Optimising the implementation of Tuberculosis Diagnostics in Kenya

An exercise in mathematical modelling and simulation

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ABSTRACT

Tuberculosis (TB) remains a threat to global health. Diagnostics assist in identifying and treating active TB and hence in reducing TB deaths and onwards transmission. Although new diagnostics are being developed, it is important to optimally implement currently available tools. A flexible framework to quantify the impact of different diagnostic implementations on TB case detection rates (CDRs) was developed. The implementation aspects considered were sample type, the testing site and the turnaround time of results. A transmission model was also developed to explore the long-term impact of each implementation scenario on the TB epidemic. The use of non-sputum samples in conjunction with molecular testing was seen to improve case detection rates (16.6 - 26.4% depending on implementation site and turnaround time) as compared to the standard-of-care. Within each sample-type, decentralised testing with rapid results saw the largest increase in CDR. The long-term analysis highlighted that implementation scenarios with higher CDRs resulted in more cases and deaths averted. However, it was also shown that even with high CDRs, scenarios focused only on active cases (as modelled here) would not eliminate TB. Fture work should consider the impact of screening the asymptomatic and latent TB population as well. Limitations of this work include that a full cost-effectiveness analysis to determine implementation feasibility was not conducted and that combination scenarios looking at simultaneous decentralised and centralised testing were not considered.

KEYWORDS

tuberculosis, diagnostics , patient pathway analysis, transmission modelling

GITHUB REPOSITORY

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

1 INTRODUCTION

Tuberculosis (TB) is an infectious disease with a significant impact on global health. 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 recorded in Lower Middle-Income Countries (LMICs) [18, 19]. Over the last two decades, these numbers have shown that while TB-related mortality has reduced (from approximately 2.4 million deaths to 1.6 million deaths), the estimated number of annual new cases has remained relatively stable. This highlights that while linkage to appropriate treatment has improved overall, there is still significant community transmission of TB.

A challenge to reducing TB transmission lies within patients being unable to access appropriate diagnostics and results (and subsequent treatment) in a timely manner. Frequently, this process is lengthy and complex, with patients having to make many (often expensive) facility visits to both provide samples for testing and to receive their results [14, 27]. Furthermore, collecting quality sputum-samples for TB testing can be difficult, especially for certain key populations (like children and individuals with HIV) [31]. These elements both contribute towards individuals falling out of care, not being diagnosed and treated and remaining infectious and at risk of death or other morbidity. This has prompted a global call to develop new TB tests, or to use available TB tests in innovative ways which: reduce the complexity of the current diagnostic pathway, use easier-to-collect samples (e.g oral swabs), bring results closer to patients and overall, increase the number of individuals being correctly diagnosed [11, 20].

However, while additional TB tests are still in the development pipeline, 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. This project aims to explore this knowledge gap by developing a framework which can be used to simulate a range of molecular diagnostic implementation scenarios. Kenya, a country on the W.H.O's list of 30 high TB burden countries, will be used as a case study [17]. Key factors which will be considered in these scenarios include molecular-testing (as opposed to smear-microscopy), sample-type in use, where testing occurs (decentralised at the facility or at a centralised lab) and how quickly results can be returned (at the testing visit or not). Scenarios will then be evaluated to determine which would diagnose the greatest number of individuals as compared to the current standard of care (SOC). Here the SOC represents the number of individuals likely to be diagnosed given the current infrastructure and patient journey followed when seeking care for TB symptoms, with the broad assumption that those diagnosed are put on treatment. A model representing this SOC has been produced in prior work [7], and will be further developed in this project. Further, a transmission model will be developed to look at the impact of these scenarios over time. Together, the simulated baseline data of these two models will then be used to evaluate the considered implementation scenarios to answer the following research question (RQ):

Research Question: *To what extent do different implementations of molecular testing change TB case detection rates and what impact do they have on 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 scenarios of diagnostic implementation change the percentage of individuals being correctly diagnosed with TB?
- Which implementation scenarios have the greatest impact on the percentage of 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 in Kenya, a further benefit to the model will be that it can serve as a generic framework for this type of analysis for other countries and for new diagnostics.

2 RELATED WORK

There are few recent analyses on the optimal implementation of TB diagnostics in Kenya that consider all combinations of test placement (centralised or decentralised), turnaround time of results (at testing visit or another visit) and different sample types (sputum or non-sputum). This work aims to contribute towards this knowledge gap by using two types of simulation models. The first of these takes the form of a patient pathway analysis (PPA) which is used to review, for a cohort of symptomatic individuals, the impact that different diagnostic implementations have on the percentage of individuals being correctly diagnosed (and treated) as compared to the SOC algorithm. The second analysis uses the results of the patient pathway analysis as inputs to a transmission model. This model is then used to review the relative impact each scenario has on the TB epidemic over time. Other work related to the use of these types of analyses in the context of TB, as well as work focused on these types of implementation factors, are described below.

PPAs present a useful framework for reviewing the impact of different healthcare diagnostic or treatment options on an outcome of interest. These types of analyses attempt to illustrate patient care-seeking behaviour and subsequent service accessibility by mapping out the journey and healthcare visits made by patients when attempting to receive care [33]. These types of analyses are frequently performed in the context of TB to highlight service delivery gaps requiring intervention. Recent work by [7, 13] 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 at, the percentage of facilities which have access to diagnostics, the likelihood of a patient accessing a site with diagnostic availability at their first visit and finally the types (and coverage) of diagnostics in use. By capturing these concepts with recent data, a national "average" patient journey from TB symptoms to diagnosis can be developed. This journey can be used to track the number of visits required to receive the diagnosis, incorporate differences between key populations (e.g HIV positive) and highlight key points at which patients are lost from care.

Prior work conducted has developed a baseline stochastic agent-based model representative of Kenya's SOC patient pathway[7]. While the model has been described elsewhere in depth, briefly it looks to simulate the potential pathways that individuals of different key populations(e.g HIV+ or those with extra-pulmonary TB) could follow when seeking care. Further, it estimates the percentage of these individuals who are either lost from care or who receive a diagnosis given the different novel tests considered. This model will be adapted and further developed to consider alternative diagnostic scenarios. In terms of scenarios, three key attributes described in the the W.H.O's latest TB diagnostic Target Product Profile (TPP) - a document describing the minimum requirements for novel tests[22] - will be considered. These three implementation aspects are sample-type (non-sputum vs sputum), the site at which testing is taking place (decentralised at the facility or at a centralised lab) and turnaround time (same testing visit or at another visit).

While there is limited research comparing all three diagnostic implementation attributes described here, other work looking at centralised vs decentralised (or point-of-care (POC)) testing has been conducted. Pooran et al conducted a comparison between centralised GeneXpert MTB/RIF (a widely used molecular test), decentralised GeneXpert MTB/RIF and decentralised smear-microscopy and considered diagnosis rates and costs per test across sites in several countries [3, 26]. Key results highlighted that compared with smear microscopy, decentralised POC GeneXpert had on average a percentage increase of 11.7% in the number of individuals diagnosed and started on treatment. Further, in the baseline scenarios considered, decentralised GeneXpert testing was estimated to be more expensive than centralised GeneXpert testing ($28.00 and $23.00 respectively) however test volumes were noted to play a significant role in these costs. Further, work by Sohn et al highlighted that decentralised GeneXpert would likely diagnose individuals with TB quicker and result in fewer TB infections being seen over time as compared to centralised GeneXpert (15 infections averted per 100,000 individuals) [29]. Similarly, this work highlighted that decentralised testing with GeneXpert would likely be more expensive that centralised testing, but again total cost and implementation feasibility would be dependent on test volumes at decentralised sites. In terms of sample type used with molecular testing, there has been a new drive to explore alternative options to sputum - one of which would be tongue swabs. However, given that these are only recently being considered in greater depth, initial research has focused first on determining test performance relative to sputum. As such, at the time of writing, although many articles define the likely ease of use and accessibility improvements that non-sputum samples may introduce, no articles on the implementation or cost-effectiveness of tongue swabs were found.

