Optimising the implementation of Tuberculosis Diagnostics in Kenya

An exercise in mathematical modelling and simulation

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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) [11, 12]. 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 [11, 12]. 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 [17, 18]. Furthermore, collecting sputum-samples for TB testing can be difficult for both the patient and the healthcare provider [18]. 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 [18]. As such, this has prompted a global call to develop new TB tests with the potential to 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, 13].

However, as these 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 they would be feasibly implemented in countries that have a range of TB diagnostics and infrastructure already in place [10]. 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) (that is, compared to the number of individuals likely to be diagnosed given the current infrastructure and patient journey followed when seeking care for TB symptoms). This process will require the simulation of the implementation of new diagnostics to different degrees and for different populations to review their impact on the overall patient pathway. Scenario results will then be 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 does combining future tuberculosis diagnostics (as described by the World Health Organization's 2024 Target Product Profile) with existing tuberculosis diagnostic tests (like smear-microscopy and GeneXpert) have on the number of individuals correctly diagnosed 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 impact the number of incorrectly diagnosed individuals (for example false positive or false negative results)?
- 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?
- How may more diagnoses could be expected from these new diagnostic combinations over time as compared to the standard of care?

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 [20]. 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 [9] 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 [9]. 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 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 facility or centralised lab) and how quickly results can be returned (same visit or at another visit). Using this information, other pre-print work conducted has developed a baseline agent-based model for Kenya's patient pathway, with the potential to replace all diagnostics with a single-novel diagnostic at different performance levels [4]. While this model has been used to help define the minimum performance criteria required of these novel tests, it could be further adapted to consider combinations of diagnostics, each with different coverage levels or aimed at different target groups. Using models of this type, different scenarios can be simulated (with multiple iterations to consider stoachsticity), with the results then being aggregated and key outcome variables subsequently calculated.

Given a set of scenarios and outcome results, it becomes important to consider how to evaluate or determine the optimal case as compared to SoC. In the context of healthcare, and TB as a part of this, there must frequently be a consideration of heath-care interventions to save-lives (in this project to achieve a large number of individuals diagnosed) and cost. If interventions are too expensive relative to available budget they become infeasible to implement and should not be considered. One methodology for considering this is the cost-effectiveness analysis, where the cost per correct diagnosis from both the patient and healthcare provider can be considered, as was done in this TB study for reviewing the currently available GeneXpert tests [22]. In this work, alternative interventions are compared based on different willingness-to-pay thresholds, where any scenario with a cost per patient above the threshold is excluded. Frequently, these types of analyses are also presented on the cost-effectiveness frontier which provides an indication of how much more effective one intervention is over another, while highlighting the difference in cost to move to that intervention [6].

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 [3, 5, 16]. 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) [5]. Further, there is the potential for recovered individuals to relapse (or become reinfected) [5]. 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 [5].

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 [3]. In this paper, the most significant focus has been placed on elements of diagnosis [3]. 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)[3]. 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[16]. 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 [16]. 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 stuff

3 METHODOLOGY

3.1 Static Analysis: Optimising TB Diagnostics

3.1.1 ***TB diagnostic standard of care in Kenya.*** Kenya is noted as one of the W.H.Os 30 countries with high TB burden, high HIV/TB co-infection and high rates of drug resistant TB. This highlights the need to find new ways of utilising available resources (like diagnostics) to have the largest impact. To understand the impact of different diagnostic implementations, it is necessary to understand what the current standard of care looks like. Kenya uses two main test types for TB diagnosis - these are the GeneXpert or the less accurate smear microscopy (if access to molecular testing through GeneXpert is unavailable)[7]. Notably, in 2019 it was estimates that 47% of individuals were tested with GeneXpert [21]. Further, in a large proportion of cases, TB testing occurs centrally - that is, at a site other than the initial one that a patient may seek care at[7]. This means that either a sample is collected from the patient and transferred to a laboratory for testing (if there is a sample referral system in place), or, the individual is required to make a visit to a different site/laboratory where testing can be accessed. As an important note, every time a new visit is required, there is potential for the individual to become lost from care as a result of external barriers (for example cost, being away from work or challenges with transport)[14]. Lastly, although tests like GeneXpert can be conducted in a short time frame (<2hours) testing and the return of results generally does not occur on the same day as sample collection.As such, individuals will need to make a subsequent visit to return to the relevant site and receive their diagnosis. This information is then used to define and model a baseline TB diagnostic journey for individuals in Kenya.

