Introduction of operational modelling in policy uptake: A case study of chest X-ray in tuberculosis screening in Kenya

Thesis submitted in accordance with the requirements of the Liverpool School of Tropical Medicine for the degree of Doctor in Philosophy by

Dr Brenda Nyambura Mungai

October 2022

I, Brenda Nyambura Mungai, confirm that the work presented in this thesis is my own original research. I have duly acknowledged any information built upon from previous studies.

Reflexivity and positionality statement

I recognize that my position and views have a potential to directly or indirectly influence the research design, execution and interpretation of the research data findings.[1] In this section, I therefore reflect on my positionality in this research process and how I addressed the challenges it posed.

I am a medical doctor with a masters in infectious disease and 13 years of professional experience in tuberculosis (TB) work at national and international levels. Initially, I worked at subnational level in Kenya as a medical officer in charge of a facility for two years before relocating to Namibia for three years. During these period I ran the TB and HIV clinics in Kenya and later in Namibia. I then pursued a Masters in Infectious Disease and Tropical Medicine for one year at Liverpool School of Tropical Medicine where I did a dissertation on "Understanding the pathways to tuberculosis care and costs involved in diagnosis in an indigenous semi-nomadic community in Samburu district, Kenya". I then returned to Kenya as a TB/HIV advisor, a position I held for three years. This experience helped me develop an understanding of the process of policy implementation at county and sub county levels. Through Centre for Health Solutions-Kenya (CHS) I offered technical and financial support to the Kenya National TB, Leprosy and Lung Disease program (NTLD-Program) for a period seven years' through the United States Agency for International Development (USAID) funding. As overall project lead for USAID funded CHS project, I was also a member of the research team conducting the 2016 Kenya National TB prevalence survey and was involved in the subsequent dissemination of the findings, including publication.[2, 3] I stepped away from my role at CHS when I joined the PhD program and was not responsible for any financial or

technical support to the NTLD during the time that I devoted to my PhD studies from 2018 to 2022.

As an insider in the TB space in Kenya, I had a good understanding on the country priorities as well as the structures involved in the policy decisions, and had access to key informants.[4] Given my in-depth knowledge of the TB space in Kenya, I was able to ask more meaningful questions and probe deeper on arising issues. The participants were comfortable with me because of my previous interaction with most of them, hence they were able to give more in-depth and truthful answers. In some instances, though, my research participants viewed me as an authority in TB and this was evident in their short responses on the processes, I however used my previous knowledge to probe more to get their points of view. I was also aware of important stakeholders that were often left out of the policymaking process and ensured I also interviewed them for their perspective.

In my experience of policymaking, I was broadly aware of the complexities faced when choosing what new tools to adopt and how to go about it. I studied the feasibility of operational modelling therefore as an interested party seeking to understand if it may be useful in the decision-making process. However, I mitigated the risk of bias by using open-ended questioning and group discussions to answer the questions of utility. I also organized the sensitization sessions and listened in as part of the team to reflect on whether this tool could contribute to closing the evidence to policy gap.

Throughout the protocol development, data collection and analysis, I was aware of my positionality and had episodes of reflection to ensure minimization of bias in my questioning and interpretation. I also had several discussions with my supervisors during the study on my positionality and how to mitigate its influence on the study process. Given my positionality outlined above, it is possible that another researcher without the same background and context may come up with varied results for the qualitative chapters (Chapter 5 and 6).

My role

I conceptualised the study with input from my supervisors, Prof Bertie Squire, Dr Ben Morton and Dr Rose Oronje. I conducted the background literature review and designed the study protocols.

I designed the study protocols for the computer-aided detection software accuracy (Chapter 2) and the prevalence of non-tuberculosis abnormalities studies (Chapter 3) with input from Prof Bertie Squire, Dr Elizabeth Joekes (radiologist), Dr Peter MacPherson (epidemiologist and statistician), Dr Ben Morton, Dr Angela Obasi, Dr Jane Ong`ang`o, Dr Enos Masini, Dr Veronica Manduku and Dr Beatrice Mugi. I applied for and obtained all the required approvals for using the Kenya prevalence survey data.

For Chapters 2 and 3, I contracted, through the African Institute for Development Policy, Delft Imaging, the commercial provider of the computer-aided detection for TB (CAD4TB) software, and the data management team at the NTLD-Program to contribute work for the computer-aided detection software accuracy study. I engaged the data management team to load the images on to the CAD4TB cloud servers. Drs Peter MacPherson, Chu Chang Ku and Marc Henrion conducted the Bayesian latent class modelling for that study.

For the prevalence of non-TB abnormalities study (Chapter 3), I adapted and modified the standard operating procedure from the Malawi LIFE AFTER pTB (LAT) study.[5] I worked with the data management team (Dickson Kirathe and Richard Kiplimo) to design the online reporting tool. I recruited the Kenyan radiologists both for the pilot and the main study. United Kingdom based radiologists were recruited through a contract with Worldwide Radiology. I trained the radiologists on the reporting tool and developed Standard operating procedures with input from Drs Elizabeth Joekes, Veronica Manduku and John Curtis. I conducted online support for the radiologists and troubleshooting for any issues with the data team. Dr Peter MacPherson conducted the statistical analysis for this study.

For Chapter 4, I developed the operational modelling with support and guidance from Ewan Tomeny. The NTLD-program team co-designed the model including validation of the pathways. I conducted the literature search, the key informant interviews and the operational modelling meetings that provided the model inputs.

For the qualitative policy chapters (five and six), I developed the protocol and all the study materials with guidance from Dr Rose Oronje. I recruited and trained the research assistant. I carried out all the key informant interviews and the operational modelling meetings. The research assistant transcribed all the interviews and I reviewed all of them. I developed the coding framework and carried out the guided qualitative content analysis with supervision from Dr Rose Oronje.

Supervisors and collaborators

Supervisors

Professor Stephen Bertel Squire, Liverpool School of Tropical Medicine

Dr Ben Morton, Liverpool School of Tropical Medicine

Dr Rose Oronje, African Institute for Development Policy

Collaborators

Role	Collaborator	Institution
Statistical analysis	Dr Peter MacPherson	Liverpool School of Tropical Medicine, UK /Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Malawi
Radiology	Dr Elizabeth Joekes	Liverpool School of Tropical Medicine, UK/Worldwide Radiology, UK
	Dr Veronica Manduku	Kenya Medical Research Institute, Kenya
	Dr Beatrice Mugi	Kenyatta National Hospital, Kenya
Operational modelling	Ewan Tomeny	Liverpool School of Tropical Medicine, UK
	Dr Ivor Langley	Liverpool School of Tropical Medicine, UK
Bayesian Latent Class Modelling	Dr Chu Chang Ku	Imperial College London, UK
	Dr Marc YR Henrion	Liverpool School of Tropical Medicine, UK /Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Malawi
Research Assistant	Hannah Mwaniki	Qualitative Researcher

Table of Contents

List of Tables

List of Figures

List of Acronyms

ACF	Active case finding
CAD	Computer-aided detection
CAD4TB	Computer Aided Detection for TB
CDC	Centers for Disease Control and Prevention
CRP	C-Reactive Protein
CS	Cabinet Secretary
CXR	Chest X-ray
DG	Director General
FGD	Focus Group Discussions
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
HIC	High Income countries
IGRA	Interferon Gamma Release Assay
IPT	Isoniazid preventive therapy
KMA	Kenya Medical Association
KMTC	Kenya Medical Training Centre
LMIC	Lower-and middle-income countries
LMICs	Lower-and middle-income countries
LTBI	Latent TB Infection
M&E	Monitoring and evaluation
MDR	Multi Drug Resistant TB
MTB	Mycobacterium tuberculosis
NCD	Non-communicable diseases
NNAK	National Nurses Association of Kenya
NSP	National Strategic Plan
NTLD-program	National TB, Leprosy and Lung Disease program
NTP	National Tuberculosis program
PEPFAR	The US President's Emergency Plan for AIDS Relief
PS	Permanent Secretary
PTB	Pulmonary TB
PTLD	Post TB Lung Disease
RESOK	Respiratory Society of Kenya
TB	Tuberculosis
TPP	Target product profile
TPT	Tuberculosis Preventive Therapy
TST	Tuberculin skin test
TWG	Technical Working Group
USAID	United States Agency for International Development
WHO	World Health Organization

List of publications (submitted and planned)

Relationship of peer-reviewed publications resulting from work in this thesis and relevant thesis chapter content:

Chapter number and Title	Manuscript title, Authors and target journal	Status	Relationship between manuscript and thesis Chapter
Chapter 2. **Accuracy of computer-aided chest X-ray screening in the Kenya National Tuberculosis Prevalence Survey**	**Accuracy of computer-aided chest X-ray screening in the Kenya National Tuberculosis Prevalence Survey** Brenda Mungai, Jane Ong'angò, Chu Chang Ku, Marc YR Henrion, Ben Morton, Elizabeth Joekes, Elizabeth Onyango, Richard Kiplimo, Dickson Kirathe, Enos Masini, Joseph Sitienei, Veronica Manduku, Beatrice Mugi, The IMPALA Consortium[†], Stephen Bertel Squire, Peter MacPherson Target journal- PLOS Global Public Health	Submitted to PLOS Global Public Health on January 7th 2022 Available as a preprint on medrxiv Mungai B, Ong'angò J, Ku CC, et al. Accuracy of computer-aided chest X-ray screening in the Kenya National Tuberculosis Prevalence Survey. medRxiv. 2021:2021.10.21.21265321. https://www.medrxiv.org/content/10.1101/2021.10.21.21265321v1.	The Chapter contains more detail on methods and key policy implications.
Chapter 3. **Prevalence of non-Tuberculosis abnormalities identified during chest X-ray TB screening**	**"If not TB, what could it be?" Chest X-ray findings from the 2016 Kenya Tuberculosis Prevalence Survey** Brenda Nyambura Mungai, Elizabeth Joekes, Enos Masini, Angela Obasi, Veronica Manduku, Beatrice Mugi, Jane Ong`angò, Dickson Kirathe, Richard Kiplimo, Joseph Sitienei, Rose Oronje, Ben Morton, Stephen Bertel Squire, Peter MacPherson Target Journal- *Thorax*	Published in the *Thorax.* Mungai BN, Joekes E, Masini E IMPALA Consortium*, et al* 'If not TB, what could it be?' Chest X-ray findings from the 2016 Kenya Tuberculosis Prevalence Survey *Thorax* 2021; **76:607**-614. https://thorax.bmj.com/content/76/6/607	The Chapter contains more detail on methods, the pilot results and key policy implications. It also includes a secondary aim of calculation of CAD4TB v6.0 software analysis scores of the images and comparison to the expert radiologist diagnosis, and detailed appendices 3-7.

Chapter 4. **Operational modelling as a means of assessing policy options for the placement of chest X-ray in the patient TB screening pathway for Kenya**	**Modelling the impact of chest X-ray in alternative tuberculosis screening pathway algorithms in Kenya** Brenda Nyambura Mungai, Ewan Tomney, Richard Kiplimo, The IMPALA Consortium[†], Ben Morton, Bertie Squire Target journal- Journal of the Pan African Thoracic Society	Planned	
Chapter 6. **Introduction to operational modelling as a synthesis method for incorporating existing data into policymaking**	**Operational modelling as a synthesis method for incorporating existing data into policymaking: The Kenya experience** Brenda Nyambura Mungai, Ewan Tomney, The IMPALA Consortium[†], Ben Morton, Bertie Squire, Rose Oronje Target journals- *Health Research Policy and Systems ,* Health policy and planning	Planned	

Abstract

Tuberculosis (TB) is among the leading infectious killers in the world. Despite increases in case detection, there are still three million people with TB who are undiagnosed, untreated or not reported to national programmes. Scaling up of systematic TB screening and use of more sensitive diagnostic tools is required to identify missing people with TB. Chest X-ray (CXR) and computer aided diagnostic (CAD) software for TB are now recommended by the World Health Organization as useful tools for TB screening and triage. Policymakers in lower-and middle-income countries must, however, contextualize this guidance and consider which tools to adopt, and how they will incorporate these into their algorithms. Operational modelling using the Witness package, a visual and interactive modelling tool, has been demonstrated to aid policymakers in decision making processes. It, however, remains unclear where operational modelling would best fit in the policy process and its influence and usefulness in the policy development process has not been formally studied.

The overall aim of this study was to generate new knowledge related to CXR use in TB screening, develop an operational model using this information and other sources, and assess if the modelling approach is a feasible technique to influence TB policy in Kenya. This mixed-methods, multidisciplinary study incorporated clinical research, operational modelling and policy analysis. Secondary retrospective quantitative analysis was conducted on cross-sectional study data using individual-level participant CXR data from adult community members who took part in the 2016 Kenya National TB Prevalence Survey. An operational model was built to assess the impact of scale up of CXR in different screening and diagnostic algorithms. Finally, a qualitative, retrospective, and prospective analysis of lung health policy in Kenya was conducted employing the policy triangle and heuristic frameworks.

This process generated novel findings related to CXR use in TB screening with important health policy implications. Firstly, the accuracy of CAD met the optimal WHO target product profile for a community TB screening tool. The specificity was lower in adults with previous TB and those aged 41 years or older hence an adaptive approach to setting CAD thresholds will be required to optimize use. Secondly, the use of CXR for TB population-based studies identified many patients with non-TB related abnormalities that would likely be missed by use of CAD. Implementation of CXR TB screening offers an opportunity to integrate disease screening efforts and improvement on all future CAD versions would require scoring for non-TB abnormalities.