To add to the PPA, it is also useful to explore the impact of different diagnostic implementations on the TB epidemic over time. Exploring disease dynamics in this way is frequently done through transmission modelling, and there are many examples of these in the context of TB. Generally, each TB transmission model tends to have its own level of complexity and area of focus [4, 8, 24]. Within these examples, there are several elements common across them. These include TB disease progression (i.e movements between uninfected, latent TB and active TB groups) as well as disease diagnosis, treatment and recovery. In the paper by Dodd et al, this latter process is defined by individuals being on treatment (based on case detection rate), individuals recovering (based on treatment completion rates) and relapse of recovered individuals [8]. This model however includes extra complexity through the incorporation of HIV and TB co-infection over time. This includes the interaction between HIV at different stages and how and its treatment impacts the the likelihood of TB acquisition, transmission and successful outcomes [8].

The model developed by Cilloni et al included HIV more simply, but added complexity to the diagnostic component [4]. Here, TB diagnosis is separated into several stages, namely in terms of 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). Overall, these elements are useful to consider in the context of this project, as different diagnostics have the potential to change the rates at which individuals move between these groups. Of the three examples, the one developed by Glaziou et al for the W.H.O's global TB estimates is the most complex [24]. This model incorporates the key elements previously described (i.e TB infection, latent TB, active TB, TB treatment, recovery and relapse), but stratifies each of these groups based on a range of factors. These include time-dependent diagnosis and treatment rates, differences between public and private sectors, HIV status (negative, positive on antiretroviral therapy and positive not on antiretroviral) 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 used for our simplified model's calibration.

Overall, the aim of this project is to develop a flexible framework through which different implementations of TB diagnostics can be explored for both a cohort of individuals as well as for a population over time. While Kenya is used as a case study in this project, the simulation models are designed such that different country contexts or different diagnostics could be rapidly modeled in the future.

3 METHODOLOGY

3.1 Patient pathways analysis: Optimising TB Diagnostic implementation

This section presents the patient pathway analysis, which is used to quantify the impact that different diagnostic implementations have on the TB case detection rate (CDR) and hence on the number of TB cases being correctly identified as compared to the SOC in Kenya. Further, the analysis will explore the impact that each implementation scenario has on the percentage of individuals accessing testing and results. The baseline model, used to represent Kenya's SOC, as well as the simulated scenarios are described below.

3.1.1 ***Patient Pathway Model.***

A patient pathway analysis is used to determine the impact of new diagnostic implementations as compared to the current diagnostic SOC in Kenya. Here, baseline results are generated through an adapted version of the Kenyan patient pathway model previously developed to support the W.H.O's update of their diagnostic TPP [7]. The new version developed in this project adds flexibility to the original model through several adaptations. Firstly, the model structure is modified to present a more generalised TB patient pathway - a visualisation of which is presented in Appendix A: Figure 5. An advantage of the generalised pathway is that the structure of the model itself is no longer country-specific. Rather, country baseline data is generated through parameterisation of the general model. This is a key research contribution 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 is 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 implementations. 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, the modification process structurally re-coded the model in R-studio to rapidly speed-up simulation time as compared to the original version developed for the W.H.O[7].

3.1.2 ***Baseline Simulation for Kenya.***

To simulate the baseline results for the Kenyan context, the generalised model is parameterised using values sourced from the literature (Appendix A: Table 5). These have initially been described by de Nooy et al and incorporate differences based on HIV and TB status [7]. Notably, these parameters are calibrated to ensure that at baseline, the percentage of individuals with TB correctly diagnosed matched the WHO's TB CDR value for Kenya at that time (57% in 2021) [23]. Using the model with these parameters, several simulations (n=100) of the baseline TB diagnostic pathway in Kenya are run for a group of 10,000 people with TB symptoms and varied HIV and TB status. In this case, multiple iterations are performed to allow for stochasticity within the pathways followed by each individual. For each run, an output excel file is generated and saved using 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. Per output file there are 35 columns, each representing a relevant status of an individual (for example HIV-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, calculated variables related to the patient care cascade and are used to show the number of individuals with TB reaching key points in the diagnostic journey. 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 determine the simulated CDR. The following processing steps are used to calculate the cascade variables for each file:

- 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. 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. Overall, this baseline data will be used to evaluate the results of the implementation scenarios described below.

3.1.3 ***Experimental set-up.***

While new TB test are still being developed, 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 NAATs can be implemented, with each implementation resulting in a potentially different CDR as compared to the considered baseline. 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 in the following ways. Firstly, in all scenarios it is assumed that there is 100% GeneXpert coverage. This is expected to improve case detection results over the baseline scenario which uses both 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 minimise these losses by bringing the diagnostics to the initial care seeking sites. With respect to turnaround time of results, at baseline individuals are required to return to the facility at a later stage. This additional visit again contributes towards a proportion of 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, it is 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 tongue swabs, while less accurate than sputum, are potentially much easier to offer and collect 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 through parameter changes - a list of which is provided in Appendix: Table 7. Using the same simulation and analysis process as the baseline, the calculated cascade data for each scenario are then compared against the SOC results to determine each scenario's relative impact. The determined CDRs for each scenario are also subsequently used as inputs into the long-term analysis described in Section 3.2. Lastly, changes to the testing rates and the percentage of individuals receiving their test results are determined.

Table 1: Modelled Diagnostic Implementation Scenarios

Scenario	Test Type	Testing Location	Return of results	Sample-Type
Baseline	GeneXpert and Smear	Mix of onsite* and off-site**	Subsequent visit	Sputum
1	GeneXpert	Mix of onsite and off-site	Subsequent visit	Sputum
2	GeneXpert	Onsite	Subsequent visit	Sputum
3	GeneXpert	Onsite	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	Testing visit	Non-sputum

* Onsite testing represents decentralised facility-based testing
** Off-site testing represents testing at a centralised lab

3.2 Transmission model: Long-term impact of diagnostic implementation scenarios

To consider the long-term effect of different diagnostic implementations on TB transmission dynamics, it is necessary to have a baseline transmission model. Once calibrated, this model is used to capture and reflect the historical TB dynamics seen in Kenya and predict the future changes in transmission, detection and treatment of TB. These baseline results are then used as a comparator against which the defined implementation scenarios 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 - 2021 [21]. 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

