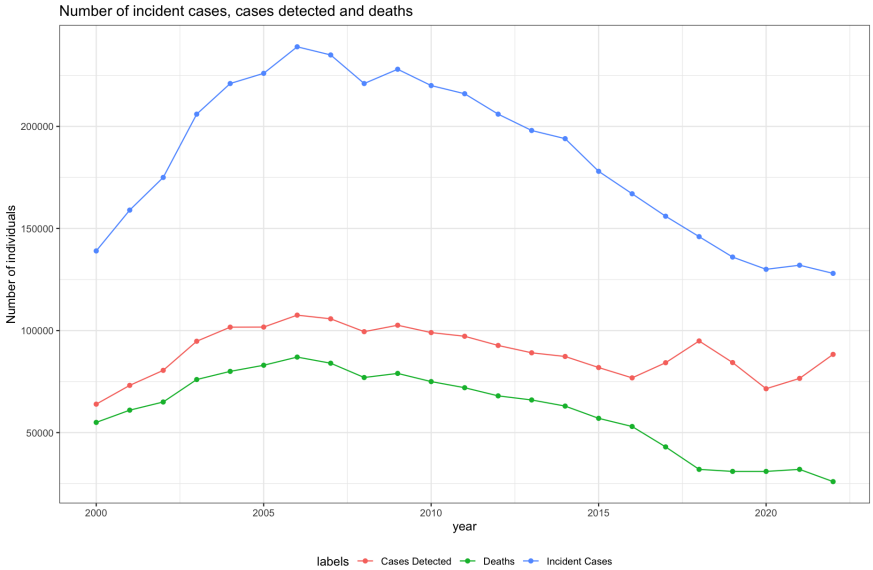


Figure 6: Mean estimates of incident cases, detected cases and deaths for Kenya between 2000-2022

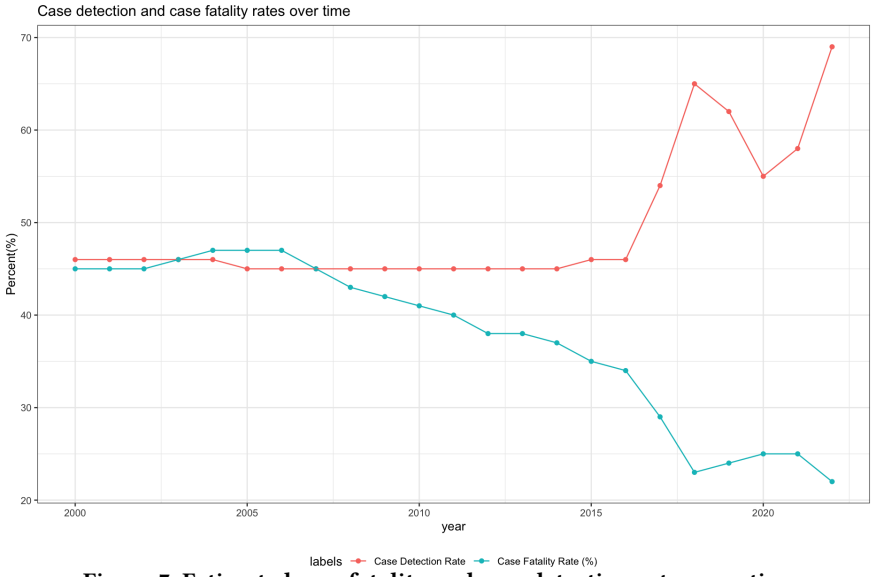


Figure 7: Estimated case fatality and case detection rates over time

B.2 Model Components

This section of the appendix fully describes the baseline transmission model components - namely the stocks, flows and variables within the Vensim model (Tables 8 and 9). These tables provide relevant component descriptions, values, equations, units, initial conditions and any parameter sources.