The modelling demonstrated that a strategy using CXR-CAD screening for all, then GeneXpert though the most expensive, had the ability to identify more persons with TB. Though a relatively new concept, operational modelling was an acceptable and feasible tool to aid in TB policymaking in Kenya and a framework for its adoption in policymaking was developed.

Acknowledgements

This thesis has truly been a multidisciplinary work of science! I would like to appreciate everyone who contributed all through from funding, to protocol development, implementation and documenting of this research.

I would first like to thank Professor Jeremiah Chakaya for starting off my PhD journey by directing me to the IMPALA funding opportunity and for being a great mentor. This research was funded by the National Institute for Health Research (NIHR) (IMPALA, grant reference 16/136/35) using UK aid from the UK Government to support global health research. I am grateful for the funding which covered my tuition fee, stipend, research costs including software purchase, publication costs and travel. Appreciation to African Institute for Development Policy for hosting me during the period of the PhD study.

To my supervisors Professor Bertie Squire, Dr Rose Oronje and Dr Ben Morton, thank you for guiding me through these four years academically, professionally and at a personal level. The supervisory combination of: years of experience in the tuberculosis field and ability to see the bigger picture (Bertie), deep understanding of policy and qualitative research (Rose) and keen eye to detail and structure (Ben), has built me as a researcher and I am eternally grateful. Appreciation also goes to my PhD advisory panel: Dr Angela Obasi, Dr Eliya Zulu and Dr Maxine Caws, for the guidance, insightful comments and encouragement. The annual meetings were always a point of reflection and were truly appreciated.

I would also like to specifically thank a team that was involved closely in my PhD research. Dr Jamilah Meghji who gave input during the conceptualisation of the study and pointed me to Dr Peter MacPherson`s direction. Dr Elizabeth Joekes and Dr Peter MacPherson who helped in conceptualising and planning the CXR study. Appreciation to Dr MacPherson, it was an honour working with you, your wealth of expertise in epidemiology, statistics and passion for new technology in TB has helped me learn a lot.

I would like to especially appreciate your patience in running the latent class model which took days! I appreciate Drs Elizabeth Joekes, Veronica Manduku and Beatrice Mugi for the radiology expertise provided throughout the course of this PhD. I am grateful to Dr Ivor Langley for introducing me to operational modelling and Ewan Tomeny for the training and support on modelling. Thanks to Hannah Mwaniki my research assistant.

I would like to offer my special thanks to the entire 2016 Kenya Tuberculosis Prevalence Survey team and the Division of National Tuberculosis, Leprosy and Lung Disease Program who provided programmatic support and data for part of this thesis. I would like to specifically mention the core members of the prevalence survey team who were instrumental during this study: Dr Joseph Sitienei (Principal Investigator), Dr Enos Masini (Co-Principal Investigator), Dr Jane Ong`ang`o (Study coordinator), the Information Technology team- (Martin Githiomi, Dickson Kirathe and Richard Kiplimo). During the course of the PhD, I received support from three different National Tuberculosis, Leprosy and Lung Disease Program managers who facilitated the implementation of this study. Thank you Drs Maureen Kamene, Elizabeth Onyango and Warqo Erjesa for engaging and facilitating me to undertake this policy PhD. I am indebted to the key informants and the staff who gave their time and support to participate in the study.

Finally, I would like to thank my family-mum, brothers and sister for making sure I stay on course. And to my partner, thank you for cheering me on. To my children, Eric and Zani (our IMPALA baby), you have been a source of inspiration! Thank you for your patience when mum had to spend hours writing! I hope through it all I have modelled resilience and keeping eyes on the prize while being the best mum I could be!

1 Introduction

This introductory chapter outlines the context, rationale, research aims and objectives, and the general methodology of the work presented in this thesis.

1.1 Background

1.1.1 Global burden of TB

Tuberculosis (TB) is a disease of global health concern with an estimated 10 million people falling ill with TB annually.[6] Prior to the COVID-19 pandemic, TB was the leading cause of death from a single infectious agent.[6] Globally, there was an 18% decline in TB case finding from 7.1 million in 2019 to 5.8 million in 2020 attributable to the effects of the COVID-19 pandemic.[6] This resulted in four million people with TB either undiagnosed or not reported to national TB programmes in 2020.[6]

In an effort to identify undiagnosed people with TB, countries have adopted more sensitive diagnostic tools, including World Health Organization (WHO)-recommended molecular rapid diagnostic tests for TB for example GeneXpert; scaled up intensified active case finding (ACF), and their screening and diagnostic algorithms to include chest X-ray (CXR) as a sensitive and efficient high-throughput initial screening test.[7-9] Digital CXRs with computer-aided detection (CAD) software algorithms that provide a probabilistic score for TB are now recommended by WHO as useful tools for TB screening and triage to improve case finding. [9, 10] However, to successfully implement this, policymakers in lower-and middle-income countries (LMICs), must contextualize this guidance, consider which tools to adopt, and how they will incorporate these into their screening and diagnostic algorithms. Additionally, they must consider the wider health systems impact of adopting these tools and algorithms.

1.1.2 CXR use in TB screening

Historically, miniature radiography for mass TB screening activities was widely utilized in high-income countries throughout the 20th century.[11-14] In LMICs, however, CXR has been used primarily as a complementary tool to support clinical diagnosis of patients who are sputum smear negative.[15] Following the findings from national TB prevalence surveys that have employed CXR for screening, there is renewed interest in the utility of CXR for TB screening, and to triage people seeking care with symptoms for further TB investigations.[16-19] In TB prevalence surveys conducted in LMICs, CXR has shown high sensitivity for pulmonary TB (PTB) (94%, 95% CI 88–98), but poor specificity (73%, 95% CI 68–77), necessitating confirmation with a microbiological test.[2, 3, 20] In addition, CXR can detect infectious, but asymptomatic TB patients. This is important as a substantial fraction of TB transmission is attributable to the often prolonged asymptomatic infectious period.[21] Mathematical modelling of various TB screening algorithms as well as diagnostic algorithms shows that CXR followed by Gene Xpert, though resource intensive, has the lowest number needed to screen to identify a case.[22]

Barriers to widespread CXR use include limited access to high quality radiography equipment, critical shortage of radiologists in LMICs, and inter-and intra-observer variations during interpretation. [11, 23-25] Increased digital CXR availability, coupled with the development of CAD software for identification of TB, has the potential to enable widespread use of CXR in screening for TB in areas with limited access to radiologists or expert clinicians.[10, 25-27]

1.1.3 Health system effects of CXR use in TB screening

An effective and sustainable TB screening program would require a responsive health system.[28] Use of CXR would likely have implications on all six of the WHO building blocks of health systems (Figure 1.2).[29] For example, there would be need for health professionals for radiological interpretations and clinical management of the identified conditions, referral mechanisms, relevant medical products and interventions, financing

and policy guidance.[29] Implementation of CXR TB screening should therefore be conducted within overall health systems planning processes to ensure the gaps anticipated are planned for.[28, 30]

Figure 1.1: The WHO health system building blocks framework.

Source: WHO 2007[29]

1.2 Kenya context

1.2.1 Burden of lung diseases and tuberculosis in Kenya

In Kenya, respiratory diseases account for 25% of the outpatient department morbidity and are among the five highest causes of mortality.[31] Pneumonia and other related diseases account for 9% of hospital admissions, and pneumonia is the second highest cause death in Kenya after malaria contributing to 12% all-cause mortality.[32] National level data on the burden of lung diseases is comprehensive for pneumonia and TB but scanty for the other lung diseases.[33] Kenya is a high burden TB country with an estimated incidence of 259 cases per 100,000 population in 2020.[6]

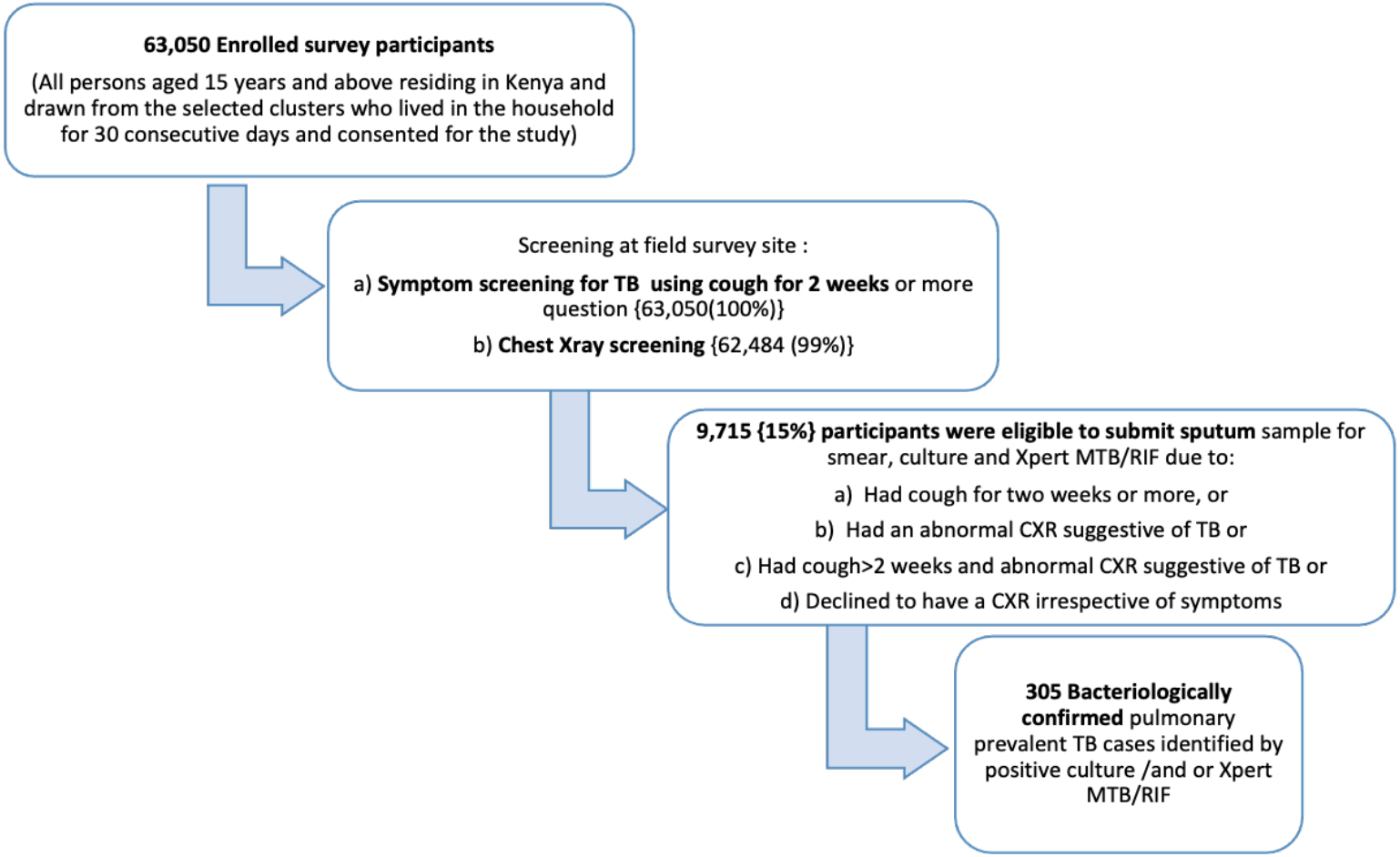
1.2.2 Overview of the Kenya National Tuberculosis prevalence survey 2016

A national TB prevalence survey carried out in 2016 showed a TB prevalence of 558 [95%CI 455–662] per 100,000 adult population. Extrapolated, this suggests that 56% of TB cases are missed in the Kenyan context.[2] The aim of the 2016 Kenya prevalence survey was to determine the prevalence of bacteriologically confirmed pulmonary TB among adults aged 15 years and older, and to assess the health seeking behaviour of TB patients and those reporting TB symptoms.[2, 3] The survey, reported fully elsewhere,[2, 3] used the WHO-recommended screening strategy including symptom questionnaire and CXR.[17] The survey procedures are summarised in subsequent chapters' section 2.3.2. Figure 1.2 below shows the prevalence survey cascade from participants enrolment to bacteriological confirmation. From the 63,050 enrolled participants, 62,484 were screened for TB using CXR, 9,175 were eligible for sputum testing (culture and GeneXpert), and 305 were bacteriologically confirmed to have TB. This PhD focused on new analyses of data from the 62,484 survey participants who had chest-X-ray TB screening conducted (Chapters 2 and 3) and consideration of how these analyses fed into the operational modelling and policy uptake (Chapters 4 and 5).

1.2.3 Kenya health system

Kenya, a country in East Africa with a population of approximately 52 million, has a devolved system of governance with one national government and 47 county governments. [34, 35] Health services delivery is a fully devolved function with implementation and provision of health services being a responsibility of the county government. The national government - in the case of health- Ministry of Health (MOH) is responsible for national health policy formulation, health regulation, capacity building, technical assistance to counties and management of national referral health facilities.[36] The NTLD-program is responsible for TB and lung health functions at national level.[37]

Figure 1.2: Kenya National TB prevalence survey 2016 cascade showing participants pathway from enrolment to bacteriological confirmation.