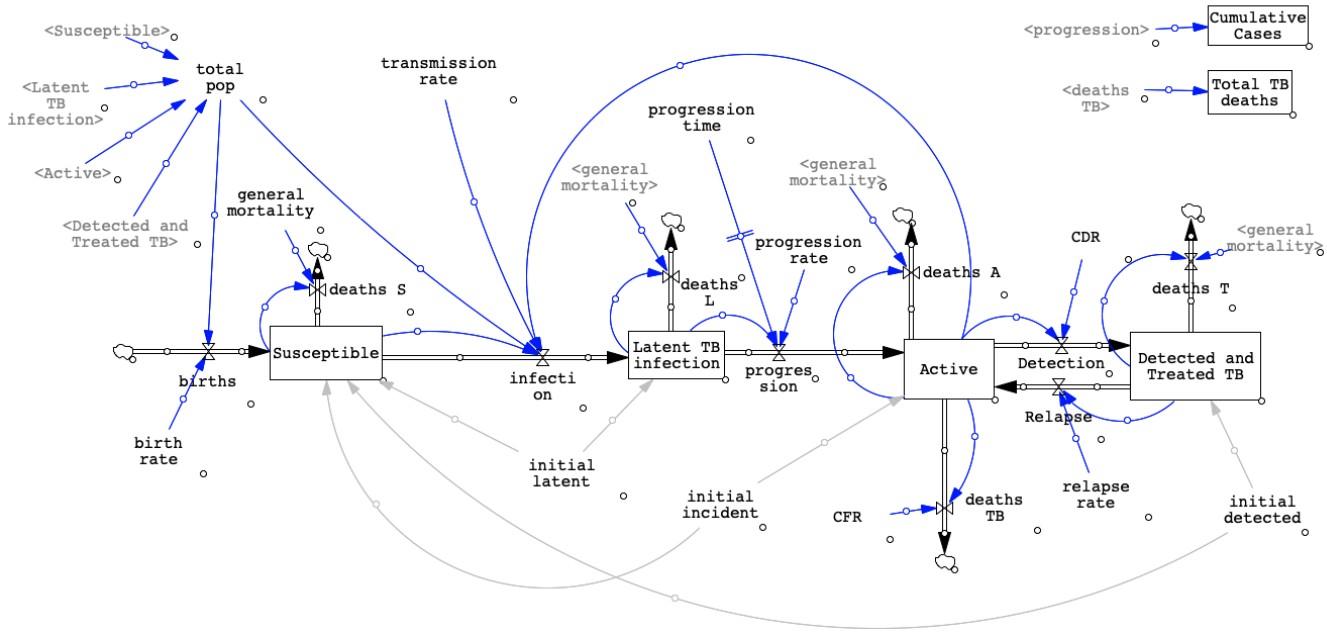

Figure 1: Stock-and-Flow D representing the baseline TB transmission model in Vensim

are used to parameterise and calibrate the baseline transmission model. Notably, for theses variables of interest, there are no missing data elements that need to be accounted for. Key visualisations of these data are presented in the Appendix and 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 (Appendix B.1: Figures 6 and 7).

3.2.2 *Baseline Transmission Model*.

To capture the historic trends of TB in Kenya, the baseline TB transmission model is developed and run in Vensim [32]. The model structure is depicted by the stock-and-flow (SFD) diagram shown in Figure 1. This developed transmission model, while relatively simple, makes use of key components as described in the literature [4, 8, 24]. The Vensim model has five stocks (or compartments) which represents the different stages of TB infection and the number of individuals in each of these groups per year. These compartments are Susceptible, Latent TB infection, Active TB and Detected and Treated TB. Two additional external stocks are included to track the cumulative number of new cases and total number of TB deaths over time (starting from 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 9.

The described 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 8). 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 [12]. In this case, the flow *progression*, which represents the number of new active cases per year, 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 hence provides confidence in any conclusions drawn from subsequent experiments. The calibration process is performed for the W.H.O's lower, mean and upper estimates in order to provide an uncertainty range for each calibrated parameter, however, in the conducted experiments the mean calibrated value is used. Further details on the calibration process and resulting values used in the baseline model can be found in the Appendix: Section B.3. Given that this model is designed in a deterministic manner, if these calibrated values are used in conjunction with the designed SFD, the baseline model can be exactly reproduced.

In conjunction with calibration, further analysis is conducted on the baseline model. This includes a sensitivity analysis to review which parameters have the greatest impact on model results. Given that the number of yearly 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 (calculated in Python) [15, 34]. 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 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. This is 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 [10].

3.2.3 *Experimental set-up.*

This section describes two experiments conducted in Vensim using the calibrated baseline 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 given different model CDRs. In each experimental scenario, it is assumed that between 2022-2041 a new constant CDR is incorporated. 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 implementation 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. The results of both of these experiments are presented in the section which follows.

4 RESULTS

4.1 Patient Pathway Analysis

Using the developed model, the baseline scenario for Kenya is simulated. The calculated cascade variables determined from this data are visualised in Figure 2. Here it is highlighted that the baseline case detection rate, or the percentage of individuals with TB who receive a TB positive result, is 57.1%. This matches the W.H.O's CDR value for 2021 of 57%, which was used to calibrate the model parameters [23]. 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 CDRs generated for each simulated scenario can then be evaluated (Table 2).

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%	26.40%

Here it is seen each that each scenario improves on the baseline, with Scenario 6 having the largest increase in CDR (an increase of 26.4%). 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 and 6) also have increased CDRs relative to their corresponding sputum-scenarios.

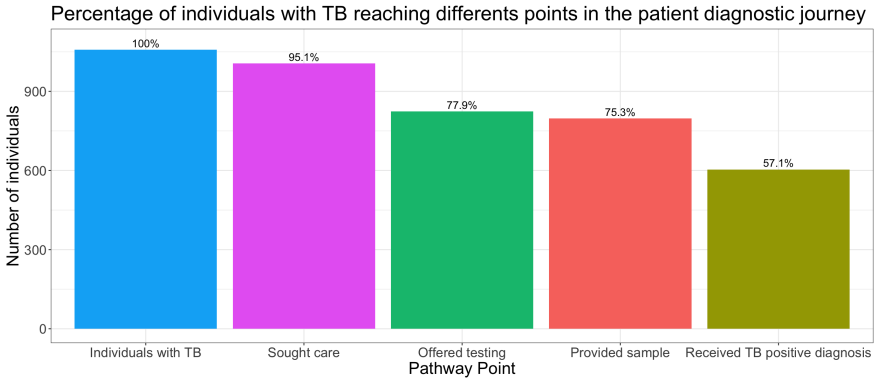

Figure 2: Visualisation of the number of individuals with TB reaching key points in the baseline TB diagnostic pathway

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). 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 increases 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 of individuals 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, of those tested, receive results compared to the current SOC. However, it is seen that with Scenario 3 and 6, where results are received at the initial testing encounter, the percentage of those tested who receive results is 100%. This is an increase of 8% from the baseline scenario.

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

Scenario	Percentage of Individuals Tested for TB	Percentage of individuals tested who receive results
Baseline	74.56%	92.01%
1	74.53%	92.02%
2	75.78%	91.95%
3	77.66%	100.00%
4	86.67%	91.95%
5	88.14%	92.04%
6	90.20%	100.00%

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 W.H.O's three incidence estimates. The resulting model output for each calibration set is presented in Figure 3, with the determined calibration parameter values given in Appendix: Table 10. Visually, Figure 3 highlights that the model output closely matches the reference data when calibrated to the lower and mean estimates, but is less accurate for the upper estimates. This is further reflected in the sum of square errors seen between the calibrated models and the W.H.O's lower, mean and upper estimates of incidence which were respectively: 555 888 429, 823 510 209, 75 542 338 440. This indicates that conclusions can be drawn, with relative confidence, for the mean-estimate calibrated model used for the remaining analyses.