Table 8: Model stocks and flows - description, formulae, values and units

Model Component	Description	Type	Formula	Initial conditions and units
Susceptible	The number of individuals who have never been infected with TB	Stock	Births - Infection - deaths S	**IC:** 3.8e+07-*initial incident-initial latent -initial detected* **Units**: People
Latent TB infection	Individuals infected with TB, but are not infectious or symptomatic	Stock	Infection - progression - deaths L	**IC:** *Initial Latent* **Units:** People
Active	Individuals with TB disease who are symptomatic and infectious	Stock	Progression + relapse - Detection - deaths TB - deaths A	**IC:** *Initial Incident* **Units:** People
Detected and Treated TB	Individuals who have been diagnosed and treated for TB	Stock	Detection - Relapse - deaths T	**IC:** initial detected **Units:** People
Cumulative Cases	The total number of new active tb cases over time	Stock	Progression	**IC:** 0 **Units:** People
Total TB deaths	Number of individuals who have died from TB disease	Stock	deaths TB	**IC:** 0 **Units**: People
Total Pop	Total number of living individuals	Auxiliary	Active + Detected and Treated TB + Latent TB infection + Susceptible	**Units:** People
Births	Number of births each month	Flow	Birth rate * Total Pop	**Units:** People/Year
Infection	Number of susceptible individuals infected with TB each month	Flow	Transmission rate *Susceptible * (Active/ Total Pop)	**Units:** People/Year
Progression	Number of individuals infected with TB who progress to active TB each month	Flow	DELAY1(Latent TB infection, progression time)* progression rate	**Units:** People/Year
Detection	Number of individuals diagnosed and treated for TB each month	Flow	Active*CDR	**Units:** People/Year
Relapse	Number of previously diagnosed individuals who acquire active TB again per month	Flow	Detected and Treated TB * relapse rate	**Units:** People/Year
Deaths TB	Number of individuals with active TB who die as a result of TB per month	Flow	Active*CFR	**Units:** People/Year
Deaths S	General deaths in the susceptible population per month	Flow	Susceptible* general mortality	**Units:** People/Year
Deaths L	General deaths in the latently infected population per month	Flow	Latent TB infection * general mortality	**Units:** People/Year
Deaths A	General deaths in the active TB population per month	Flow	Active* general mortality	**Units:** People/Year
Deaths T	General deaths in the diagnosed and treated population per month	Flow	Detected and Treated TB * general mortality	**Units:** People/Year

Table 9: Model Parameters - description, values and source

Model Component	Description	Value or Equation	Units	Source
Birth rate	The yearly birth rate per individual	0.028	1/Year	Yearly crude birth rate per 1000 people in 2021 [1]
General mortality	The monthly crude death rate per individual	0.008	1/Year	Yearly crude death rate per 1000 people in 2021 [2]
CFR	The yearly rate at which individuals with active TB die	0.45+RAMP(-0.015, 2007 , 2022)	1/Year	Developed using WHO mean estimates on yearly case detection rate (approximated with a ramp function)[16]
Transmission Rate	Rate at which a susceptible individual may interact with and be infected by an individual with TB	0.368	1/Year	Calibrated
Progression Time	The time delay between individuals with latent TB moving to active TB	3.966	Year	Calibrated
Progression Rate	The rate at which an individual with latent TB moves to having active TB	0.156	1/Year	Calibrated
CDR	The rate at which individuals with active TB are diagnosed	SMOOTH(0.46+RAMP(0.022 , 2016 , 2021), 2)	1/Year	Developed using WHO mean estimates on yearly case detection rate (approximated with a ramp function)[16]
Relapse rate	Rate at which a person who has previously been treated with TB experiences diseases reactivation	0.004	1/Year	Calibrated
Initial Latent	The starting number of individuals with latent TB in the model	988 381	People	Calibrated
Initial Incident	The starting number of individuals with active TB in the model	1 971 009	People	Calibrated
Initial detected	Initial number of individuals being treated with TB	215 000	People	Calculated from WHO estimate data

B.3 Model Calibration

The model calibration process looks to define the appropriate values for six parameters, namely the: transmission rate, relapse rate, progression rate, progression time, initial incident value and initial latent value. Through calibration it is expected that the simulated results will match, as closely match as possible, the reference or calibration data. In this project, the calibration data is the WHO's estimates on TB incidence (new cases) in Kenya between 2000-2022. During calibration a value range and initial guess is chosen for each parameter. These are then used as inputs to Python's "scipy.optimise.minimise" function. A further input to this process is an error function which is used to determine the difference between the calibration data and the simulated results. This error has been simply defined as the sum of square differences between the reference incidence data and the model's "progression" data over the given time-frame. Calibration was conducted against all three W.H.O incidence estimates (lower, mean and upper) and calibration values were produced in each case. Table 10 provides a full summary of each parameter, its description, the initial guess and value range and the final calibration values determined. While the mean calibration value is used for all experiments, the lower and upper bound values are shown to provide an uncertainty range for these estimates.