This figure adapted from the Kenya prevalence survey publication.[2, 3] The PhD focused on new analyses of data from the 62,484 participants who had chest-X-ray screening conducted (Chapters 2 and 3) and consideration of how these analyses fed into the Operational Modelling and Policy Uptake (Chapters 4 and 5).

1.3 Study rationale

Following the prevalence survey results dissemination, there was impetus to seek how best to include CXR use in the TB screening and diagnostic algorithms policy in a bid to accelerate TB case finding. I was interested to explore how diagnostic screening strategies could be implemented to improve pick up of disease and reduce the risk of community transmission. This was the starting point for this PhD thesis.

Similar to the impact assessment framework (IAF) by Mann et al, [38] the questions that the TB policymakers were battling with were:

- Effectiveness analysis: What is the effectiveness of CXR in finding persons with TB in the community? What is the accuracy of CAD software in the Kenya context?
- Equity analysis: Who would CXR and CAD screening benefit?
- Health system analysis: What would be the health system effects (human resource implications, infrastructure, procurement, referral system for management of other conditions)?
- Scale-up analysis: What would be the projected impacts of scale up?
- Policy analysis: How do the various screening and diagnostic algorithms applying different tools compare to each other?

I therefore sought to help address some of the concerns that the Kenyan policymakers had through this PhD study. Operational modelling using the Witness package, a visual and interactive modelling tool, had been demonstrated to aid policymakers in the decision making process, by enabling projection of health system and patient impacts of introducing new diagnostic algorithms. [39-43] This study explored the role of operational modelling in guiding policymakers in assessing CXR algorithm options for TB screening in Kenya and project the likely health system impact of CXR roll out. Virtual operational

modelling was a new concept in Kenya. Additionally, the study looked at the utility and feasibility of integrating the modelling in the policymaking process.

1.4 Aim and objectives

The overall aim of my PhD study therefore was to generate new knowledge related to CXR use in TB screening, develop an operational model using this information and other sources, and assess whether operational modelling is a feasible technique to support evidence-informed TB policymaking in Kenya. Our findings would be useful to guide in adoption of operational modelling as a policymaking tool.

Specific objectives:

1. To evaluate the accuracy of automated chest x-ray interpretation for tuberculosis in the 2016 Kenya National Tuberculosis Prevalence Survey
2. To describe and determine the prevalence of non-TB thoracic pathology detected during CXR screening using images from the 2016 Kenyan TB prevalence survey
3. To assess policy options for the placement of CXR in the patient TB screening and diagnostic patient pathway in Kenya using operational modelling
4. To describe an approach for including predictive modelling as a synthesis method for maximising use of existing data in evidence-informed policymaking

1.5 Methodology overview

This research combines the multidisciplinary approach of clinical research, operational modelling and policy analysis to promote the translation of evidence to policy implementation and incorporation into routine practice. This section gives an overview of the study design and methodology used per specific objective. The full methodology description will be covered in more detail in chapters 3-7 of the thesis.

Objective 1 and 2- Secondary retrospective quantitative analysis was conducted on cross-sectional study data using individual-level participant CXR data from adult community members who took part in the 2016 Kenya National TB Prevalence Survey.[3]

For objective 1, the anonymized, compressed 62,484 DICOM X-ray images from participants in the Kenya TB Prevalence Survey were uploaded from the digital archive onto the Delft Computer Aided Detection for TB (CAD4TB) cloud server. These images were processed and analysed using CAD4TBv6 software. [44]

For objective 2, a random sample of 1140 adult (≥15 years) CXRs classified as "abnormal, suggestive of TB" or "abnormal other" during field interpretation from the TB Prevalence Survey were reviewed. Each image was read (blinded to field classification and study radiologist read) by two expert radiologists, with images classified into one of four major anatomical categories and primary radiological findings. A third reader resolved discrepancies.[45]

Objective 3- A quantitative study using Witness (a discrete event and continuous process simulator package) to develop an operational model.[39] This model was to assess the impact of scale up of CXR in different triaging and diagnostic algorithms. The model inputs included findings from the prevalence survey, WHO guidance on CXR use in TB models, expert interviews, TB program data and literature review. In addition, input from the computer aided detection software, non-TB pathology studies and key informant interviews in policy analysis (Objective 1, 2 and 4) fed into the model.

Objective 4- A qualitative, retrospective and prospective analysis of lung health policy in Kenya employing the policy triangle and heuristic frameworks.This involved desk reviews of the policies, observation and semi-structured interviews of the key actors in policy formulation in Kenya.

1.6 Thesis outline

Chapter 1 sets the scene with general introduction, context, rationale aims and objectives as well as general methodology.

Chapter 2 evaluates the diagnostic accuracy of CAD software and explores its role in TB screening activities in LMICs.

Chapter 3 then describes a retrospective study on the prevalence of non-tuberculosis findings when chest X-rays were used in the 2016 Kenya National TB Prevalence Survey.

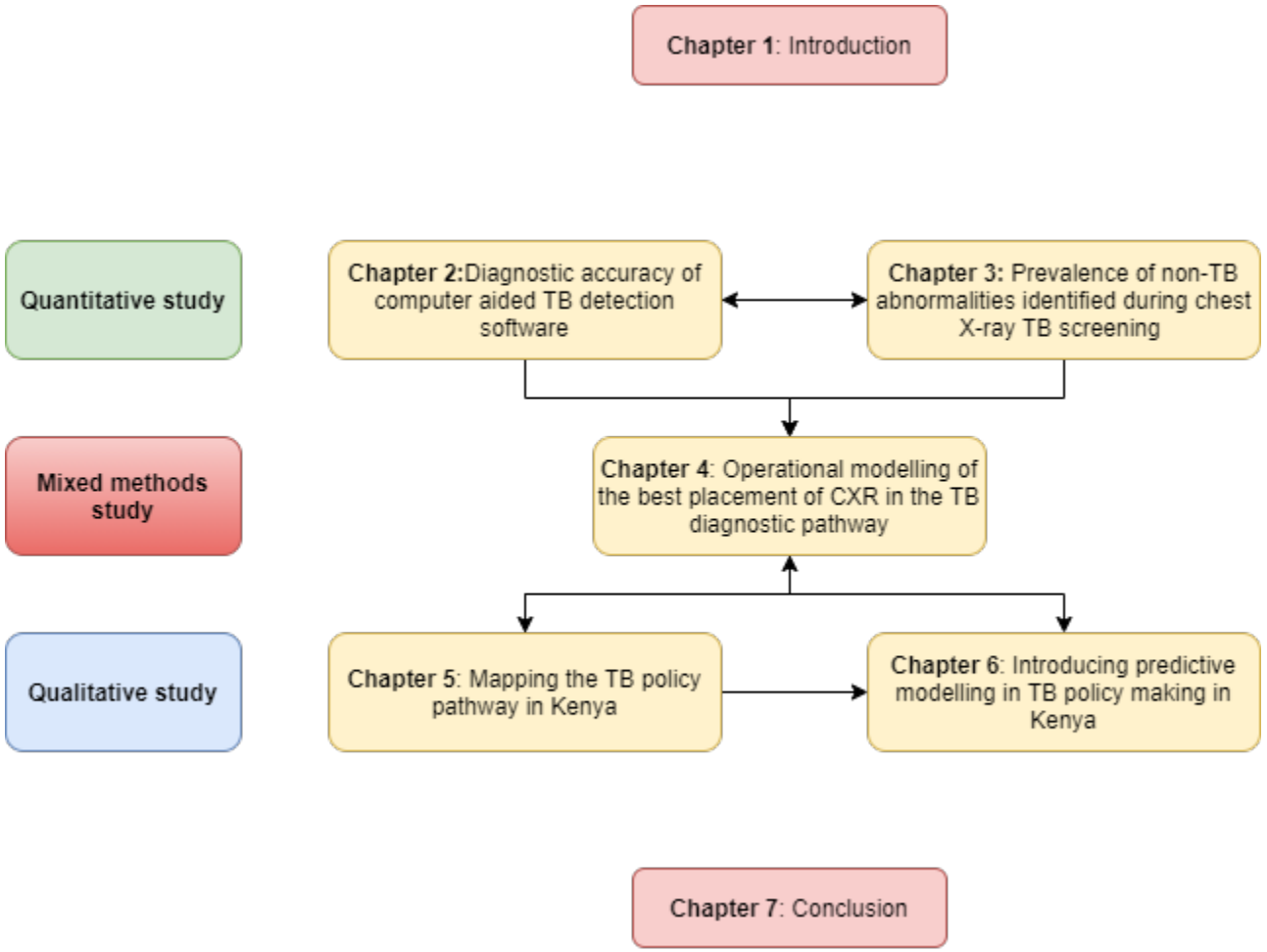
Chapter 4 uses findings from Chapters 2&3 as well as other data sources as inputs to the development of an operational model assessing different placements of CXR in diagnostic and screening algorithms.

Chapter 5 refers to a qualitative study that sought to understand steps to policy in lung health processes involved and actors involved. The findings from Chapter 4&5 then help in the development of a framework of integrating operational modelling into policymaking in **Chapter 6**.

The main conclusions, recommendations and way forward are discussed in **Chapter 7**.

The novel work in this PhD is presented in five stand-alone chapters (Chapters 2-6) each with introduction, literature review, methodology, results, discussion, and conclusion sections in accordance with the STROBE guidelines. In addition, the key policy implications are captured at the end of each study chapter.

Figure 1.3: A schematic diagram of the PhD thesis outline.



This figure shows the thesis outline as well as the type of study conducted for the respective chapters.

2 Accuracy of computer-aided chest X-ray screening in the Kenya National Tuberculosis Prevalence Survey

2.1 Introduction

As outlined in Chapter 1, following the WHO recommendation on the use of digital CXR and CAD software for systematic TB screening, there was need to determine the accuracy of CAD in community-based TB screening.[9] This chapter presents a review of literature on CAD software in TB screening, a study on its accuracy in community-based screening in Kenya, and the policy implications of the findings.

2.1.1 Aim of the study

The aim of the study was to evaluate the accuracy of the Computer-Aided Detection for Tuberculosis version 6 (CAD4TBv6) system for TB screening using a large data set (n=61,848) from the 2016 Kenya National TB prevalence survey. A Bayesian modelling approach was applied, to evaluate the accuracy of CAD4TBv6 and clinical officer CXR interpretation against the microbiological reference standard used within the prevalence survey.

The hypothesis was that CAD4TBv6 diagnostic sensitivity and specificity would meet the target product profile (TPP) for a test to identify people with presumptive TB, but that accuracy would vary between population groups, implying that an adaptive approach to CAD screening would be required.[46]

2.1.2 Study implications

The study findings were used to help inform operational modelling inputs on the accuracy of CAD if it was to be used as an alternative to human readers during CXR roll out in Kenya. The operational modelling on CXR in Kenya is as outlined in Chapter 4 of this thesis. It is important to determine the performance of CAD in population based screening to help inform policy and practice on use of CAD across different population groups and screening strategies.

This study has been submitted for publication and is available as a preprint (Mungai BN, Ong'ang'o J, Chu Chang et al. Accuracy of computer-aided chest X-ray screening in the Kenya National Tuberculosis Prevalence Survey. medRxiv. 2021).[44]

2.2 Literature review

With over 95% tuberculosis (TB) cases and deaths occurring in developing countries, there is need for substantially improved case detection to find the "missing millions" and accelerate action to achieve the sustainable development goals to end TB by 2030. [47-50] CXR with CAD software for TB has been recommended for TB systematic screening for adults and adolescents aged 15 years and older.[9] However, supporting data have predominantly come from clinical triage settings yet CAD diagnostic accuracy is likely to vary considerably across different screening strategies and populations. [51-53] Calibration of CAD in different contexts and settings is therefore required.[9]

CAD software provides a probabilistic score for TB and offers a potential high throughput solution to the limitation of shortage of radiologists and inter-and intra-reader variability presented in section 1.1.2.[25, 51, 52, 54-56] CAD software has been demonstrated to significantly outperform expert human readers for the selected objective of TB detection, and reduce TB treatment initiation time. [55, 56] Previous evaluations of CAD software have been mostly conducted in triage testing use situations i.e. Patient initiated health care pathways where the prior probability of TB and/or other pathology is higher than in community-based screening. [51, 53, 55, 57] There is scarce data available to evaluate accuracy in community-based TB screening interventions.

As countries like Kenya plan to adopt the new WHO guidelines, some of the implementation considerations will be performance of CAD in community-based TB screening ACF activities.[25, 27] TPPs summarize the performance and operational characteristics a test should have to address the end-users need.[46, 58] A community-based triage or referral test for identifying people with presumptive TB should be used at the entry point to the health care system.[46] At the minimum, it should have

overall sensitivity of >90% compared to the confirmatory test with >70% specificity.[46] Optimal TPP should have overall sensitivity of >95% with a sensitivity of >80%.[46] This study therefore sought to evaluate if CAD accuracy in community-based TB screening met the minimum and optimum TPP.