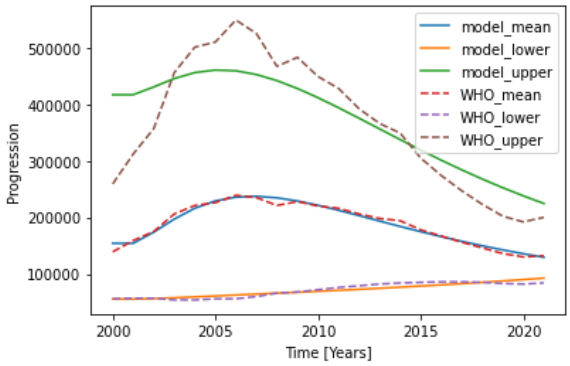

Figure 3: Model calibration results against the World Health Organization's lower, mean and upper estimates for incidence between 2000-2021

Together with the calibration, stability and sensitivity analyses are also conducted. In terms of system stability and equilibrium, the outputs of each stock are considered up to the year 3000 (Appendix: Figure 8). The plots highlight that the *Susceptible* stock increase exponentially with time and does not tend to an equilibrium point. Conversely the other stocks (*Latent TB infection, Active TB, Detected and Treated TB*) all show differing rates of exponential decay. As time extends, these stocks appear to tend towards zero - suggesting that this is a likely equilibrium point - but neither a zero nor a constant value before the year 3000 (Appendix: Table 11). This highlights that if the SOC would remain in place, TB would decrease over time but would not be eliminated in Kenya.

For the sensitivity analysis, the *progression* flow is the focal variable and the resulting plots (tornado and Sobel indices') 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 >8300 individuals per year). Conversely, the initial detected, birth rate and relapse rate variables have a minimal impact on *progression* (a deviation of <500 individuals per year). Figure 10 highlights the Sobel indices for four rate variables. 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 transmission rate (Sobel indices 0.3). Of the remaining two variables, progression time has a small impact (total and first order Sobel indices <0.1), and relapse rate has almost 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 effect on *progression*. The differences in the Sobel indices between time points highlight the differential effects of TB dynamic properties at different points in the 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.

Using the developed baseline model, experiment 1 and 2 are conducted. For Experiment 1, where CDR 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 decreases relative to the baseline scenario. Here it can be seen that at 100% CDR, 31 111 deaths and 335 300 cases 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 70.5% and 72.9% respectively, is not zero. 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, as well as for the cumulative number of cases and TB deaths. In each case, the variables are plotted over time between 2000-2041 in conjunction with a close-up plot between 2030-2041 to better see differences in these values. Similarly to 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 1-3). Further, Scenario 6 (the decentralised non-sputum scenario) had the highest estimated CDR in the patient pathway analysis (83.5%), and correspondingly saw the largest number of TB deaths and cases 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 a greater than 55% reduction as compared to the baseline values, they are still non-zero.

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 each diagnostic implementation scenario

Scenario	Case Detection Rate (%)	Increase in CDR from baseline	Total TB Deaths	TB deaths averted	TB deaths in 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%)

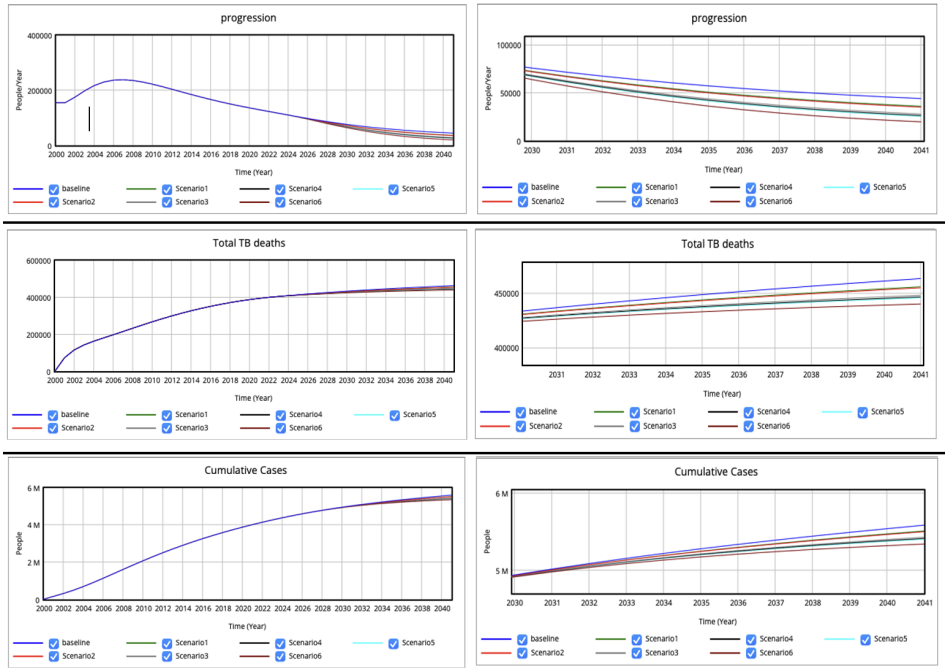

Figure 4: Plots of progression, cumulative cases and total TB deaths for each diagnostic implementation scenario for the simulated period 2000-2041, and in close-up for 2030-2041

5 DISCUSSION

5.1 Patient pathway analysis: Scenario Impact

The initial patient pathway analysis highlighted several key results regarding the implementation factors with the largest effect on CDR. Scenario 1 shows that conducting all diagnostic testing with molecular tests, as opposed to a combination of molecular testing and smear-microscopy, results in a relatively large improvement in CDR (an increase of ~6.3%). This is seen without additional implementation changes in sample type, testing location and turnaround time of results. This improvement in CDR is likely a direct result of eliminating the use of smear-microscopy, which although relatively cheap and easy to implement, is known to have a significantly lower sensitivity when diagnosing TB as compared to GeneXpert [30]. When including decentralisation of molecular testing (scenario 2), only a small additional gain is seen in CDR unless implemented with results being returned at the same visit as in scenario 3. Here the rapid return of results prevents individuals being lost from care as a result of not being able to return to the healthcare facility for a subsequent visit. Overall, when moving from the baseline scenario which includes GeneXpert and smear-microscopy, to scenario 3 which focuses on same-visit return of results through GeneXpert molecular testing - an increase of 14.7% in the number of individuals diagnosed is seen. Although not directly comparable given that there is existing usage of GeneXpert in Kenya, this does reflect within the range of values seen in the work by Pooran et al [26]. Here, although the impact differed by country, decentralisation of GeneXpert was seen to have an average 11.7% increase in the number of individuals diagnosed.

The last implementation aspect considered is that of non-sputum samples, modelled in this work as tongue swabs. This represents one of the first instances where the implementation of non-sputum samples for TB diagnosis in the adult population has been considered at scale. Although non-sputum samples have been shown to have reduced accuracy as compared to sputum samples, the results have highlighted the large potential impact that these types of samples could have on CDR. In the results, an average CDR increase of 10.86% is seen when comparing sputum scenarios and their non-sputum equivalents (i.e scenario 1 with scenario 4, scenario 2 with scenario 5 and scenario 3 with scenario 6). These improvements stem from the assumption that there will be high patient and provider accessibility and acceptability for these sample types [6]. This would mean that quality non-sputum samples would be easier for patients to produce, could be produced by all patients and are easier to collect and more likely to be offered by healthcare providers. This would be particularly pertinent for countries like Kenya that have high HIV/TB co-infection, given that a large proportion of individuals with HIV cannot produce sputum (~20%) and hence would struggle to be tested[25]. Ethically, it should be noted that the impact of these alternative sample types looks at a population and not an individual level. As such, there is potential that each individual tested has a higher likelihood of receiving an incorrect result and of experiencing the subsequent consequences, however, on the whole many other individuals are receiving testing when they otherwise would not have. This highlights a key accuracy vs access trade-off. That is, could a test with a lower accuracy than current standard molecular testing be used at scale, if that test is able to reach and provide results to a larger number of people. While this trade-off has been highlighted here, ultimately it would be up to policy makers to determine what is or is not acceptable for their healthcare system.