Table 10: Calibration set-up and results

Parameter	**Description**	**Initial guess and calibration Range**	**Calibration Result** mean (lower-upper)
Transmission Rate	Probability of susceptible individual being infected with TB given an interaction with someone with active TB disease	0.05 (0,0.1)	0.368 (0.62 - 0.373)
Relapse Rate	Rate at which a person who has previously been treated with TB experiences diseases reactivation	0.1 (0.004,0.1)	0.004 (0.004-0.004)
Initial incident	The starting number of individuals with active TB in the model	100 000 (1, 3 000 000)	1 971 009 (123 501 - 3 000 000)
Progression rate	The rate at which an individual with latent TB moves to having active TB	0.08 (0,0.2)	0.156 (0.2 - 0.139)
Initial latent	The starting number of individuals with latent TB in the model	100 000 (1, 3 000 000)	988381 (277 566 - 2 991 882)
Progression Time	The delay time (in years) between individuals moving from the Latent to Active TB compartments	2 (1,5)	3.966 (3.895 - 5)

B.4 Equilibrium and Stability Analysis

This section presents the stability analysis conducted for the baseline model. The relevant parameters and differential equations needed to describe the change in each stock are listed below (Equations 1-5). A visualisation of the stock values over an extended time-frame (up to the year 3000)is provided in Figure 8. Further, Table 11 provides an excerpt of data points over the last 50 years of the considered time-frame.

Let:

S(t) = S = Susceptible
L(t) = L = Latent TB
A(t) = A = Active TB
T(t)=T=Detected and treated TB
N(t)=N= Total Population

b= birth rate = 0.028
μ = general mortality = 0.008
β = Transmission probability = 0.368
p = Progression rate = 0.156
d = Progression time = 3.966
γ = Case Detection Rate = 0.57 (after 2021)
r = relapse rate = 0.004
m = TB mortality = 0.225 (after 2021)