2.3 Methods

2.3.1 Study Design

This was a retrospective analysis of cross-sectional individual-level participant data from adult community members who participated in the 2016 Kenya National TB Prevalence Survey.[3]

2.3.2 Study population and Kenya TB prevalence survey procedures

The 2016 Kenya prevalence survey has been detailed in section 1.2.2. This was a nationwide cluster-based survey with a total of 63,050 participants recruited at community level (Figure 1.1). For this study, there were 61,848 (99%) analysable CXR images out of the 62,484 survey participants who had CXR taken, all aged 15 years and above.

Prevalence survey participants completed a questionnaire to elicit TB symptoms. Subsequently, a digital posterior anterior CXR (CXDI, Delft Imaging, The Netherlands) was digitally acquired, and uploaded to a digital archive. Study Clinical Officers who had received intensive one-week training in CXR interpretation independently read each film, blinded to bacteriological results (clinical officer characteristic are summarised in Chapter 8 Appendix 1). Clinical officers classified CXRs as either: A) normal; B) abnormal, suggestive of TB; or C) abnormal other, in line with published definitions.[3] Participants with a CXR classified as “abnormal, suggestive of TB” by either one of the Clinical Officers, or with a cough of more than two weeks or who declined CXR screening were eligible for sputum collection.

Two sputum samples (spot and following morning) were obtained from eligible participants and transported to the National Tuberculosis Reference Laboratory and tested with GeneXpert MTB/Rif. Solid culture using Lowenstein Jensen medium

(incubation at 37°C) was conducted on all samples and reported as negative if there was no growth after eight weeks. To confirm the presence of *Mycobacterium tuberculosis* complex, all visible colonies grown on culture media were confirmed by acid-fast bacilli (AFB) microscopy and tested for presence of Mycobacterium protein 64 (MPT64) by SD Bio line Immunochromatographical assay. Geno-Type Mycobacterium AS (Hain Life Science) test kits were used to identify presence of non-tuberculous mycobacterium.[2, 3]

Participants with bacteriologically-confirmed pulmonary TB (sputum GeneXpert and/or culture-positive) were referred for TB treatment; participants with CXR abnormalities and no bacteriological evidence of TB were linked to health facilities for clinical assessment. HIV testing was not undertaken as part of TB prevalence survey activities. In line with national guidelines, participants referred for TB treatment were offered HIV testing at referral facilities.

2.3.3 Study procedures and definitions

The analysis was conducted between January 2020 and October 2021. A total of 62,484 anonymised, compressed DICOM CXR images were uploaded from the prevalence survey digital archive to the Delft Imaging CAD4TB cloud server and analysed using CAD4TBv6. [59] Results were provided as probabilistic scores, ranging from 0 to 99, with higher scores indicating a greater probability of TB. The reference standard for this analysis was bacteriologically-confirmed TB, defined as sputum GeneXpert and/or culture positive with MTB speciation. Analysis was conducted independently; the commercial provider (Delft Imaging) was not part of the study team and had no role in study design, data collection, analysis, or interpretation of results.

2.3.4 Statistical analysis

Dr Peter MacPherson a Wellcome Trust Fellow & Reader in Population Health led the statistical analysis. Dr Chu Chang Ku (Imperial College London) and Dr Marc YR Henrion (Liverpool School of Tropical Medicine) conducted the Bayesian modelling.

The characteristics of prevalence survey participants were summarized using means (with standard deviations), medians (with interquartile ranges), and percentages, and compared by clinical officer CXR interpretation. We used the Kruskall-Wallis test to investigate differences in CAD4TBv6 scores between Clinical officer interpretation groups, and Chi-square and Fisher's exact tests for categorical participant characteristics. Distributions of CAD4TBv6 scores were summarized by medians and 95% highest density intervals (HDI) and compared by whether sputum was collected or not, and by sputum bacteriological status.

For the primary outcome, the accuracy (sensitivity, specificity, and area under receiver-operator curve [AUC]) of CAD4TBv6 was compared with the bacteriological reference standard. As collection of sputum was conditional on either a participant reporting having cough of two weeks or greater or a Clinical Officer CXR classification of "abnormal, suggestive of TB", Bayesian latent class modelling was employed to infer disease prevalence within the portion of the study population without TB symptoms or CXR signs suggestive of TB, and to estimate the sensitivity, specificity, and AUC of CAD4TBv6 at thresholds ranging from 0 to 99. The model also produced output estimates of the underlying status of active pulmonary TB, and the sensitivity and specificity of Clinical Officer CXR interpretation as a screening tool and of sputum bacteriological results for the underlying true TB status. Full model details and diagnostics are reported in Chapter 8 Appendix 2. We placed informative priors on the overall prevalence of TB, inferred by the prevalence survey results, and weakly informative priors on other model parameters. To aid model convergence, we fixed specificity of the combined bacteriological reference standard (GeneXpert or culture positive) to be 99%.

Models were fitted in Stan using the cmdstanr interface, with convergence assessed by inspecting trace plots across three sampling chains and Gelman-Rubin statistics. Inference was based on summarising 12,000 post-warm-up samples. We plotted model posterior summary estimates of sensitivity and specificity across CAD4TBv6 thresholds, and compared to optimum (sensitivity: 95%, specificity: 80%) and

minimum (sensitivity: 90%, specificity: 70%) TPP for a community or referral test to identify people with presumptive TB. [46] In secondary analysis, we restricted model sensitivity and specificity estimates for participants by age group, sex, chronic cough status and history of previous TB treatment, and summarised as a function of CAD4TBv6 threshold, estimating what accuracy would be achieved by setting an overall screening CAD4TBv6 threshold to achieve the optimum TPP sensitivity cut-off (95%). We did not stratify by HIV status, as there was substantial missing data and testing was not performed in the prevalence survey. All analysis was done using R v4.1.1 (R Foundation for Statistical Computing, Vienna).

2.3.5 Ethical considerations

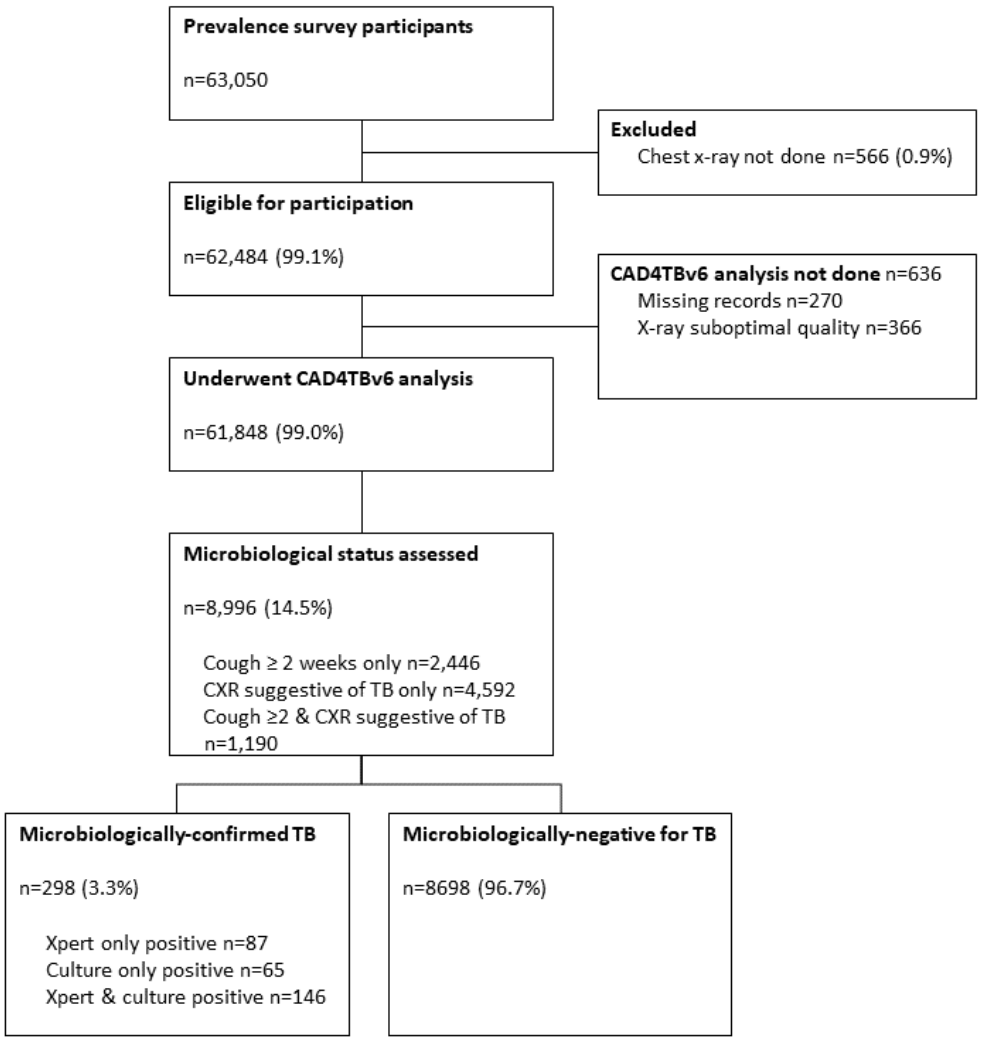
This study was conducted as part of the Kenya Prevalence survey ethics approval SSC 2094 by the Kenya Medical Research Institute. Participants provided written informed consent for survey activities. Additional approval was obtained from the Division of National Tuberculosis, Leprosy and Lung Disease program which is the custodian of the survey data. The data was processed within the Kenya Health Informatics System Governance [60] and General Data Protection Regulations.[61] All CXR images were deleted from the Delft Imaging server after analysis as contractually stipulated.

2.4 Results

2.4.1 Participant characteristics and Field Reader chest X-ray interpretation

A total of 62,484 CXR images were uploaded for CAD4TBv6 processing. After exclusion of 636 images that were either not analysable by the CAD4TBv6 software or had missing clinical data, 61,848 (99.0%) were included for analysis (Figure 2.1).

Figure 2.1: Participant flowchart and results of prevalence survey investigations



This figure shows a cascade from enrolment (n=63,050) to the number eligible for the CAD4TB analysis (n=61,484). From that sub-set, those who underwent microbiological assessment were 14.5% and 3.3% of those were bacteriologically confirmed to be positive.

Of the 61,848 participants whose images were analysed, 58.5% (36,187) were women and 70.7% (43,754) were aged <45 years (Table 2.1). Two thousand and eighty-four (3.4%) had previously been treated for TB, and 58 (0.1%) were currently being treated for TB. Overall, HIV positive status was self-reported by 1,577/31,495 (5.0%) of participants with data available.

Clinical officers classified 50,045 (80.9%) CXRs as “normal”, 5,045 (8.2%) as “abnormal, other”, and 6,758 (10.9%) as “suggestive of TB” (Table 2.1). Compared to participants with CXRs classified by clinical officers as “normal” or “abnormal, other,” participants with CXRs classified as “suggestive of TB” were more likely to be men, self-report positive HIV status, report TB symptoms including cough, prolonged cough, fever, weight loss and night sweats, and have been previously treated for TB. CAD4TBv6 scores were significantly higher among participants whose CXR were classified as “suggestive of TB” (median: 52, IQR: 46-62), compared to those classified as “normal” (median: 43, IQR: 24-46) or “abnormal, other” (median: 48, IQR: 45-53), $p<0.0001$.

Table 2.1: Characteristics of participants in Kenya National TB prevalence survey, by Clinical Officer chest X-ray interpretation