5.2 Patient pathway analysis: Cost considerations

In conjunction with determining the acceptable benefit and risk trade-offs, it should be noted that the choice of diagnostic implementation is often constrained by other factors. Decentralising testing to the primary healthcare level requires significant financial investment - both in terms of the equipment required (at least one device at each site), as well as logistical and staffing support [5]. Further financial investment would also be required to account for the larger volume of tests, and the greater number of individuals, moving through the healthcare system as a result of the increased access to testing that these scenarios provide. Overall, these required investments could make some implementation scenarios infeasible, particularly in many of the LMICs that might benefit the most. A limitation of this work is that it does not provide a full cost-effectiveness analysis (CEA) to determine the feasibility of each implementation strategy relative to the baseline. In work by Pooran et al and Sohn et al [26, 29], it is shown that decentralised testing has the potential to be cost-effective, however this is highly dependent on the number of sites being considered, the volume of tests being performed (especially if sufficient capacity is required to return results at the same visit) and the infrastructure that is already in place. While the CEA was not conducted in this analysis, if site-level volume data were to be available for all sites across Kenya, this would be a key element for future work. However, even without the CEA, potential feasibility conclusions could be drawn. For example, scenario 4 could be considered a high-impact lower-cost implementation strategy as it would only require a change to the sample-collection process without any substantial investments in additional infrastructure.

5.3 Transmission modelling

In conjunction with the patient pathway analysis of the scenarios, the transmission modelling process explored the long-term effect of each. Initially, exploring the equilibrium points within the model indicated that without further intervention, TB would not be eliminated in Kenya over the next several hundred years. This highlights the need for additional interventions which focus on reducing TB transmission by identifying and subsequently treating TB cases. Looking at the impact of the six diagnostic interventions explored, it was shown that scenarios which improved CDR the most, had the biggest impact on the TB epidemic. That is, the higher the CDR, the lower the cumulative number of deaths and new cases over time. Further, the analysis indicated that scenario 6 would have the highest CDR at ~83.5%, and would result in a reduction of ~56% in TB deaths and new cases by 2041 as compared to the SOC. However, even though this is a substantial reduction, it would still result in over 900 deaths and more than 19,500 new cases being recorded in that year. This highlights the need for both new innovative diagnostic tools that could further improve the CDR in each scenario

(for example a more accurate non-sputum based test) as well as a need to further invest in ensuring people make it into and are not lost from care. One element of this could take the form of increased community engagement and education - to ensure people are aware of TB and its symptoms and know when, where and how to seek care for them [16] - or to better financially support patients given the often catastrophic costs (a W.H.O defined indicator of TB) they face during diagnosis and treatment. However, even if measures that increased CDR to near 100% of active TB cases were implemented, the modelling analysis shows that while fewer deaths and cases would be recorded, TB elimination would not be achieved over the next two decades. Generally, the bulk of TB case detection is passive and reliant on individuals seeking care for symptoms (as has been modelled here) [28]. It is thus likely that to further reduce TB transmission and the number of new cases and deaths recorded, additional screening and active case finding within the asymptomatic and latent TB populations may be required. Given that community TB screening is frequently a mass undertaking, with multiple logistic and financial constraints, determining to what degree this needs be conducted ,in order to have a substantial effect on the epidemic, would be an important part of future work.

5.4 Additional Limitations and Future work

There are several additional limitations to this work which should be noted. Firstly, some assumptions have been made with respect to the effect that each diagnostic implementation would have - especially with regards to non-sputum samples. As described, recent research has focused on performance of these samples, predominantly as tongue swabs, with molecular testing. While it assumed by many that these will have positive effects on test accessibility, particularly for those who cannot produce sputum, if further research shows that the uptake, accessibility and feasibility of non-sputum samples in implementation is not to the degree modelled here, the CDRs presented may be slight overestimates. If other non-sputum sample types were to be modelled - for example as stool collected from the adult population - this could be especially true. Another limitation is that to manage scope and complexity the analysis has focused on the adult population. Children frequently have a more complex journey to TB diagnosis and face additional diagnostic challenges. As such, exploring the impact of the implementation scenarios, as well as the difference in impact between the adult and child population would be useful future work to conduct. This would be especially true for non-sputum samples given that children are known to struggle with the production of sputum and could hence greatly benefit from alternative sample types [9]. Further, while individuals with HIV were considered in the patient pathway analysis, the transmission modelling considered all individuals in a single group. This was done as managing the different stages of HIV, its treatment and co-infection with TB requires significantly more complexity in the model (as seen in work by Dodd et all [8]). To better see the long-term effect of these diagnostic implementations on each HIV group, it could be a useful to include in the transmission model. A last limitation is that the scenarios did not include any combinations of centralised and decentralised testing. These combination scenarios may be more realistic as it is likely that in many countries centralised testing could work best in urban areas, where a high volume of tests are conducted, and that decentralised testing would be more appropriate in remote areas that are harder to reach and test fewer samples. Like the CEA, an analysis of this type would make the most sense if it could be conducted with site location and volume data.

5.5 Reflections on model structure

Lastly, it is useful to reflect on the structure of the two models. The patient pathway model, although only utilised for Kenya in this case, has been designed in a flexible and generalisable manner. That is, the structure is such that if other countries were to be explored, the model would only require an update to the input parameters. Further, the required input parameter structure and the resulting output variables all follow the same format. This would make it easy to rapidly simulate and compare between countries, with little extra work required beyond the collection of the parameter data. This is important, as the magnitude of the effect of each diagnostic scenario would be different per country based on its underlying healthcare structure and patient population [7]. Further, the model is flexible, and could be re-utilised to explore different combinations of diagnostics, including initial screening steps, as well as novel diagnostics as they become available. Similarly, given the way the patient pathway analysis and the transmission model connect through the changing CDRs, the simulation of new scenarios would not require additional changes to the transmission model. Further, simulating new countries would only require the calibration process to be repeated with the new country reference data. Overall, the structure and set-up of the the two models would make them ideal for re-use in future work. Lastly, it should be noted that the patient pathway model is stochastic. This allows for randomness in patient behaviour to be incorporated in the output, but, would mean that results may differ slightly if the experiments were repeated (although the final conclusions would remain the same). Notably, this difference is minimised with the large population size and multiple simulation iterations. Conversely, the transmission model is deterministic, meaning that if it is set-up identically as described above, the same results should be achieved.