3.1.2 ***Baseline Patient Pathway Model.*** To determine the optimal implementation of TB diagnostics in Kenya, it is necessary to have baseline results to evaluate against. These results are generated through an adapted version of the patient pathway model described in [4]. The patient pathway model maps out, using a decision tree format, an individual's journey through the healthcare system from the point at which they develop TB symptoms up until diagnosis or becoming lost from care. Within the decision tree, branch probabilities represent the likelihood of an individual following a specific sub-pathway. This allows for patient pathways to be made up of different test types and number of visits and for some patients to be lost from the system along the way. The model also allows for different groups of individuals to have higher likelihood of following one pathway as compared to another. These groups are dependent on HIV status (positive or negative) and TB status (pulmonary or extra-pulmonary). HIV is included as a factor in this model given the high rates of HIV/TB co-infection in many countries and the adverse effects that untreated HIV can have on TB outcomes. This original model which simulated TB diagnosis in Kenya has been adapted in several ways for this work.

The most significant adaptation is that the model structure has been changed to represent a more generalised TB patient pathway model that can be made country specific using the branch parameters (Appendix A: Figure 3). The generalised model is a key contribution to this work as it will allow for multiple countries to be rapidly modelled in the future using the same structure and inputs and having the same standardised output set.Further, the model it set-up 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 future experimentation. Overall, these adaptations will allow for easy analysis and comparison between different countries, diagnostics and diagnostic algorithms. Further, this generalisation included structurally re-coding the model in R-studio to rapidly speed-up simulation time. The key adaptation which will be used in this work is to allow for different diagnostics (and their overall effect on the diagnostic algorithm) to be compared.

3.1.3 ***Baseline Simulation for Kenya.*** To simulate the baseline results specifically for the Kenyan context, the developed generalised model is then parameterised using relevant values sourced from the literature. These have initially been described in [4] but are summarised in Appendix A: Table 2. Notably, these parameters are calibrated to ensure that in the model's baseline, the percentage of individuals with TB correctly diagnosed matched the WHO's TB case detection rate for Kenya at that time (57% in 2021) . 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=20) of the baseline TB diagnostic pathway in Kenya are run. Multiple iterations are performed to allow for stoachsticity 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.

3.1.4 ***Baseline Data Structure and Analysis.*** 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 3.

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 variables which are calculated are related to the patient care cascade and are used to show the number of individuals with TB who reach key cascade 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 case detection rates (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 consider those 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
- Do 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 then calculated to produce a single set of variables for all baseline simulations. A cascade visualisation of this baseline data is shown in Figure 1. This baseline data will act as the comparator against which new diagnostic implementations will be evaluated.

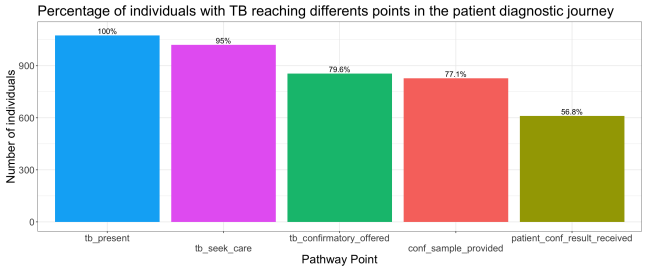

Figure 1: Visualisation of the number of individuals with TB reaching key points in the baseline TB diagnostic pathway

3.1.5 ***Experimental set-up: Optimal diagnostic implementations.*** While there is significant development of new TB diagnostics occurring, currently, the mostly widely used and available diagnostics are those like the GeneXpert test. However, even if only this diagnostic is considered, there are multiple ways in which it can be implemented. Each of these implementation scenarios could result in improved case detection rates in Kenya, as compared to the considered baseline, but would require significant investment in additional GeneXpert machines. For this analysis, the potential impact of GeneXpert under different usage scenarios is considered. In each case, an element of implementation either improves the number of correct results being generated (through a more accurate test) or increases the number of individuals accessing testing and results (by reducing the number of facility visits required). These scenarios are described, alongside their potential impact on baseline, in Table 1 below. These scenarios are simulated using the developed model by changing certain parameters - a list of which is provided in the Appendix (Table 4). With these parameters, the same simulation and analysis process as described for the baseline is followed. The calculated cascade data for each scenario, along with the case detection rates, are then compared against the baseline situation to determine each scenario's relative impact. The determined case detection rates for each scenario are also subsequently used as inputs into the long-term impact analysis described in Section 3.2.

