# Optimising the implementation of Tuberculosis Diagnostics in high burden countries - an exercise in mathematical modelling and simulation

Submitted on: **22-12-2023**

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## 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) [8, 9]. 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 [8, 9]. 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 [12, 13]. Furthermore, collecting sputum-samples for TB testing can be difficult for both the patient and the healthcare provider [13]. 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 [13]. 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 [5, 10].

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 [7]. 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. This process will require the simulation of the implementation of new diagnostics to different degrees- at an individual level- and for different populations. Scenario results will then be evaluated against the baseline data of an existing TB diagnostic model for Kenya to answer the following research questions (RQ).

**Research Question:** *In the context of TB diagnosis in Kenya, what combination of new and existing TB diagnostic tests will correctly diagnose the largest number of individuals as compared to the standard-of-care, at different levels of budget availability?*

Further sub-research questions include:

- To what extent does targeting novel diagnostics only at specific population groups, for example HIV positive people, impact the overall number of individuals diagnosed?

- 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 reducing the diagnostic access gap vs reducing the gap in delivering TB results?

- Which scenarios result in diagnosing the greatest number of individuals under no-budget vs budget constraint scenarios?

- 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 health-care visits required to be made by each patient when attempting to receive care [14]. 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 [6] 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 [6]. 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 [2]. 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 [15]. 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 [4].

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 [1, 3, 11]. 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) [3]. Further, there is the potential for recovered individuals to relapse (or become reinfected) [3]. 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 [3].

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 [1]. In this paper, the most significant focus has been placed on elements of diagnosis [1]. 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)[1]. 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[11]. 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 [11]. 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.

## 3 METHODOLOGY

This work looks to build on a prior model and adapt its usage to consider new implementation scenarios. While the use case for this adapted model will be to consider new and developing TB diagnostics and their optimal combination in Kenya, the final version produced will exist as a novel generic framework which could be applied to other countries, other diagnostics and potentially other diseases with similar patient pathways. The work is broken down into two sections. The first and more lengthy section considers using an adapted model to simulate a range of different diagnostic combinations and determine which are most effective and feasible to implement. The second considers taking the optimal solution and reviewing its impact over a time-frame of several years, as opposed to only a single cohort of people.

Some of the key steps required for each section of work to be completed are highlighted below, and are also included in the project plan presented in Section 5.

Optimal diagnostic implementation

- **Baseline exploration:** This section requires running, exploring and analysing the data produced by the SoC model for Kenya. This includes aggregating the multiple runs (which account for stochasticitiy) and developing the scripts to calculate the relevant outcome variables needed to answer the defined research and sub-research questions. This includes the number of individuals diagnosed, the relevant cost of testing, the number of people who access a diagnostic (regardless of whetehr results are received), the number of each type of diagnostic done, the number of correct and incorrect diagnoses, the number of individuals lost from care and the differentiation in these numbers by HIV status and TB status.

- **Scenario definitions:** Define a set of diagnostic implementation scenarios which consider the impact of different combinations of existing and future diagnostics (as defined by W.H.O) on the number of individuals diagnosed in Kenya as well as on other important outcome variables. This includes defining which target groups are being considered per diagnostic as well as what coverage of each diagnostic is used

(for example, all of one diagnostic, equal distribution, one diagnostic for HIV positive and another for HIV negative)

- **Generic Model Adaptation:** The baseline model considers only one new diagnostic at a time and does not allow for differentiation by group. The new generic agent-based model will build on the baseline (in Python) to incorporate multiple diagnostics at different coverage levels and for different target groups. Further, the model must be maintained to allow different elements of the patient pathway to be included or excluded, as well as to take in parameters from an external file.

- **Scenario Model Adaptation:** For each scenario, it must be determined how each diagnostic will affect the patient pathway and for which individuals (e.g HIV positive or extrapulmonary TB). This knowledge must then be transferred into relevant model parameter values which change the underlying pathway structure that those individuals would follow. The generic model is then set-up to run the multiple scenarios and pull the relevant parameters in each case so as to simulate the new patient pathway results.