6 CONCLUSION

This work developed a novel, flexible framework that utilised two modelling techniques to determine the short and long-term impact of different diagnostic implementation scenarios on the TB epidemic in Kenya. It was shown that scenarios which increased the CDR the most, resulted in the largest reduction in new cases and TB related deaths over time. In terms of modelled scenarios, the two implementation aspects which had notable impact were decentralised testing with results returned in the same testing encounter as well as the use of non-sputum sample types. The combination of these two aspects (modelled in scenario 6), resulted in the largest increase in CDR - 26.4% above that in the standard-of-care. It was also shown that the return of results in the same visit was the only implementation aspect to increase the percentage of people who received results (of those tested). In terms of the percentage of individuals tested for TB, slight increases in this rate were seen with decentralised testing, but the use of non-sputum samples increased this value the most (at least a 10% increase between each

sputum scenario and its corresponding non-sputum equivalent). The transmission modelling showed that scenarios with high CDRs (like scenario 6), could achieve a reduction in new cases and deaths of up to ~56% from the standard of care, however, it was also seen that these rates would be insufficient to eliminate TB in Kenya over the next two decades. This highlights the need for additional screening and diagnostic interventions within the asymptomatic and latent TB groups. Given that the use of non-sputum samples in the form of tongue swabs is relatively new in its consideration, this work provides one of the first reviews of this sample type in an implementation context (outside of test performance). While this contributes to the literature, the lack of other implementation research on this matter has meant that certain assumptions on the effect of these samples on the patient pathway have been made. Additional future work would be to include combination scenarios between centralised and decentralised testing as well as to conduct a full CEA to determine scenario feasibility. Lastly, given the flexibility of the developed models, it would be useful to replicate this analysis for other countries with different healthcare infrastructure and population groups to determine how this would effect the impact of each implementation scenario.

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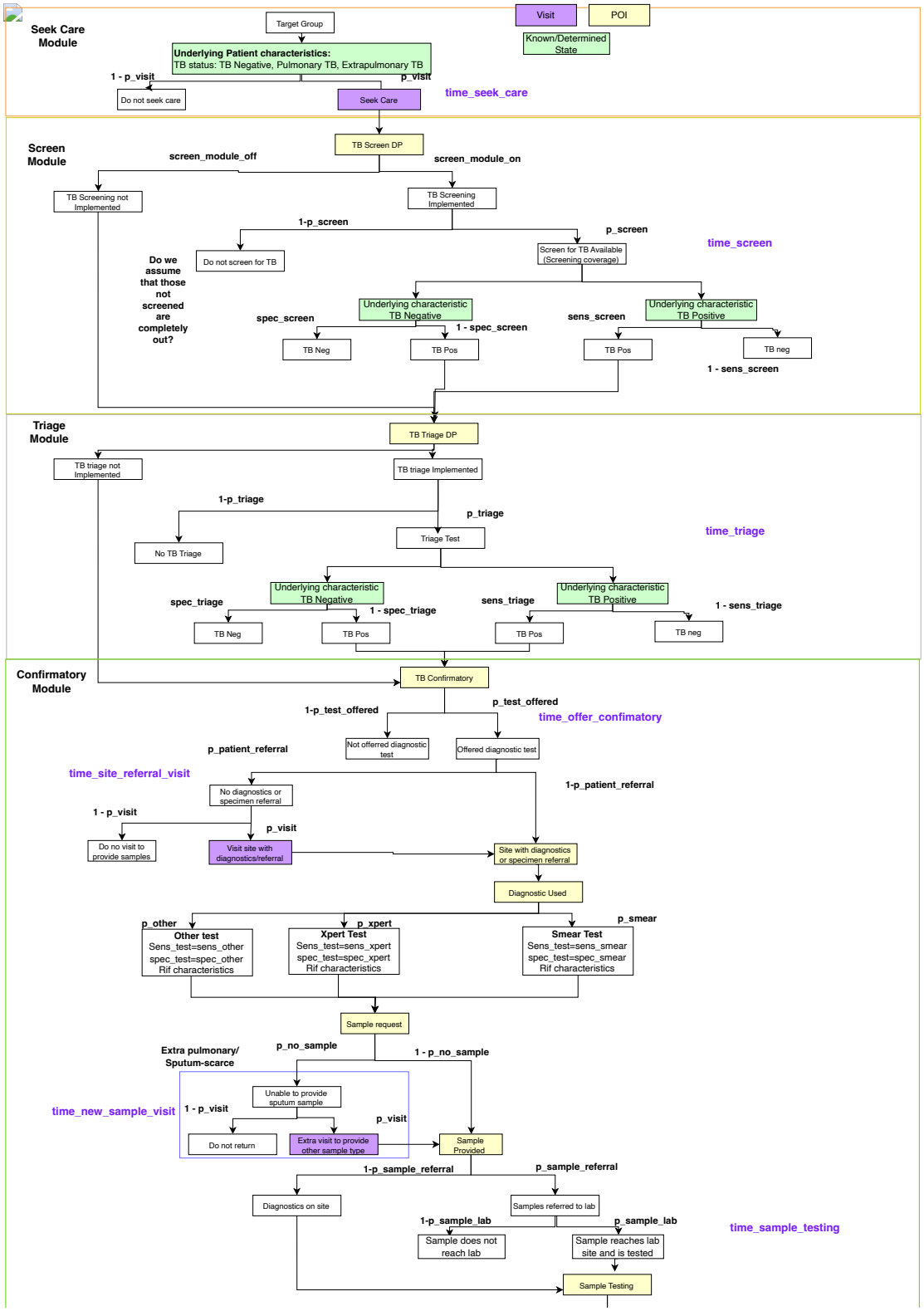
Appendix A STATIC ANALYSIS: OPTIMAL IMPLEMENTATION OF TB DIAGNOSTICS

This appendix provides relevant parameters and outputs for the patient pathway analysis which explores the impact of different diagnostic implementations. The baseline parameter values are provided in Table 5, with relevant values sourced from the original patient pathway model [7]. Figure 5 presents the decision tree representing the generalised patient pathway developed in this work. Model output variables used for analysis are detailed in Table 6 and Table 7 describes how baseline parameters are changed when simulating 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	0.96	0.96	0.96	0.96
spec_rif_xpert	0.98	0.98	0.98	0.98
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