3.2 Dynamic Analysis: 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 predict future changes in transmission, detection and treatment of TB into the future. These baseline results are then used as a comparator against which new interventions are evaluated. The baseline model development and experimental set-up is described below.

3.2.1 ***Historical TB data in Kenya.***

To develop an appropriate transmission model, it is useful to have an understanding of any past TB data that may be available. In this case, data from the W.H.O is available for Kenya between 2000 - 2022 [15]. Key data variables include estimates (lower,mean and upper) of incidence for all cases, incidence in the HIV population, number of deaths, case detection rate and case fatality rates. These pieces of data will be used for paramaterising and calibrating the transmission model. Notably, for the variables of interest there are no missing data elements that need to be accounted for. Key visualisation of this data are presented in the Appendix - these include a plot of the three estimates of incidence as well as a plot of the mean case fatality and case detection rates (Figures 4 and 5).

3.2.2 ***Baseline Transmission Model.***

A stock-and-flow diagram (SFD) representing the developed baseline transmission model is presented in Figure 2. This SFD represents a simplified TB transmission model utilising key model components described in the literature [3, 5, 16]. The model is developed in Vensim [19], 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. An additional stock is included to track the cumulative number of new cases over time. 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 timestep.

Table 1: Modelled GeneXpert implementation scenarios

Scenario	Description	Test Type	Testing Location	Turnaround time of results	Impact on Baseline
Baseline	Individuals tested through either GeneXpert or smear. Testing can occur onsite but is predominantly centralised and perfromed offsite. Test results are provided at subsequent visits.	GeneXpert and Smear	Mix of onsite and offsite (centralised)	Subsequent visit	N/A
1	Individuals tested through GeneXpert. Testing can occur onsite but is predominantly centralised and perfromed offsite. Test results are provided at subsequent visits.	GeneXpert	Mix of onsite and off site (centralised)	Subsequent visit	Testing occurs fully with GeneXpert, as opposed to a proportion with smear microscopy, hence a greater number of correct results will be generated.
2	Everyone receives a decentralised GeneXpert. Results provided at subsequent visits	GeneXpert	Onsite (decentralised)	Subsequent visit	A greater number of correct results are generated. Further, all sites have testing capacity, hence fewer people are lost from care as a result of needing to attend another facility.
3	Everyone receives a decentralised GeneXert and gets result in same visit	GeneXpert	Onsite (decentralised)	At testing visit	A greater number of correct results are generated. All sites have testing capacity, hence fewer people are lost from care as a result of needing to attend another facility. All results are available at the time of testing and a subsequent visit to collect results is not required.

These have been provided, alongside the relevant component descriptions and units, in Appendix B: Table 5.

The model equations also make use of parameters which define various model 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 literature while others have been defined through the calibration process (Appendix B: Table 6. 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. 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. This is needed to have confidence that the conclusions drawn from subsequent experiments will be applicable in the real-world. Further details on the calibration process can be found in the Appendix: Section B.3. Overall, using the SFD and corresponding equations and parameters, the baseline transmission model can be reproduced in Vensim. Lastly, 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 new cases is used during calibration, this flow has been chosen as the key variable considered during the sensitivity analysis. In this case, both Tornado plots in Vensim and Sobel indices in Python are used to conduct the sensitivity analysis.

3.2.3 ***Experimental set-up.*** Given the calibrated baseline transmission model, the simulation time horizon is then expanded. This is used to predict the magnitude of certain TB elements into the future. For this analysis, the time horizon is set to end at 2031 - 10 years post the model calibration point - and assumes no changes to any parameters in the model. Several components key to tracking the TB epidemic include the total number of new cases as well as the total number of TB related deaths. Using the baseline model, the magnitude of these components is noted for the year 2031. Following this, the model is then used to simulate the long term impact of the three scenarios described in Table 1. Here, the resulting simulated case detection rates from each scenario are used as inputs to the transmission model. In each scenario, the case detection rate determined from the static analysis is used as the case detection parameter in the transmission model, between 2021-2031 (i.e for the next 10 years). This is repeated for each scenario, with the corresponding time-series results then plotted. Using the Vensim plots, the difference in the total number of cases and deaths between each scenario and baseline at the end time-point is then analysed.