$$N = S + L + A + T \tag{1}$$

$$\frac{dS}{dt} = bN - \mu S - \beta\left(\frac{SA}{N}\right) \tag{2}$$

$$\frac{dL}{dt} = \beta(\frac{SA}{N}) - \mu L - pL(t-d) \tag{3}$$

$$\frac{dA}{dt} = pL(t-d) - (\mu + m + \gamma)A + rT \tag{4}$$

$$\frac{dT}{dt} = \gamma A - (\mu + r)T \tag{5}$$

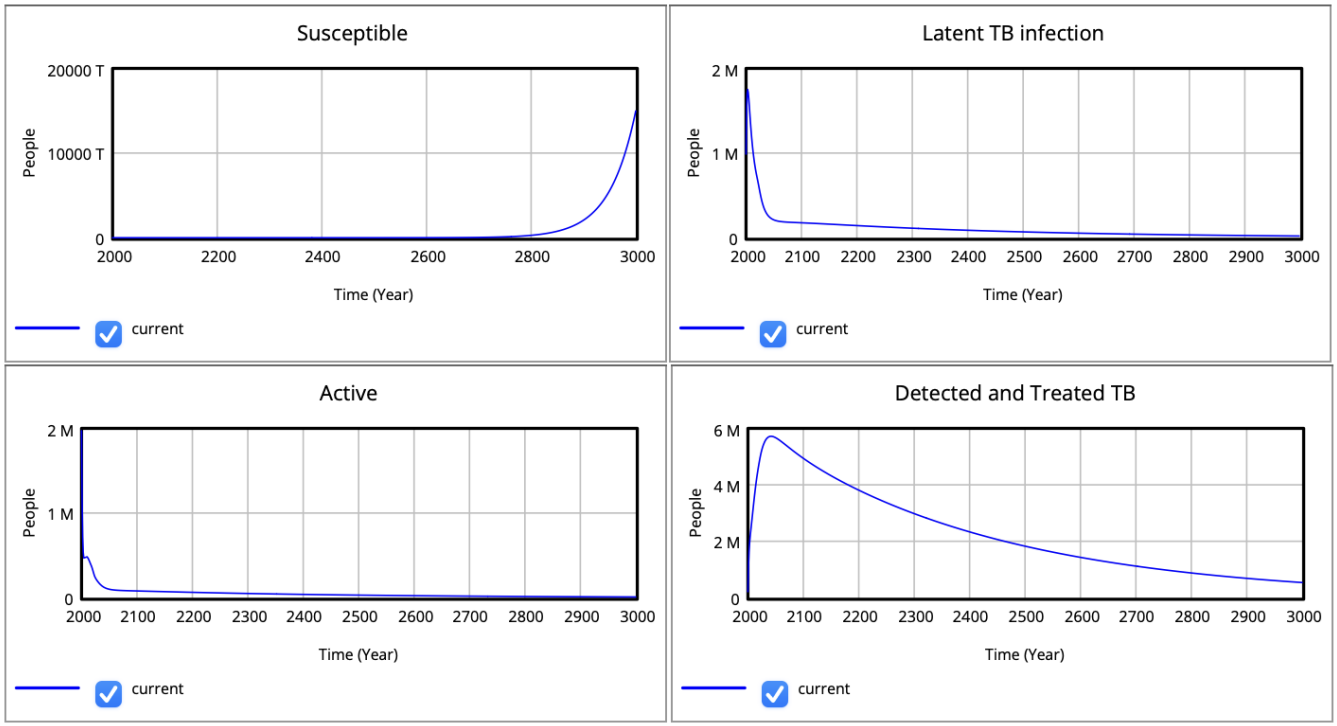


Figure 8: Extended time frame baseline simulation used to explore equilibrium and stability

Table 11: Data excerpt of stock values between the years 2950 - 3000

Year	Susceptible	Latent TB Infection	Active	Detected and Treated TB
2950	5.56 x 10^{15}	23 009	10 189	607 639
2960	6.78 x 10^{15}	22 453	9942	592 959
2970	8.26 x 10^{15}	21 911	9702	578634
2980	1.1 x 10^{16}	21 382	9468	564 655
2990	1.23 x 10^{16}	20 865	9239	551 013
3000	1.5 x 10^{16}	20 361	9016	537 701

B.5 Sensitivity Analysis

This section presents the results of the sensitivity analysis in the form of a Tornado plot, and plots of the first-order and total Sobel indices for the time points 2005 (peak incidence) and 2015 (when incidence is declining).

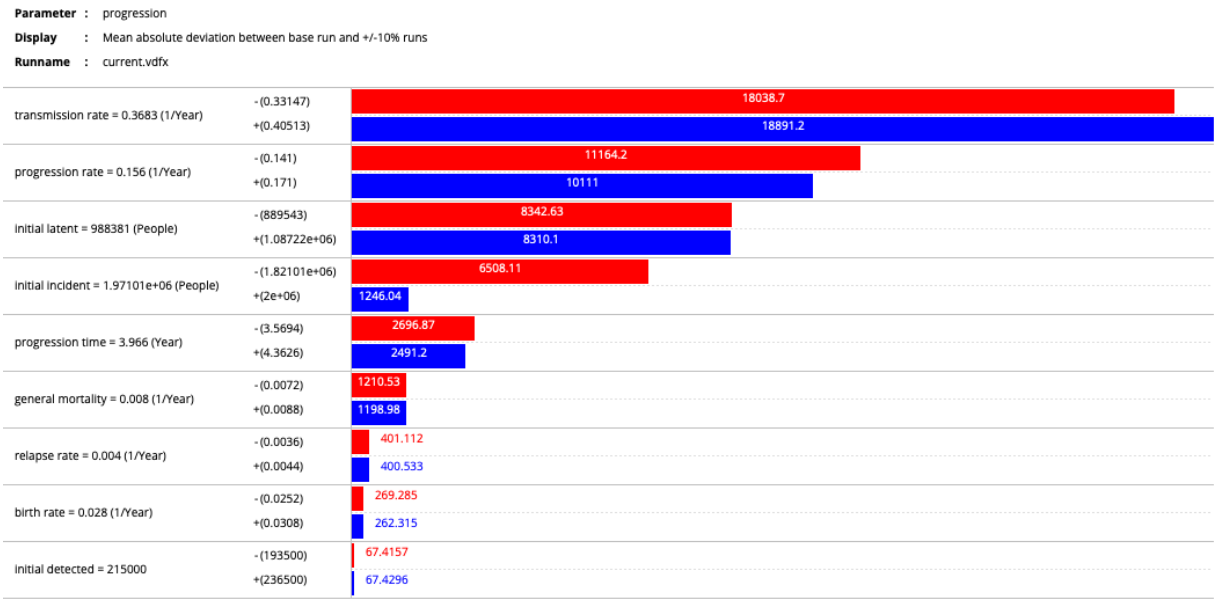


Figure 9: Tornado plot representing the impact of varied model parameter values on the model flow *progression*