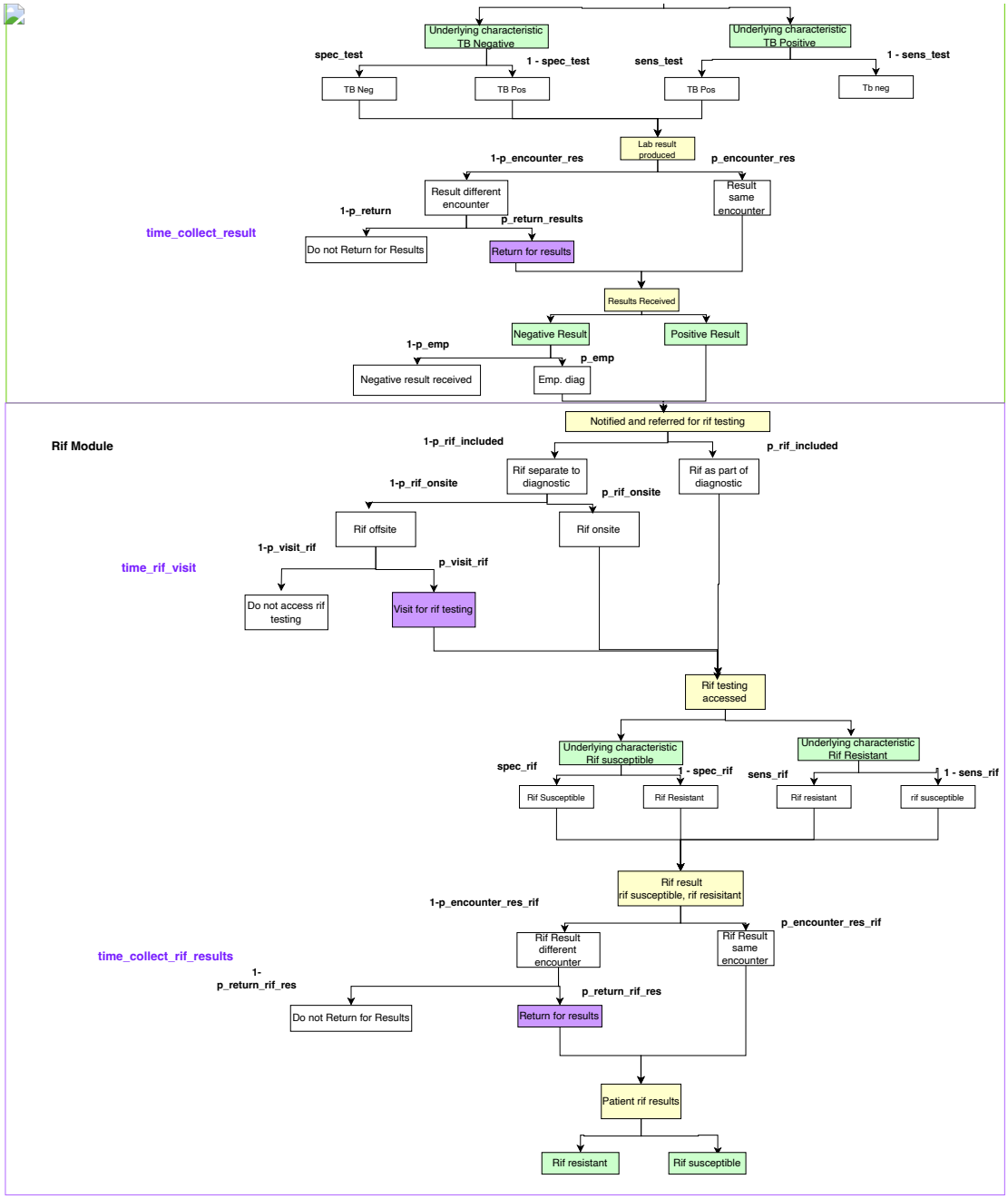


Figure 5: Generalised Patient Pathway Model

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 so as to impact the diagnostic algorithm. Table 7 below highlights which parameters are changed and to what value for each scenario. Notably, within this table, any parameter written as "baseline" remains unchanged for that scenario (i.e keep the standard of care value). 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 and equilibrium analyses.

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 inform the development of the transmission model. 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 number of TB related deaths. Figure 7 highlights the estimated percentage of case fatality and case detection rates over time. Notably, the estimates of incidence are used as the calibration data for the baseline model (Section B.3).

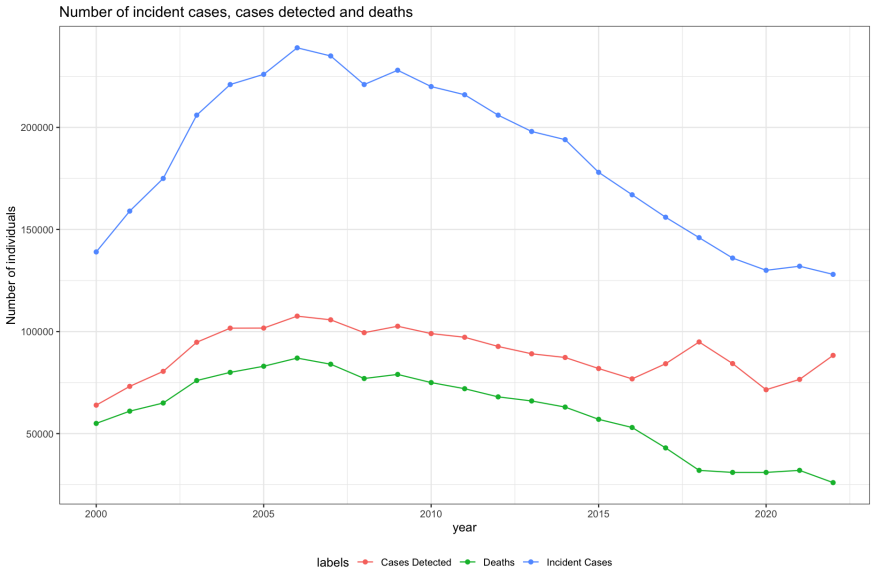


Figure 6: Mean estimates of incident cases, detected cases and deaths for Kenya between 2000-2022

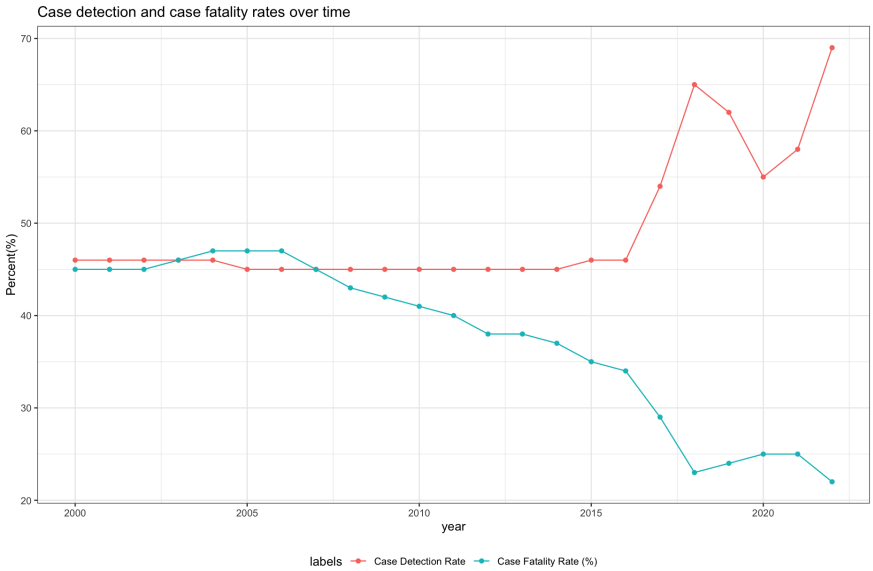


Figure 7: Estimated case fatality and case detection rates over time

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 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)[21]
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)[21]
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

Table 9: 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

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 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 2000-2021. 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 output of the stability analysis conducted for the baseline model. As additional information, the complete differential equations representing the transmission model, along with the relevant parameters, 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 period to highlight how stock values continue to change with time.

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)