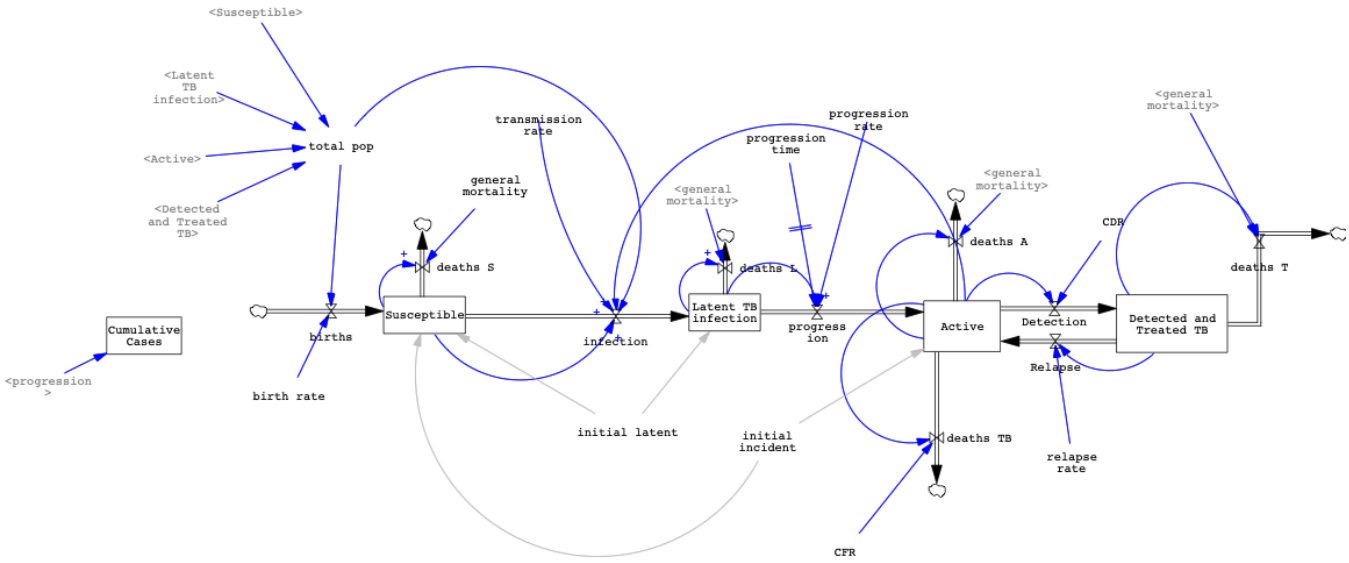

Figure 2: SFD representing the baseline TB transmission model

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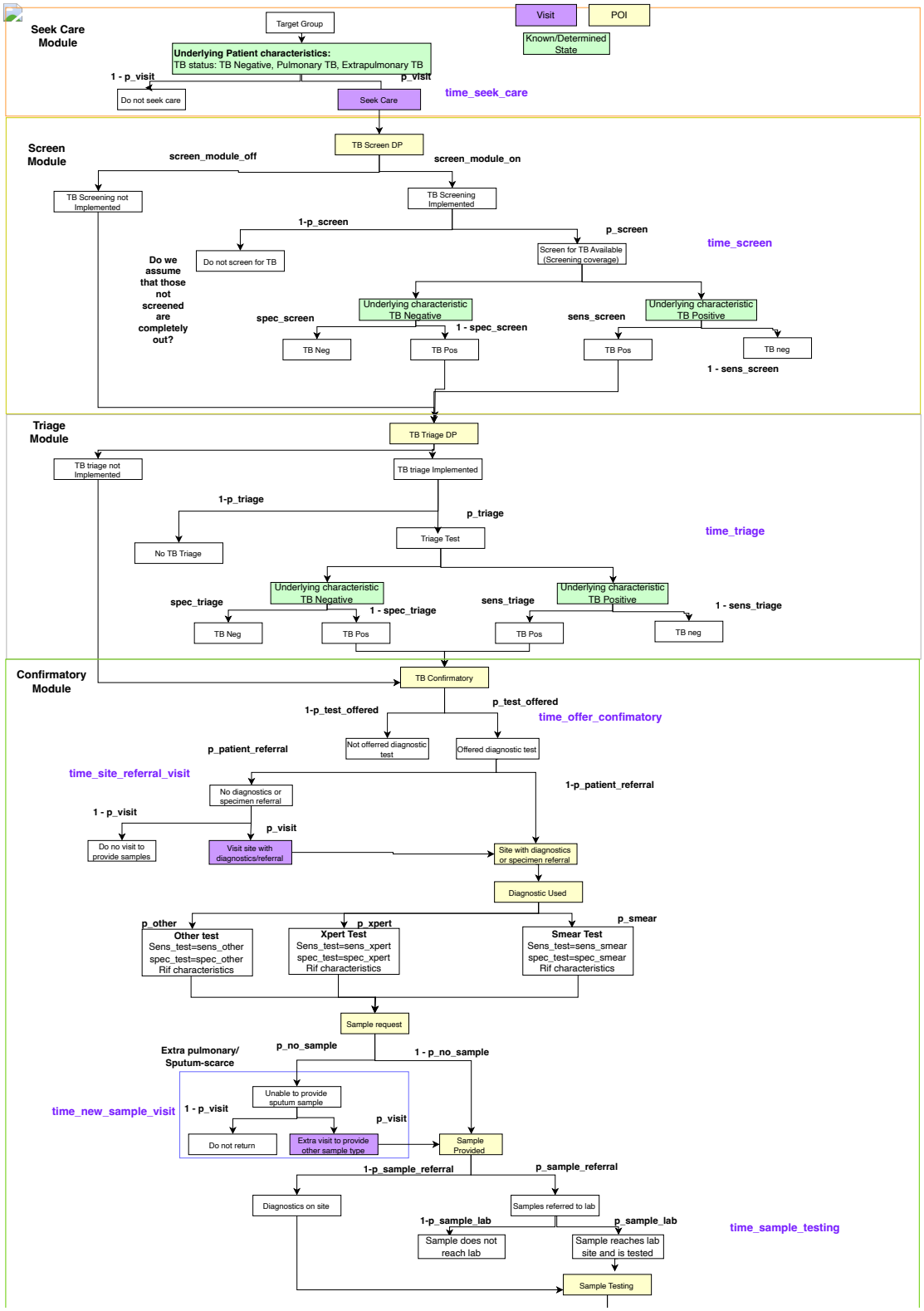
Appendix A STATIC ANALYSIS: OPTIMAL IMPLEMENTATION OF TB DIAGNOSTICS

This appendix provides further information and figures relevant to the static analysis which explores the impact of different diagnostic implementations on the number of individuals diagnosed. This is performed through a patient pathway decision tree model as visualised in Figure 3. The baseline parameter values are provided in Table 2 and Table 3 provides a description of each of the model output variables. Lastly, Table 4 describes which baseline parameters are changed, and to what value, for each simulated scenario.

Table 2: 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	0.84	0.84	0.84	0.84
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	0.85	0.81	0.82	0.82
spec_xpert	0.98	0.98	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 not screen for TB
Screen for TB Available (Screening coverage)
Do we assume that those not screened are completely out?
Underlying characteristic TB Negative
Underlying characteristic TB Positive
spec_screen
sens_screen
1 - spec_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
sens_triage
1 - spec_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
Not offerred diagnostic test
Offered diagnostic test
p_patient_referral
time_site_referral_visit
1-p_patient_referral
No diagnostics or specimen 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