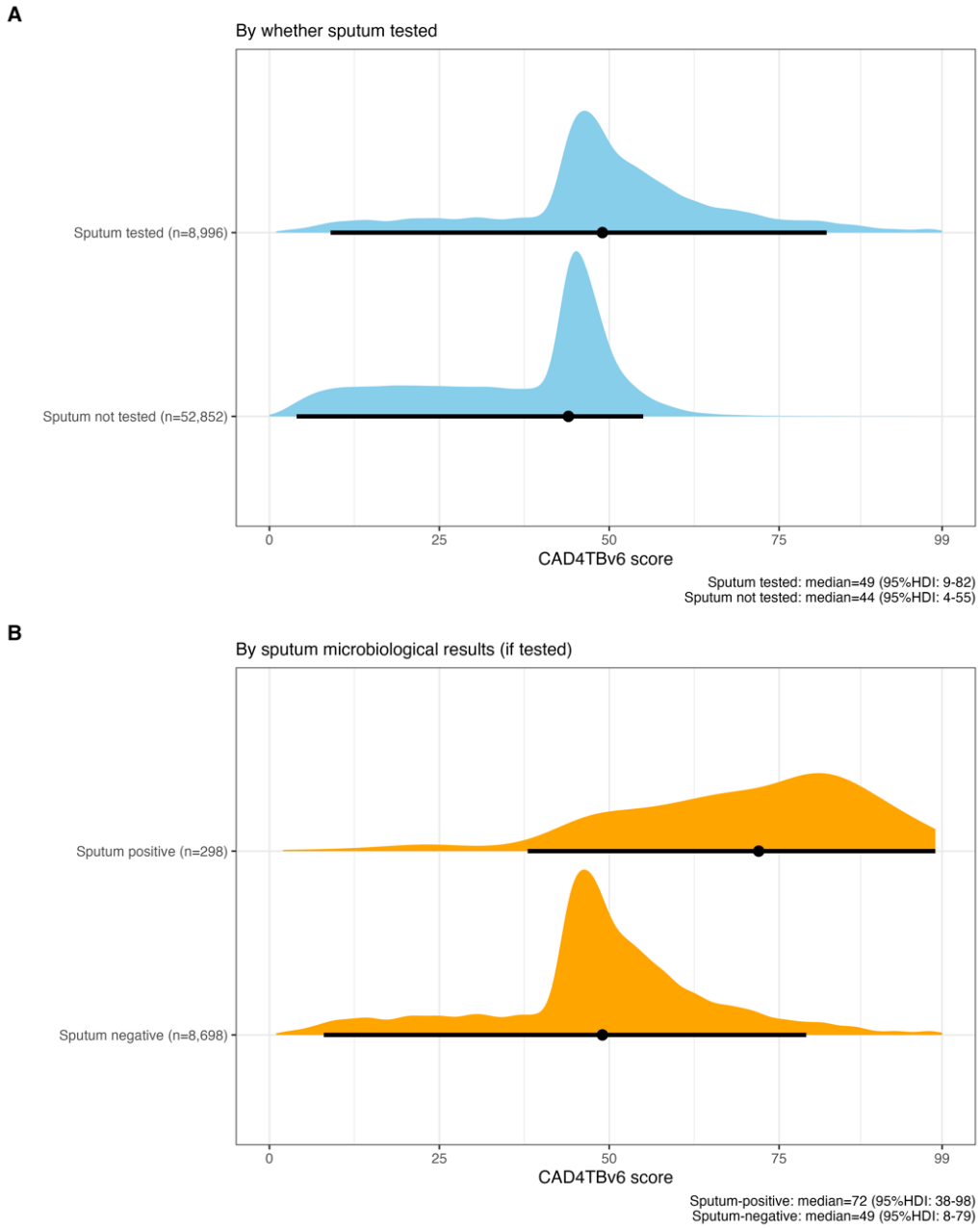
	Normal (N=50,045)	Abnormal, other (N=5,045)	Suggestive of TB (N=6,758)	Total (N=61,848)	P-value[†]
Age group					< 0.001
15 – 24 years	16,305	403 (8.0%)	742 (11.0%)	17,450	
25 - 34 years	13,400	627 (12.4%)	1,167 (17.3%)	15,194	
35 - 44 years	9,072 (18.1%)	765 (15.2%)	1,273 (18.8%)	11,110	
45 - 54 years	5,553 (11.1%)	831 (16.5%)	1,032 (15.3%)	7,416	
55 - 64 years	3,210 (6.4%)	901 (17.9%)	957 (14.2%)	5,068 (8.2%)	
65+ years	2,505 (5.0%)	1,518 (30.1%)	1,587 (23.5%)	5,610 (9.1%)	
Sex					< 0.001
Women	29,432	3,410 (67.6%)	3,345 (49.5%)	36,187	
Men	20,613	1,635 (32.4%)	3,413 (50.5%)	25,661	
HIV-status[*]					
Missing	23,895	2871	3,587	30,353	
HIV-negative	24,985	2,055 (94.5%)	2,878 (90.8%)	29,918	< 0.001
HIV-positive	1,165 (4.5%)	119 (5.5%)	293 (9.2%)	1,577 (5.0%)	
Cough					< 0.001
No	43,989	4,065 (80.6%)	4,752 (70.3%)	52,806	
Yes	6,056 (12.1%)	980 (19.4%)	2,006 (29.7%)	9,042	
Cough>2 weeks					< 0.001
No	47,859	4,504 (89.3%)	5,484 (81.1%)	57,847	
Yes	2,186 (4.4%)	541 (10.7%)	1,274 (18.9%)	4,001 (6.5%)	
Fever					< 0.001
No	47,088	4,408 (87.4%)	5,566 (82.4%)	57,062	
Yes	2,957 (5.9%)	637 (12.6%)	1,192 (17.6%)	4,786 (7.7%)	
Weight loss					< 0.001
No	49,173	4,921 (97.5%)	6,212 (91.9%)	60,306	
Yes	872 (1.7%)	124 (2.5%)	546 (8.1%)	1,542 (2.5%)	
Night sweats					< 0.001
No	45,546	4,046 (80.2%)	5,077 (75.1%)	54,669	
Yes	4499 (9.0%)	999 (19.8%)	1,681 (24.9%)	7,179	
Current TB					< 0.001
No	50,023	5,043	6,724 (99.5%)	61,790	
Yes	22 (0.0%)	2 (0.0%)	34 (0.5%)	58 (0.1%)	
Previous TB					< 0.001
No	49,171	4,883 (96.8%)	5,710 (84.5%)	59,764	
Yes	874 (1.7%)	162 (3.2%)	1,048 (15.5%)	2,084 (3.4%)	
CAD4TBv6 score					< 0.001
Count	50,045	5,045	6,758	61,848	
Median	43.0	48.0	52.0	44.0	
Q1, Q3	24.0, 46.0	45.0, 53.0	46.0, 62.0	27.0, 48.0	

[*]HIV testing was not undertaken in prevalence survey. Number show participants who had their self-reported HIV status collected. [†]P-values calculated by Kruskull-Wallis test for CAD4TBv6 scores, Fisher's exact test for current TB treatment, and Chi-square test for all other categorical variables.

2.4.2 CAD4TBv6 scores by sputum testing and bacteriological TB status

Sputum was collected from 8,996/61,848 (14.5%) participants, of whom 298 (3.3%) had bacteriologically-confirmed TB. CAD4TBv6 scores were higher among participants who had sputum tested in the prevalence survey (median: 49, 95%HDI: 9-82) than where sputum was not tested (median: 44, 95%HDI: 4-55) -Figure 2.2. The median CAD4TBv6 score for participants with bacteriologically -confirmed TB was substantially higher at 72 (95%HDI: 38-98) compared to 49 (95%HDI: 8-79) for participants with bacteriologically-negative sputum results.

Figure 2.2: Distribution of CAD4TBv6 scores in Kenya National TB prevalence survey



A) Distribution (median and 95% highest density interval) of CAD4TBv6 scores by whether prevalence survey participant's sputum was tested or not. B) Distribution (median and 95% highest density interval) of CAD4TBv6 scores by sputum bacteriological results. 95%HDI: 95% highest density interval.

Overall, 4,678/8,996 (52.0%) of participants with sputum collected were women and the median age was 45 years (IQR: 30-61). Among those tested, more men had bacteriologically-confirmed TB (185/4318, 4.3%) than women (113/4678, 2.4%, p<0.0001). Conditional on being tested, bacteriologically-confirmed TB was higher among those with cough of more than two weeks (3.9%, 140/3636) compared to those with no cough or cough of less than two weeks (2.9%, 158/5360, p=0.022), and among participants with weight loss (5.8%, 39/671) compared to those without weight loss (3.1%, 259/8325, p<0.0003). Conditional on testing, participants who had previous TB treatment were more likely to be bacteriologically positive (7.3%, 81/1109) than those who had not been previously treatment (2.8%, 217/7887, p<0.0001).

2.4.3 Model estimated TB prevalence and accuracy of Clinical officer CXR interpretation, sputum testing and CAD4TBv6 screening

Model Gelman-Rubin statistics were all <1.01 and trace plots showed good mixing across chains (Supplemental Text 2). Mean posterior estimates of the prevalence of bacteriologically-confirmed pulmonary TB were 568 per 100,000 (95% credible interval [CrI]: 478-654) overall, 927 per 100,000 (95% CrI: 783-1090) for men, and 314 per 100,000 (95% CrI: 246-391) for women.

From the model, we estimated that the overall sensitivity of clinical officer CXR interpretation as “suggestive of TB” for bacteriologically-confirmed TB was 43.7% (95% CrI: 23.8-66.4%) and specificity was 89.2% (89.0%-89.6%) –Table 2.2. However, in stratified analysis, sensitivity of Clinical officer CXR interpretation was considerably higher (84.8%, 95% CrI: 70.0-94.2%) and specificity was lower (54.1% 95% CrI: 51.3-56.9%) among participants who had previously been treated for TB. Accuracy was similar when stratified by sex and chronic cough status. The posterior mean sensitivity of the combined sputum or GeneXpert or culture reference standard for the true underlying TB status was estimated to be 70.0% (95% CrI: 56.8%-84.6%)

overall, and was 97.0% (95% CrI: 96.5%-97.5%) among participants with cough for two weeks or longer.

Table 2.2: Model-based accuracy of screening and diagnostic tests for TB latent class

	Sensitivity (%)	95% CrI	Specificity (%)	95% CrI
Clinical officer CXR interpretation "suggestive of TB"				
Overall	43.7%	23.8 - 66.4%	89.2%	89.0 - 89.6%
Men	48.4%	27.7 - 71.0%	87.1%	86.6 - 87.5%
Women	40.3%	21.0 - 63.2%	90.9%	90.6 - 91.2%
Cough >2weeks	53.5%	33.1 - 74.2%	83.1%	82.7 - 83.6%
No cough >2weeks	43.0%	23.1 - 65.9%	89.7%	89.5 - 90.0%
Previous TB	84.8%	70.0 - 94.2%	54.1%	51.3 - 56.9%
No previous TB	42.2%	22.1 - 65.4%	90.5%	90.3 - 90.8%
Sputum GeneXpert or culture				
No cough >2weeks	70.0%	56.8 - 84.6%	99% (fixed)	--
Cough >2weeks	97.0%	96.5 - 97.5%	99% (fixed)	--
Against minimum Target Product Profile				
CAD4TBv6 (for sensitivity 90%) CAD: 61	90% (fixed)	--	90.4%	88.1 - 92.6%
CAD4TBv6 (for specificity 70%) CAD: 47	98.3%	97.6 - 98.8%	70% (fixed)	--
Against optimum Target Product Profile				
CAD4TBv6 (for sensitivity 95%) CAD: 55	95% (fixed)	--	83.2%	79.9 - 86.6%
CAD4TBv6 (for specificity 80%) CAD: 53	96.2%	95.0 - 97.3%	80% (fixed)	--

CrI: Credible interval

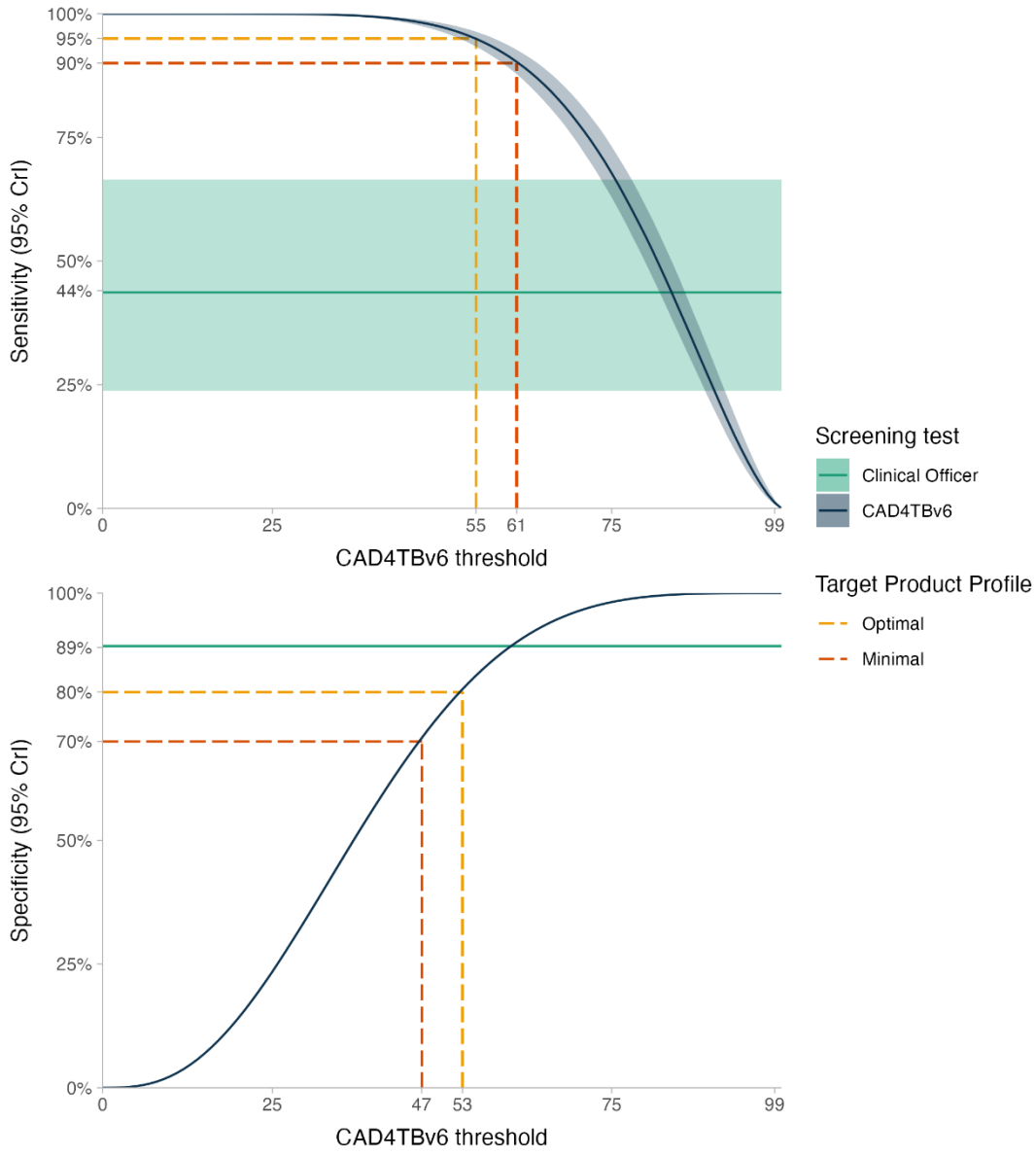
This table compares the model based accuracy of CAD4TB v6 (minimum and optimum TPP) with clinical officers' field interpretation

Area under the curve

Figure 2.3 below shows the posterior mean estimate of the AUC for CAD4TBv6 was 96.7% (95% CrI: 95.9%-97.4%). With CAD4TBv6 thresholds set to achieve a sensitivity of 90% (minimum TPP) or 95% (optimum TPP) mean specificity was 90.4% (95% CrI: 88.1%-92.6%) and 83.2% (95% CrI: 79.9%-86.6%) respectively. With CAD4TBv6

thresholds set to achieve a specificity of 70% (minimum TPP) or 80% (optimum TPP), mean sensitivity was 98.3% (95% CrI: 97.6-99.8%) and 96.2% (95.0-97.3%).