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

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

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

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

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

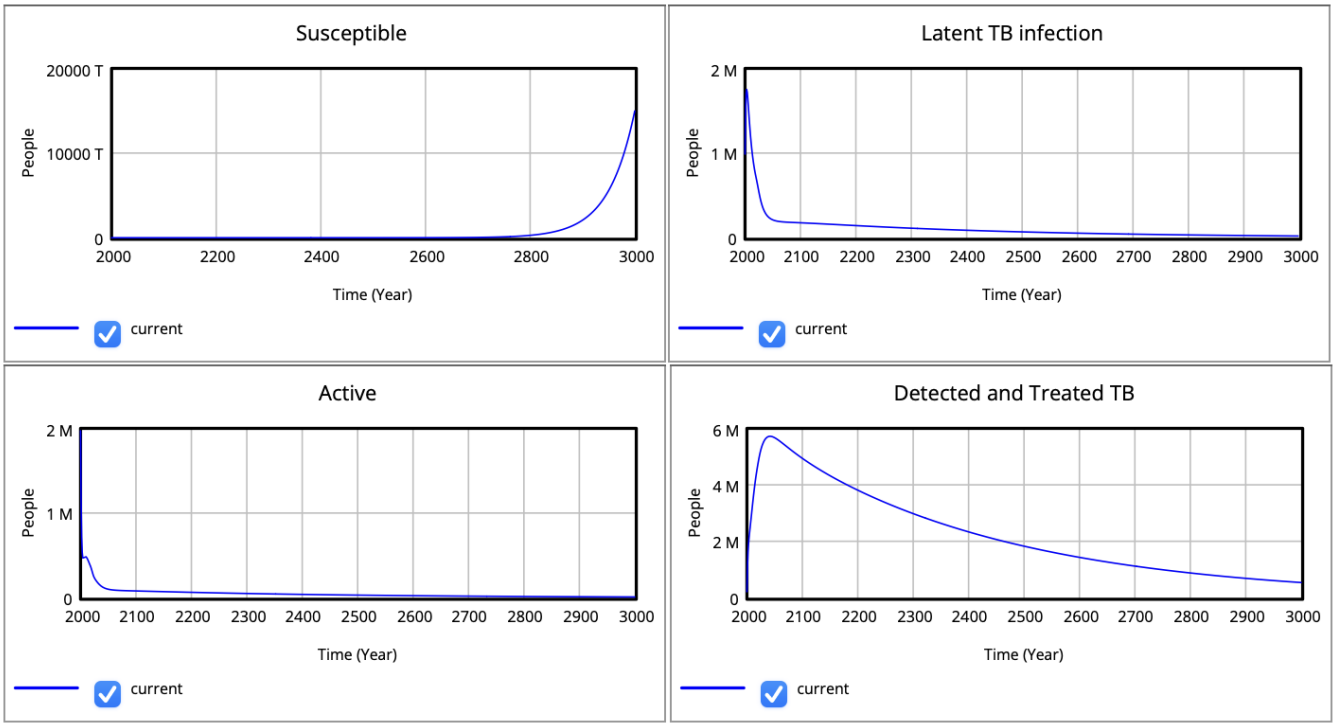


Figure 8: Extended time frame baseline simulation used to explore equilibrium and stability

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

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

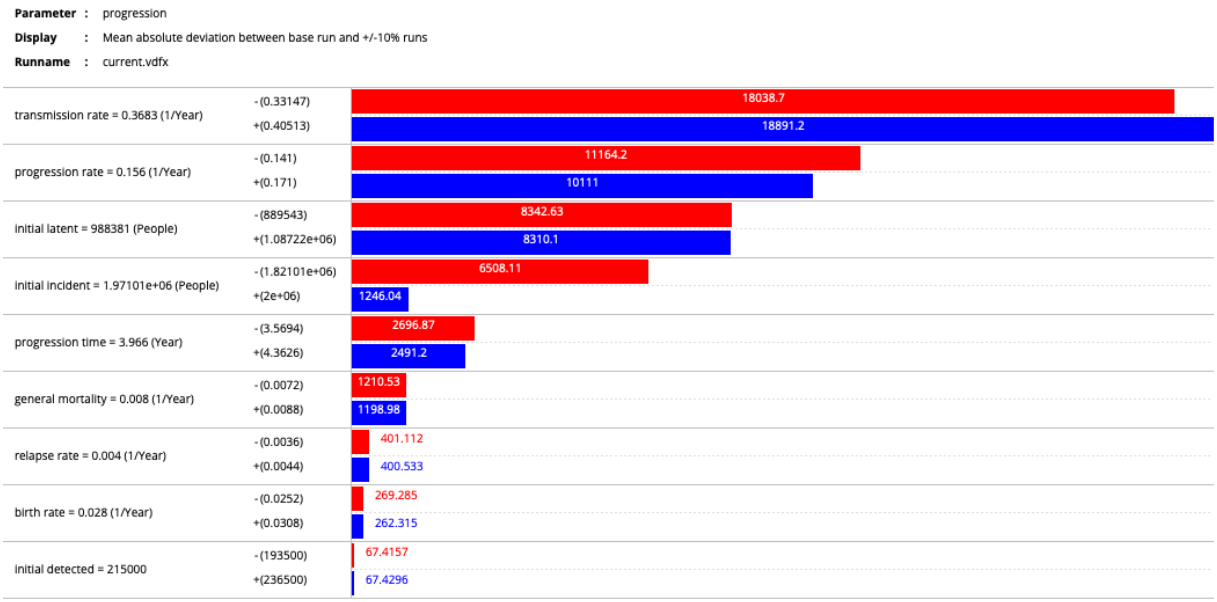


Figure 9: Tornado plot representing the impact of varied model parameter values on the model flow *progression*

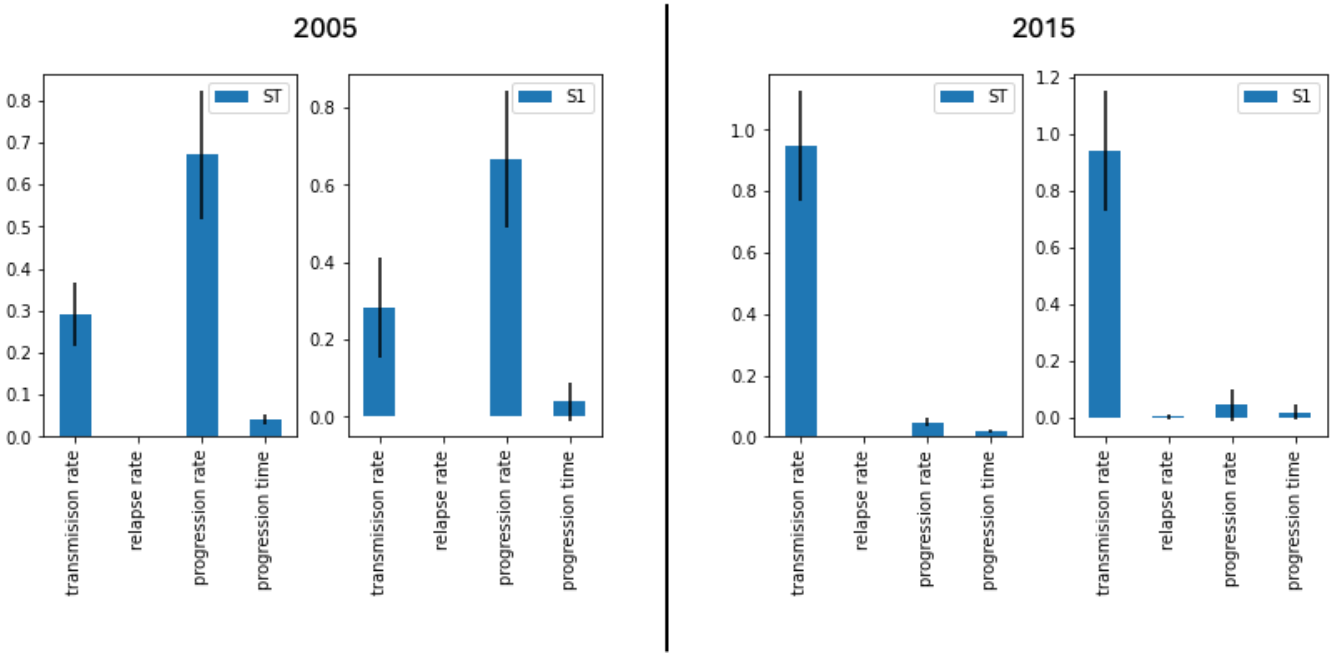


Figure 10: Plots of the of the first-order Sobel indices and total Sobel indices for the *progression* flow for 2005 and 2015

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%)