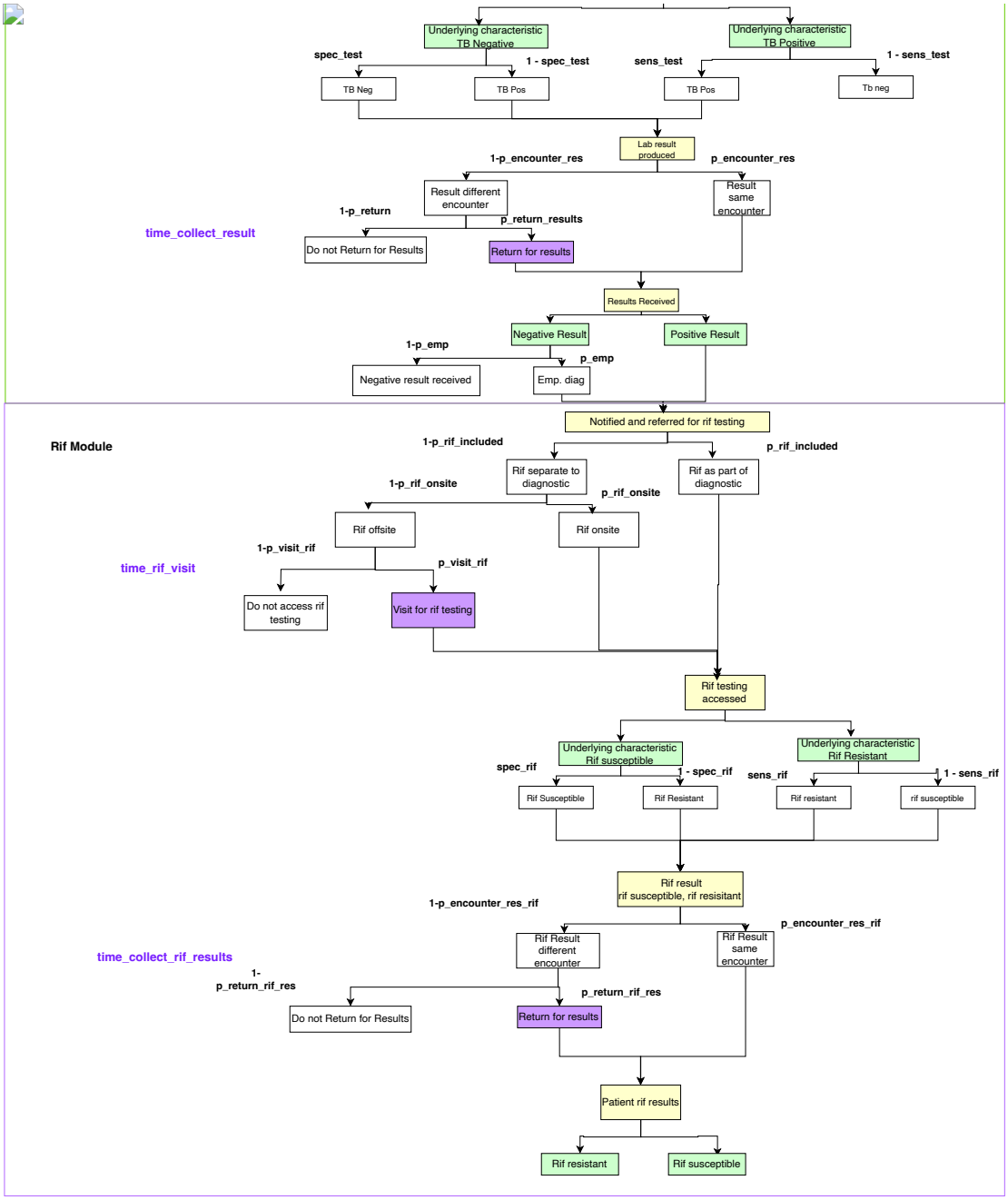


Figure 3: Generalised Patient Pathway Model

Table 3: 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 4 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 4: Parameter value changes per scenario

Parameter	**Scenario 1**	**Scenario 2**	**Scenario 3**
p_patient_referral	baseline	baseline	0
p_xpert	1	1	1
p_smear	0	0	0
p_sample_referral	baseline	0	0

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 4 and 5 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 4 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 5 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).