Figure 2.3: Model-based sensitivity and specificity of CAD4TBv6 for bacteriologically-confirmed pulmonary TB at minimum and optimum target product profile thresholds

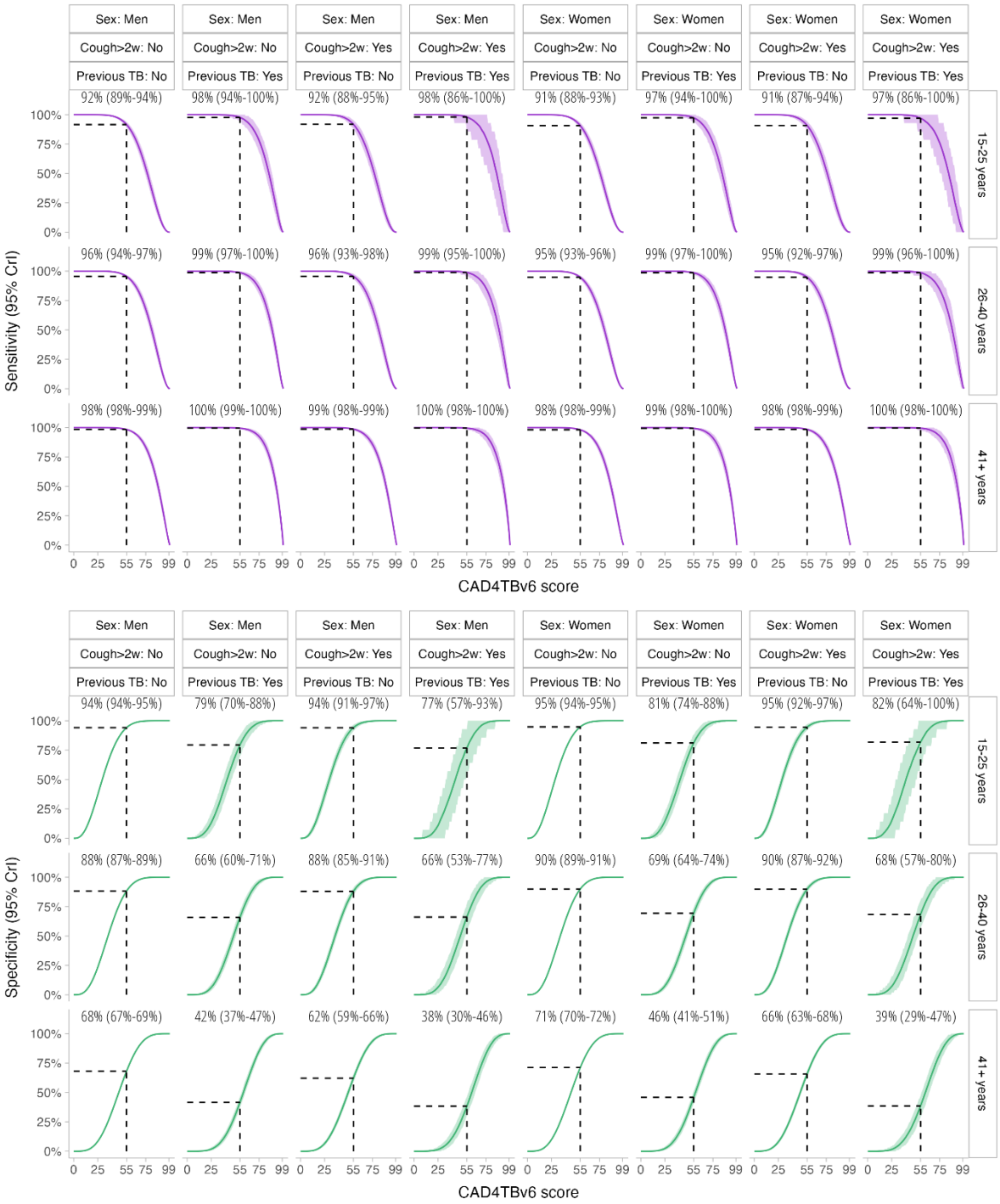


The figure shows AUC CAD4TBv6, A) Sensitivity at optimum and minimum TPP, green band shows clinical officers modelled sensitivity B) Specificity at optimum and minimum TPP and clinical officers specificity at 89%.

CAD4TB v6 performance by age, sex, cough and previous TB history

When model estimates were stratified by participant characteristics (age, sex, presence of cough of more than two weeks, history of previous TB), substantial variation in the sensitivity and specificity of CAD4TBv6 for bacteriologically-confirmed pulmonary TB was present (Figure 2.4). With the CAD4TBv6 threshold set to 55 to achieve overall sensitivity of 95% for the optimal TPP within the prevalence survey population, sensitivity was highest among participants aged 41 years and older, who had previously been treated for TB and who had cough for more than two weeks. In contrast, specificity was lowest among participants previously treated for TB, and among older participants.

Figure 2.4: Sensitivity and specificity of CAD4TBv6 by prevalence survey participant characteristics, with threshold set at optimal target product profile to achieve overall sensitivity of 95% (CAD4TBv6=55)



At CAD4TB threshold set at 55, sensitivity and specificity is similar in men and women. Sensitivity higher in 41+years and those previously treated for TB and Specificity in the same group.

2.5 Discussion

This is the first study, to the best of our knowledge, to evaluate the accuracy of computer-aided CXR screening for TB in a community-based prevalence survey. Highly specific GeneXpert and culture tests were used as the bacteriological reference standard, with Bayesian latent class modelling employed to infer disease prevalence within the portion of the study population without TB symptoms or CXR signs suggestive of TB. Overall in the screening population, CAD4TBv6 met both the minimum and optimum TPP for a community-based referral test for identifying people with a possible diagnosis of TB.[46] Very high sensitivity was demonstrated in participants in older age groups (41 years or older), those with reported cough>2 weeks and participants with previous TB history. Conversely, participants in older age groups and those with previous TB history had lower specificity. Computer-aided CXR screening is an accurate tool that could be used to support community TB screening in high burden countries where access to radiologists and clinicians is limited. To optimise screening accuracy and efficiency of confirmatory sputum testing, we recommend that an adaptive approach to screening threshold definition is adopted based on participant characteristics.

Accuracy and potential modes of implementation of CAD for community-based TB screening

Community-based ACF for TB is effective at reducing TB prevalence if delivered with sufficient and sustained intensity to high burden populations.[62, 63] However, operationalisation of ACF in a resource limited setting has been challenging due to substantial resourcing requirements and suboptimal TB screening and diagnosis tests.[24, 64] The availability of portable/ultra-portable CXRs and CAD offer a potential solution to conduct community-based ACF for at risk groups in densely populated urban areas where TB transmission is now concentrated.[55] The study demonstrated that, overall within the prevalence survey population, CXR based screening in combination with CAD is highly accurate. CAD gives the additional flexibility for TB programs to vary the

threshold for sputum testing with a saving of up to 50% of GeneXpert tests.[55] Given the limited resources available to National TB Programmes, by varying the CAD screening threshold, the number of TB cases deemed acceptable to be missed can be balanced against how much money is available to spend on expensive confirmatory sputum investigation.[55] By adopting an adaptive threshold within population groups, we believe that further gains in accuracy and programme efficiency can be gained. CXR and CAD as tools for community-based TB screening ACF, additionally offer the potential for individuals and TB programmes, including: earlier diagnosis; identification of asymptomatic TB, potentially reducing transmission; reductions in false positive bacteriological tests with harm from prolonged unnecessary treatment; and reduction in catastrophic costs.[21, 55, 56]

CAD accuracy finding is likely to be generalizable

The prevalence survey participants though randomly selected at population level, had a higher enrolment of women who accounted for 59% of the enrolled participants.[2, 3, 17] Overall, there was a high participation rate of 83% (63,050 enrolled out of the 76,291 eligible), higher amongst women than men (87% vs 77%).[2, 3] The survey findings reveal that TB prevalence is higher among males than females, and yet more women are more likely to participate in health surveys implies that future surveys need to be adjusted to better represent the male population. Despite this shortcoming, the population-based sample in the prevalence survey currently gives the closest possible approximation to population-level patterns of disease characterised by persistent coughing. The higher participation rate in women is a finding similar to other TB prevalence surveys.[65] The CAD accuracy finding in our study is therefore likely to be generalizable to other countries in sub-Saharan Africa with high burden of TB and HIV.

Though our study focused on one software (CAD4TBv.6), other comparable software that had the CE (Conformité Européenne) marking by January 2020 (Lunit Insight CXR, Lunit Insight; and qXR v2, Qure.ai.) may perform similarly or better than this.[9, 55] Rapid

advances have been made in CAD software development, with a total of 12 software solutions identified in March 2021 and version updates occurring frequently. [27, 55] Regular updating of WHO guidelines is therefore required to keep pace with these advances. As national TB programs adopt CAD technology into screening activities, in addition to performance, other implementation considerations include; overall cost, cost-effectiveness, compatibility of the X-ray systems, input image format, integration with any patient archiving systems, customer service and support, data protection, and ability to detect other non TB conditions.[25, 27, 55] Conditions other than TB may be as, or more prevalent than TB in high TB prevalence settings, and require comprehensive approaches to ensure participants in TB screening programmes are linked to appropriate care. [45] As will be discussed in Chapter 3, TB screening programs should plan for this and take into consideration resource implications to ensure additional health benefits through the identification of populations at risk of diseases other than TB. In addition to diagnostic accuracy; clinical utility, acceptability and feasibility of using CAD should be assessed.[58]

CAD specificity varies by age and previous TB history

In our secondary analysis we found that accuracy varied considerably by participant characteristics, specifically age and previous TB history. Similar to a previous study in Bangladesh among adults attending primary health care for triage setting, there was no significant difference in performance of CAD4TBv6 between men and women.[55] The lower specificity of CAD4TBv6 in the older age groups and those with prior history of TB is a finding similar to previous studies.[51, 55, 57] There are numerous anatomical and pathophysiological changes occurring in old age that could explain this lower age-related specificity, including age-related changes and sequalae of life-course accumulated lung damage.[66] People with prior TB have lung changes that could lead to difficulty distinguishing old vs active disease, leading to low specificity.[51, 55, 57] Further algorithm training with images from older populations may result in refinement of CAD software with improvements in specificity. C-reactive protein, an indicator of systemic

inflammation, has been shown to be a potentially useful triage tool for TB among people living with HIV.[67-69] A two stage screening of CAD with symptom screen followed by CRP or other novel screening tests in older populations and in participants with previous TB history could improve specificity, although this requires further investigation.

A strategy with CAD should be considered in TB prevalence surveys

In prevalence surveys, image classification criteria are set to a low threshold for referral for sputum testing, and non-expert readers like Clinical Officers are trained to interpret with higher sensitivity and lower specificity to avoid missing prevalent TB cases.[17] We found that, overall, the sensitivity of Clinical officer CXR interpretation ("suggestive of TB") for the underlying true TB status was lower (44%) and specificity was higher (89%) than anticipated,[9] but that sensitivity was substantially higher (84%) and specificity lower (54%) among participants with previous TB, and with no appreciable differences by other participant characteristics. This overall low sensitivity is not usually identified by other analyses that compare clinical CXR interpretation to a microbiological reference standard, and that assume that sputum testing is 100% sensitive. From our latent class model, we can then infer that true TB cases that are bacteriologically-negative are likely to have minimal or no CXR abnormalities (unless previously treated for TB), and so are currently undetectable without new, more sensitive TB diagnostic tests. As in other studies, we have demonstrated that CAD at varied thresholds achieves higher sensitivity than human readers.[23, 52, 55] CAD has a high throughput and has been shown to reduce the time to treatment [25, 56]. Additionally, CAD has the benefit of flexibility of varying thresholds, with a higher threshold improving the positive predictive value and reducing the number of GeneXpert tests required to diagnose a patient by up to 50% while maintaining sensitivity above 90% [55]. For TB prevalence surveys, we recommend, based on accuracy, that a strategy including CAD should be considered, developed through

operational modelling (see Chapter 4) and supported by formal health economic analyses to determine the health system feasibility of wide scale implementation. Mathematical transmission modelling studies will likely be required to investigate potential impact on longer term trends of TB incidence, prevalence and mortality.