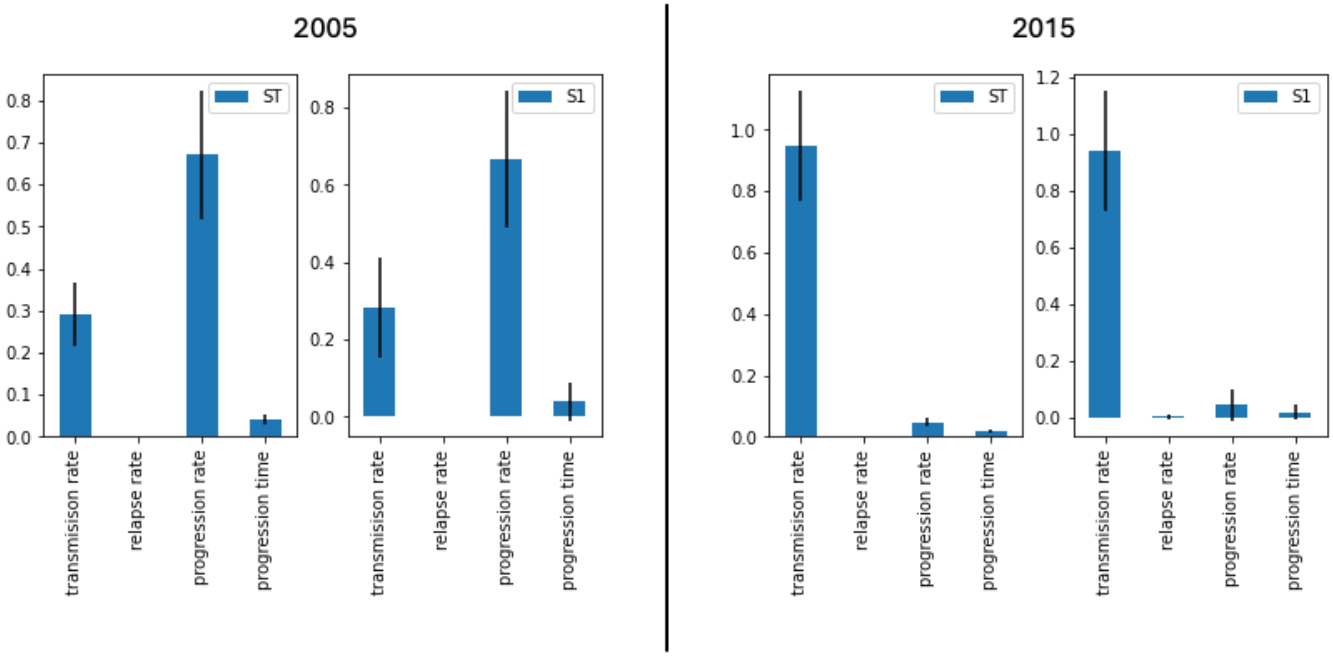


Figure 10: Plots of the of the first-order Sobel indices and total Sobel indices for the *progression* flow for 2005 and 2015

B.6 Experiment 1: Results

This section presents the results from Experiment 1. In this experiment, the impact of increasing CDR and its effect on the number of cases and deaths over a two-decade period is explored. These results are presented in Table 12 and highlight that as CDR increases, the total number of deaths and cases decrease as compared to the baseline scenario. Further, for the scenario for 100% CDR, the number of cases and deaths in 2041 is reduced 70.5% and 72.9% respectively. While this is a significant reduction, it is important to note that even with a 100% CDR rate (i.e all individuals with active TB are diagnosed and treated) TB would not be eliminated over the next two decades.

Table 12: Experiment 1: Simulated TB deaths, deaths averted, cumulative cases, cased averted and the percentage change in deaths and cases in the final year of simulation for different CDRs

Scenario (CDR increase)	Case Detection Rate (%)	Total TB Deaths	TB deaths averted	TB deaths 2041 (% change from baseline)	Cumulative Cases	Cases Averted	New Cases in 2041 (% change from baseline)
Baseline	57	463 512	-	2190 (0%)	5 583 870	-	43 965 (0%)
5%	62	457 437	6 075	1825 (-16.7%)	5 523 370	60 500	37 427 (-14.9%)
10%	67	452 332	11 180	1542 (-29.6%)	5 470 900	112 970	32 015 (-27.18%)
20%	77	444 275	19 237	1138 (-48%)	5 384 670	199 200	23 660 (-46.2%)
30%	87	438 246	25 266	872 (-60.2%)	5 317 040	266 830	17 596 (-60%)
40%	97	433 593	29 919	689 (-68.5%)	5 262 790	321 080	13 053 (-70.3%)
43%	100	432 401	31 111	646 (-70.5%)	5 248 570	335 300	11 910 (-72.9%)