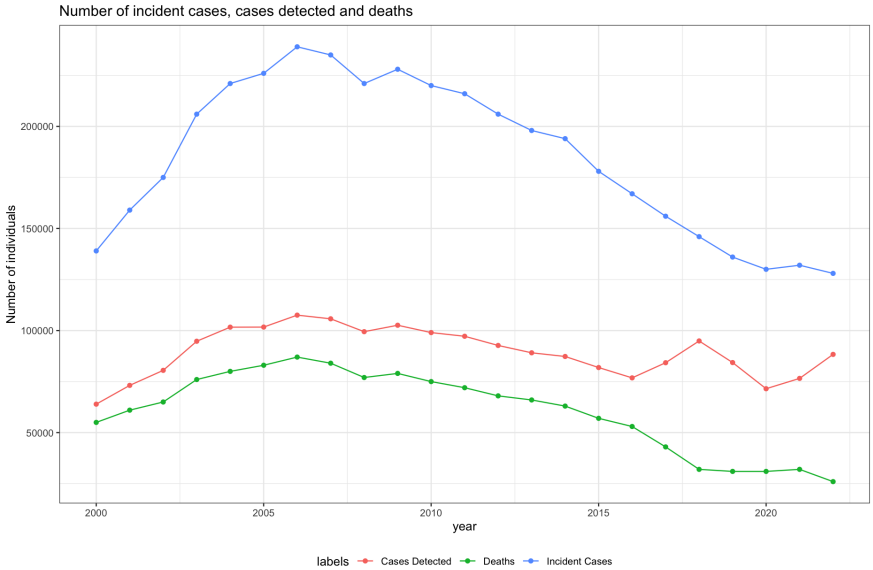


Figure 4: Mean estimates of incident cases, detected cases and deaths for Kenya between 2000-2022

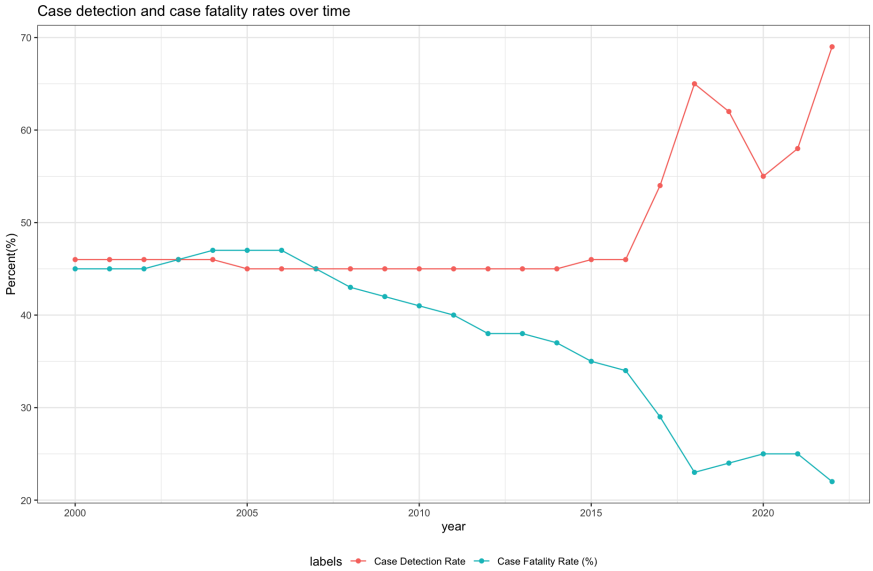


Figure 5: Estimated case fatality and case detection rates over time

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 5 and 6). These tables provide relevant component descriptions, values, equations, units, initial conditions and any parameter sources.

Table 5: 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* **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:** 55000 **Units:** People
Cumulative Cases	The total number of new active tb cases over time	Stock	Progression	**IC:** 0 **Units:** People
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/12)	**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 6: 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)[15]
Transmission Rate	Rate at which a susceptible individual may interact with and be infected by an individual with TB	0.3683	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	0.1559	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)[15]
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	988 380	People	Calibrated
Initial Incident	The starting number of individuals with active TB in the model	1 971 009	People	Calibrated

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 as closely match as possible the reference or calibration data. In this project, the calibration data is the WHO's mean 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. Table 7 provides a full summary of each parameter, its description, the initial guess and value range and the final calibration value selected.

Table 7: Calibration set-up

Parameter	Description	Initial guess and calibration Range	Calibration Result
Transmission Rate	Rate at which a susceptible individual may interact with and be infected by an individual with TB	0.05 (0,0.1)	0.3683
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
Initial incident	The starting number of individuals with active TB in the model	100 000 (1, 3 000 000)	1 971 009
Progression rate	The rate at which an individual with latent TB moves to having active TB	0.08 (0,0.2)	0.1559
Initial latent	The starting number of individuals with latent TB in the model	100 000 (1, 3 000 000)	988 380
Progression Time	The delay time (in years) between individuals moving from the Latent to Active TB compartments	2 (1,5)	3.966