Strengths and limitations of the study

A major strength of our study is the use of a large population based data set from a well-conducted, WHO-approved TB prevalence survey.[2, 17] Analysis of the CXRs was blinded to bacteriological status, and we used a robust bacteriological reference standard.[70] Our model prevalence estimates are slightly higher than empirical estimates obtained from the prevalence survey (especially for men: 927 per 100,000 [783-1090] in our analysis vs. 809 per 100,000 [656-962] in the weighted prevalence survey estimate) ;[2] this is to be anticipated as our model accounted for less than perfect sensitivity of sputum diagnostic tests (GeneXpert and culture) to estimate the underlying true prevalence of disease. Limitations include our results being model-based and are dependent on the validity of the model assumptions; to achieve computational efficiency, we fixed the specificity of the bacteriological reference standard to be 99%. Study participants were aged 15-years and above and we therefore cannot comment on the diagnostic accuracy of CAD4TBv6 in children. The study only included bacteriologically-confirmed TB; assessment of accuracy in participants with sputum negative TB (clinically diagnosed) or extra-pulmonary TB (pleural) is challenging to undertake. We also were not able to stratify performance by HIV status as testing was not systematically conducted during the prevalence survey. This would have been important for an in-depth subgroup analysis in a high TB-HIV prevalence setting. Kenya has a HIV prevalence of 4.9% with approximately 1.6 million people living with HIV and an estimated HIV-positive TB incidence at 70/100,000.[47, 71] We therefore expected a lower CAD specificity in our setting as CXR is known to be less sensitive in immunocompromised patients with

pulmonary TB.[72-75] We recommend further evaluation of CAD software in high TB-HIV prevalence settings and further studies on accuracy within HIV-positive populations.

2.6 Conclusion and recommendations

In conclusion, the END TB strategy calls for concerted efforts to find and treat the missing cases of TB through new and effective approaches to systematic screening.[49] We have demonstrated that CAD4TBv6 is an accurate tool for community based TB screening in Kenya and met the TPP in this population. In resource limited settings where radiologists are scarce, an adaptive approach to setting screening thresholds could further improve screening accuracy and efficiency.

2.7 Key policy implications

Following the release of the WHO 2021 TB screening guidelines recommending use of digital CXR and CAD for mass screening, countries will consider adoption of this guidance in their context. From our findings and the new guidelines, the following policy recommendations should be considered.

2.7.1 Country level recommendations

2.7.1.1 Development of DCXR and CAD TB screening policy guidance

Due to the COVID 19 pandemic, there was a drop of TB notifications globally by 18% and countries will need to increase case finding interventions.[6] Some countries, Kenya included, have a budget to roll out digital CXR and CAD within the current Global Fund grant (2020-2022) to scale up active case finding activities. Our findings, demonstrate that CAD is an accurate tool will help scale up TB screening and it performs better than trained clinical officers who are more available in health facilities than at community level.

However, as countries consider uptake of these new tools (DCXR-CAD), the health system effects of introducing these need to be carefully considered. While availability of

evidence of the effect has been demonstrated, costing and feasibility studies should be considered as part of the decision making processes. Operational modelling as outlined in Chapter 4 of this thesis could be a tool to help countries with projection of the health system and costing implications during policy formulation.

Once the feasibility and the health system effects are determined, updating of country policy documents guidelines for DCXR-CAD is required for most countries. A committee will be required to assess the current TB screening situation, identify priority groups, screening algorithms and choice of tools. In Kenya, during the validation meeting described in Chapter 6, formation of such a sub-committee was proposed and this has been set up and I was nominated as the chair.

This committee should also help develop guidance on the software to procure and the steps to determining the adaptive threshold scores. In our study, CAD4TBv6 met the optimal TPP for screening. We expect other CE approved CAD software (Lunit Insight CXR, Lunit Insight; and qXR v2, Qure.ai.), to have comparable performance.[55] Countries should include other considerations for example, overall cost, cost effectiveness, compatibility of the X-ray systems, input image format, integration with any patient archiving systems, customer service and support, data protection, and ability to detect other non TB conditions as they decide which CAD software to procure.[25, 27, 55]

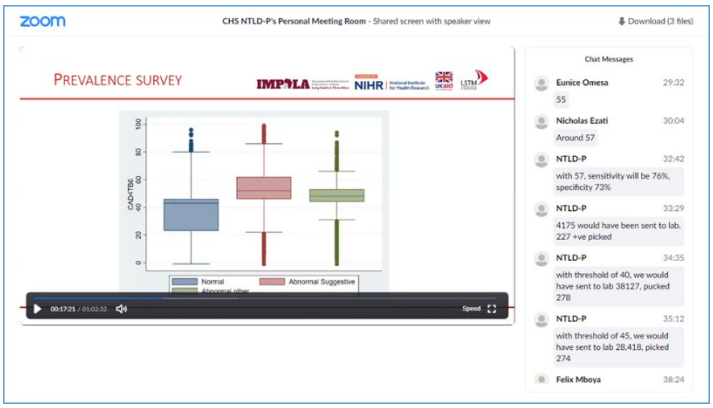
During the Global Fund grant writing, I was asked to make a presentation to the NTLD-program team as they contemplated inclusion of CAD in the proposal. This was an opportunity to share the preliminary findings from this chapter, and also other relevant aspects of my PhD. My reflections on my participation in the discussion were captured in a blog. I have included the blog here (Box 2.1), as it helps to situate this chapter in relation to the coming chapters in this thesis. It also demonstrates how the data presented in this chapter helped provide country level, context specific information to help in the Global Fund proposal writing.

Box 2.1: Unpublished blog on contribution to evidence informed policy in Kenya May 2020

My contribution to evidence informed policy in Kenya

Kenya is currently applying for the Global Fund grant proposal due August 2020 for the 2021-2024 funding cycle [76]. The TB allocation is USD56 million and a further USD 8M for finding missing people with TB. Part of the key interventions that the Kenya Division of National TB, Leprosy and Lung Disease Program (DNTLD-P) is proposing to include as part of active case finding is chest X-ray screening with use of computer aided software for reporting.

A committee was formed to gain understanding of the Computer-Aided Detection for Tuberculosis (CAD4TB)[59] and evidence of its use in Kenya to inform practical roll-out. The committee set up a series of meetings in May 2020 that involved information from the developer, evidence of use in Kenya and views from countries that have rolled it out widely. As a PhD student carrying out a study on Lung Health policy, I was requested to share a presentation on my preliminary findings.



My study was the first to do validation of the CAD4TB software in Kenya using 62,000+ CXRs from the Kenya prevalence survey 2016. My presentation focused on the CAD4TB scores, receiver operator curves and the steps into how Kenya will determine the cut-off scores. We had a discussion on the cut-off threshold tradeoffs using prevalence survey as an example. In addition, I shared the scores from the non-TB abnormalities. During the session, I highlighted cardiomegaly as a highly prevalent non-TB abnormality from my study findings. The session was very interactive with a lot of questions centered on cut-off scores and usefulness of CAD4TB.

The key outcomes from the meeting was a great understanding of CAD4TB in the Kenya context and the complementarity it offers to the radiologists. Kenya will be adopting computer aided software and plans to implement this starting in a few facilities and this will provide lessons for nationwide scale up.

To quote the chair of the GF writing committee tasked with this, "The team has successfully held two meetings where there has been invaluable discussions around CAD4TB; its operations, cost, user acceptability, software updates, internet dependability, threshold level (sensitivity vs specificity) and we got a presentation on work that has been done in the country which provided more insights on the same."

The team is also aware of the opportunity to identify other conditions during TB screening exercise. With cardiomegaly possibly due to hypertension, the NTLD will integrate other services during the screening activity including blood pressure monitoring. The head of the TB program on a later engagement confirmed that they will budget for digital blood pressure machines to aid in screening. We recognize that a single BP reading is not diagnostic, but it could serve as an indicator for further follow-up.

The link between research and policy is indeed not linear. As RAPID framework by ODI describes there are various aspects that interplay.[77] In my case, there was a window of opportunity with the overlap of political, evidence and links. As a researcher, I had links with policymakers having engaged them from the beginning and they therefore understood of what my research entails. When the opportunity presented itself for adoption of the software, this I will call the political sphere, they reached out to me to have the in country evidence. I would say I have contributed to evidence informed policy adoption! However, there is indeed a greater opportunity for my work to inform more in this sphere.

2.7.2 Global level recommendations

2.7.2.1 Recommendation of CAD use for prevalence survey

For TB prevalence surveys, this study has demonstrated the accuracy and the potential utility of CAD in population based screening. Additionally, CAD offers high throughput with elimination of the inter/intra-reader variability that occurs with human readers. It is recommended that future prevalence surveys should include CAD in the diagnostic strategy.

During the dissemination of this findings during the 52nd UNION conference, WHO reached out to have further discussions on the findings and implications for future prevalence surveys. There is an opportunity to engage further and possibly conduct a similar study in the other countries that have done or are planning to conduct prevalence surveys.

2.7.2.2 Recommendation for more CAD studies

Although CAD has been demonstrated to have high overall accuracy for the Kenyan population, more studies are needed among sub groups-HIV populations and children. This will enable countries have more information on how to apply CAD within these groups.

Additionally, CAD scores focus on the probability of TB and for most software other non-TB abnormalities are not considered. Improvement on all future CAD versions should be made to score for other non-TB abnormalities. In the next chapter of this thesis, a sub-study reviewed a sample of the prevalence CXRs to determine prevalence of other non-TB abnormalities in Kenya.

3 Prevalence of non-Tuberculosis abnormalities identified during chest X-ray TB screening

3.1 Introduction

This chapter presents a review of literature on the prevalence of non-TB thoracic abnormalities during mass TB screening activities, a pilot and a main study that was conducted to quantify non-TB abnormalities, and the policy implications of the findings.

3.1.1 Aim of the study

The aim of the main quantitative study presented in this chapter was:

a) To describe and quantify the nature of non-TB abnormalities on CXRs classified as abnormal during the 2016 Kenya National TB prevalence survey to inform the health system needs.
b) The secondary aim was to calculate CAD4TB v6.0 software analysis scores of the images and compare to expert radiologist diagnosis.[78]

The hypothesis was that the use of CXR during TB screening would identify a substantial number of people with non-TB abnormalities that would also be missed by CAD software, who may require further clinical attention.

This retrospective study used data collected during the Kenya prevalence survey 2016 (see section 2.3.2 for full details) and was published in 2021 (Mungai BN, Joekes E, Masini E, et al. 'If not TB, what could it be?' Chest X-ray findings from the 2016 Kenya Tuberculosis Prevalence Survey. Thorax. 2021.). [45]

3.1.2 Study implications

The findings of this study were used to help inform operational modelling projections to estimate the range and prevalence of non-TB thoracic conditions for which health service provision will be required in Kenya, if CXR TB screening is rolled out. The operational modelling on CXR in Kenya is as outlined in Chapter 4 of this thesis. It is vital to determine the prevalence of non-TB pathology to prospectively estimate potential

'off-target' effects of CXR TB screening on the healthcare system prior to implementation. The intention was to inform national policy and practice on what package should be in place to have a coordinated and integrated health system approach to a CXR TB screening policy.

3.2 Literature review

As outlined in Chapters 1 and 2, there is renewed interest in the utility of CXR for TB screening, and triaging people seeking care with symptoms for further TB investigations.[9, 16-18] Use of CXR for mass TB screening will potentially identify other conditions, especially those related to complications of a rising burden of non-communicable diseases (NCDs) in LMICs, including cardiovascular disease, chronic respiratory disease and cancer.[79] If such conditions are identified they are likely to have implications for both clinical management and prevention. As such, there may be implications for all six of the WHO building blocks of health systems (Figure 1.2) as outlined in section 1.1.3, for example, need for health professionals for radiological interpretations and clinical management of the identified conditions, referral mechanisms, medical products and interventions, financing and policy guidance.[29]

A short narrative report from Europe in the 1940s highlighted a significant number 1225/3423 (35%) of non-tuberculous findings in mass radiography screening.[13] Similarly, in a Vancouver study, the rate of unknown non-TB disease was 2.6/1000 in radiographs during "operation doorstep" screening.[14] There were three previously unknown cases of non-TB lung disease identified for every new TB case diagnosed.[14] There is however no contemporaneous evidence about the prevalence of non-TB abnormalities identified during TB prevalence surveys and mass radiographic TB screening interventions. In addition, though CAD4TB demonstrated high accuracy for community-based TB screening in Chapter 2, it is not calibrated for detection of non-TB abnormalities.[25, 80]

Systematic screening/ACF programs focus on early detection of active TB.[12] Countries like Kenya, are currently planning the adoption of CXR screening for mass community TB screening activities, as well as in healthcare settings.[26] However, the burden of non-TB CXR abnormalities during these mass screening activities and how this will be managed is unknown. Countries and national TB programs require information on the prevalence of these conditions to ensure health system preparedness during roll out of mass TB screening activities.

3.3 Methods

3.3.1 Study Design

This was a secondary retrospective analysis of cross-sectional study data using individual-level participant CXR data from adult community members who took part in the 2016 Kenya National TB Prevalence Survey.[3] The summary of the Kenya National TB prevalence survey is captured in section 2.3.2.