- **Scenario Analysis:** Simulate each scenario for multiple runs and save the results. Using the saved individual level scenario results, aggregate the data to determine the key outcome variables per scenario. Outcome variables in this case match those defined in the initial baseline data exploration. Summarise results into a single dataset, with one row of outcome variables per scenario. Lastly, apply costing mechanisms to determine the total cost of each scenario.

- **Evaluation and Scenario Optimisation:** Evaluate key outcome variables against the baseline data, depending on the specific sub-question and filter out only those scenarios which diagnose more individuals than baseline and meet the cost constraints being considered. With the scenarios that remain, optimise as far as possible between cost and number of individuals correctly diagnosed with TB, so as to identify scenarios that both improve on Kenya's baseline and are potentially feasible to implement.

Impact over time

- **Baseline Transmission Model**: Develop a dynamic mathematical model which incorporates TB transmission, TB progression, diagnosis and treatment. Use country level data for the last two decades to fit model parameters to produce as accurate estimates of TB notifications as possible. Given an acceptable baseline transmission model, estimate the number of new infections and notifications over the next several years, under the assumption that the current standard of care remains the same.

- **Model optimal diagnostics**: Adapt the transmission model to incorporate the effect of the optimal diagnostic combination (from the static analysis) on the detection of TB. Use the adapted model to project the new number of infections and notifications over the same time-frame into the future.

- **Impact Evaluation**: Evaluate the potential impact of the new diagnostic combination on TB in Kenya by comparing these results with that of the standard of care. Key outcomes to consider are the long-term change in prevalence as well as the general notification rate.

## 4 RISK ASSESSMENT

There are several potential risks related to this project. These are highlighted below along with potential mitigation strategies. The first risk considered is any potential difficulty in adapting the Kenya model to run with multiple diagnostics targeted at different groups. Mitigation in this step would be to start with the simplest case and build up, step-by-step. Further, it is noted that since this is the key step upon which most of the project is founded, if a solution is not found after a reasonable amount of effort, it would be best to reach out for guidance and or discussion with supervisors as soon as possible.

A second risk is potential scenario "overload". There are multitudes of scenarios which would cover different target groups, diagnostics or coverage levels. It is important to decide on a manageable amount to both simulate with the model (as this will take time) and subsequently evaluate against the baseline or SoC model. Having very many scenarios may also make it difficult to interpret the optimal case. To mitigate, it will be necessary to discuss with the AMC supervisor (linked to policy makers) on some of the core scenarios to consider. With these core scenarios, all project elements can be developed (i.e evaluation code, model development and long-term analysis) and if time may permit, extra scenarios could be included.

The biggest risk to the project is the long-term analysis. There are many complexities which can be introduced when considering a dynamic, time based model as compared to the initial more static version. TB transmission is complex to model as there are many factors which could be incorporated. As such, it could be challenging to creating a simple transmission model that is still complex enough to capture all the disease dynamics.To mitigate this risk it will be important to scope out the work clearly and discuss with supervisors which factors may be most relevant to include. Further, although this step is listed as one of the end items (as it is reliant on the optimal combination), the work for building the baseline transmission model can be conducted simultaneously.

## 5 PROJECT PLAN

For part-time students, the practical element of the thesis is expected to begin mid-January 2024 following the finalisation of the thesis design. Given that the draft thesis is to be submitted by mid-June, this provides approximately 22 weeks of part-time work on the project. This time frame, in conjunction with the goals and objectives defined in the methodology section, has been used to develop the planned project timeline below. Within this timeline, there are also several weeks allocated to thesis writing as well as a buffer period to allow for project delays should any challenges arise during the project implementation.
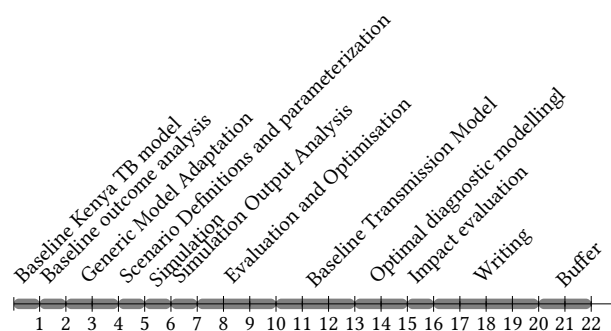


**Figure 1: Expected Project Timeline**

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