This cross-sectional study was conducted in two parts: 1) A pilot was conducted between December 2018 and January 2019 2) The main study conducted between May and July 2019. The pilot study was conducted to trial and refine a list of selected CXR diagnoses, to refine standard operating procedures (SOPs) for reporting and to estimate a sample size for the main study.

3.3.2 Study Population

The Prevalence Survey reported elsewhere[2, 3] and described in section1.2.2 and 2.3.2, was a population-based cross-sectional study conducted in 2015-2016. The aim was to determine the prevalence of bacteriologically confirmed PTB among adults (≥15 years) and to assess health seeking behaviour. The survey used the WHO recommended screening strategy comprising symptom questionnaire and CXR.[17] There were 63,050 enrolled participants, 62,484 (99%) underwent CXR screening. [2, 3]

3.3.3 Study procedures

The classification of CXRs during the Kenya TB prevalence survey is detailed in section 2.3.2. Digitally acquired posterior-anterior CXRs were uploaded to a digital archive. Independent, blinded reading of each film was conducted by two clinical officers in the field who had undergone an intensive one-week training in CXR interpretation. The training was conducted at Kenyatta National Hospital, the largest referral and teaching hospital in the country offering specialized services. The training was a class based practical training facilitated by radiologists that involved review of the quality of chest X-rays and interpretation. The clinical officers then had test sessions on CXR interpretation as part of the learning assessment. Each image was classified as either: a) normal; b) "abnormal, suggestive of TB"; or c) "abnormal other". Any participant with a CXR classified as "abnormal, suggestive of TB" by either one of the clinical officers, or with a cough of more than two weeks, was eligible for sputum collection. Those with bacteriologically confirmed TB were referred for treatment and those with other CXR abnormalities were to be linked to a health facility.

3.3.4 Pilot study

3.3.4.1 Methodology

An on-line, study specific CXR reporting tool with radiological definitions which comprised four major anatomic categories: lung parenchyma, heart and great vessels, and the pleura and mediastinum was developed (Appendix 3 and Appendix 4). For each major anatomical area, a list of most common radiological diagnoses was developed, taking into consideration Kenyan disease epidemiology. During reporting of the CXRs, readers were required to select one or more primary diagnoses as participants could have more than one diagnosis, followed by the option of selecting up to two differential diagnoses (Appendix 5). Due to limited specificity of CXR in many disease presentations, allowing for alternative diagnostic options was designed to capture those cases where a single, confident primary diagnosis could be not made. This study was aimed at deriving

the prevalence of a final diagnosis rather than exploring image characteristics for each disease, the proforma did not capture detailed descriptions of each film.

Five radiologists were identified for the pilot: three consultant radiologists from Kenya who had been part of the National TB Prevalence Survey team and two from the United Kingdom (UK) (Table 3.1). Prior to the pilot readings, a test set of 20 X-rays was read independently by all radiologists, followed by discussion in a consensus meeting to ensure uniformity in reporting and application of the tool. This was a collaborative exercise to agree on definitions.

Once consensus on definitions and reporting approach had been reached by the radiologists, each pilot image was read by a single radiologist only.

3.3.4.2 Sampling

From a systematic literature search conducted, data to inform sample size estimates for prevalence of pulmonary abnormalities from similar settings in the pilot study were unavailable. The study team therefore pragmatically set out to read 500 images (150 abnormal suggestive of TB; and 350 abnormal other) during the pilot, after which the detected prevalence of a set of predetermined pathologies was used to calculate a representative sample size for the main study. Once sampled, the labels of “Abnormal, suggestive of TB” and “Abnormal other” were removed to reduce the risk of bias.

3.3.4.3 Pilot results

A total of 484 (97%) images were reported, 16 images were not read within the set time frame. The reporting was as follows: 288 (60%) as abnormal, 178 (37%) as normal, 8 (2.3%) were not interpretable. The abnormalities included: Heart and/or great vessel abnormalities 174 (37%), lung parenchyma abnormalities 116 (24%), pleural abnormalities 39 (8.2%) and mediastinal abnormalities 8 (1.7%) (Figure 3.1). In the images in the “abnormal other” category n=344, cardiomegaly was most prevalent at

122 (36%) and great vessel abnormalities at 79 (23%) (Figure 3.2). In the "abnormal suggestive of TB" category n=122, old or latent TB was the most prevalent finding at 17(13.9%) and active PTB at 16(13.1) %. Cardiomegaly in this category was at 9(7%) (Figure 3.3).

Figure 3.1: Abnormalities reported on CXRs by major diagnostic categories for the images reported during the pilot study

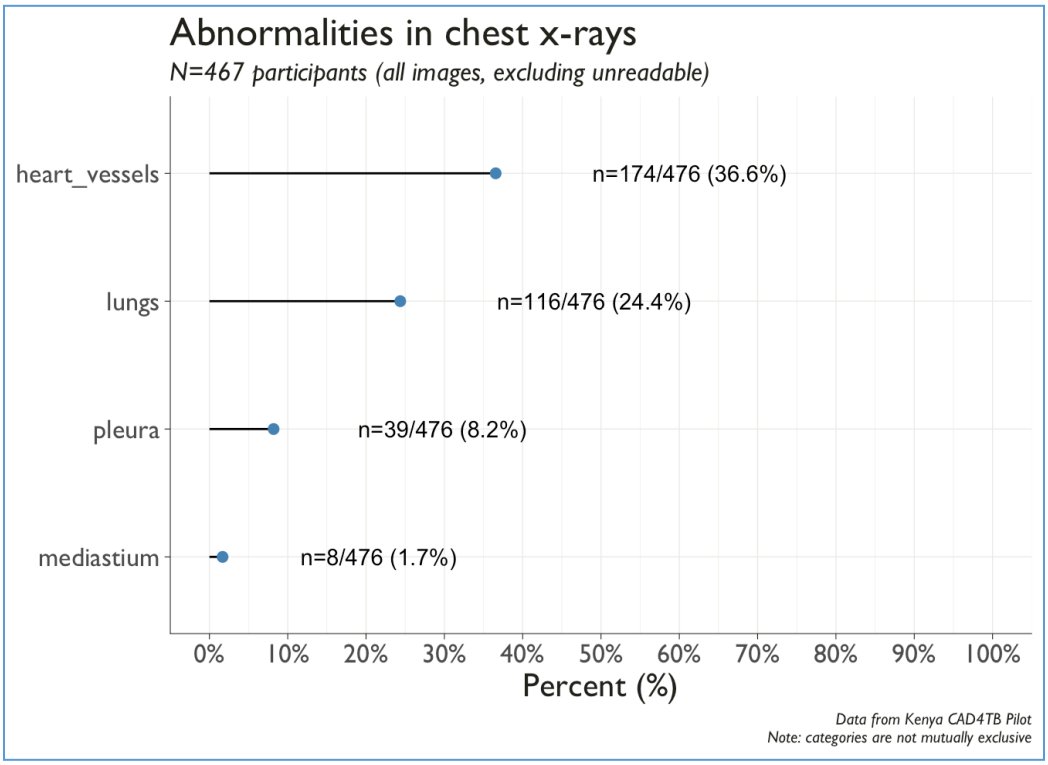


Figure 3.2: Prevalence of radiological abnormalities reported in the images from the "abnormal other "category during the pilot study

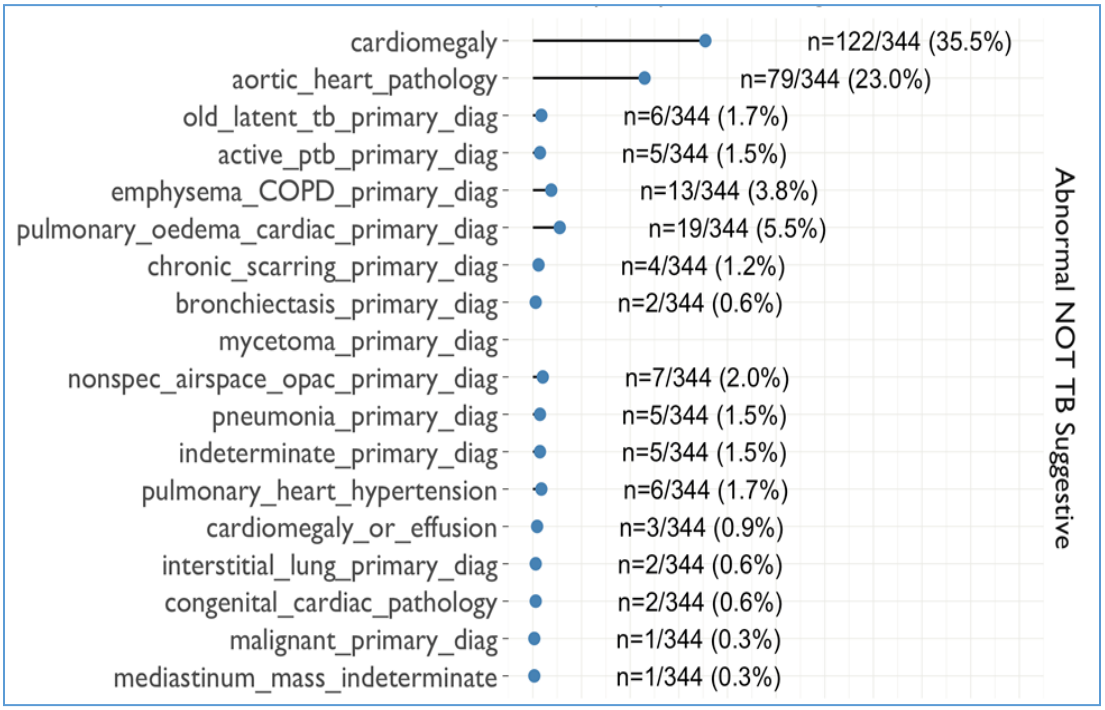
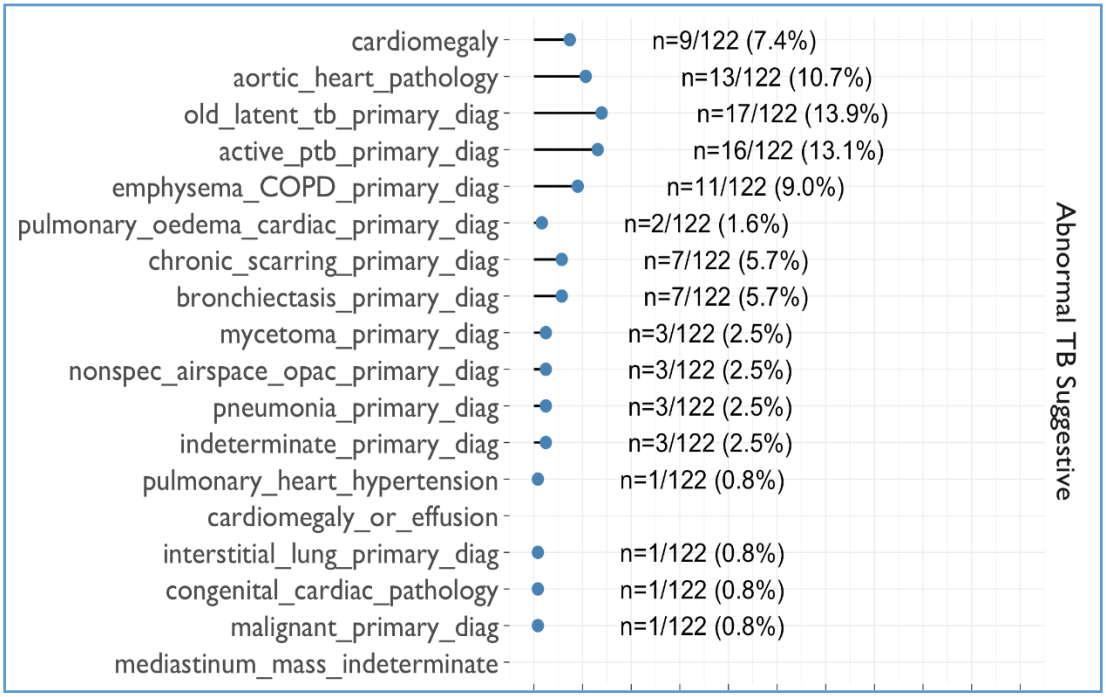


Figure 3.3: Prevalence of radiological abnormalities reported in the images from the "abnormal suggestive" TB category during the pilot study



3.3.5 Main study

3.3.5.1 Methodology

The CXR reporting tool, online electronic platform system (Figure 3.4and Figure 3.5) and SOP (Chapter 8 Appendix 3) were revised with input from the pilot experience. The list of changes made after the pilot study were captured in Appendix 6. The reporting tool was revised to have a primary diagnosis and one differential diagnosis only. A number of probable diagnoses that were not selected during the pilot and were felt to be rare were excluded and a free text box introduced for radiologists to type in any diagnosis not in the list provided. The final list of diagnosis is shown on Table 3.2. In addition, for every primary diagnosis, a drop-down certainty level score was introduced. The score was 0-3 (0-Not certain, 1-slightly certain, 2-Moderately certain, 3-Highly certain.

Figure 3.4: Snapshot of the modified online CXR reporting system for use by the radiologists during the main study

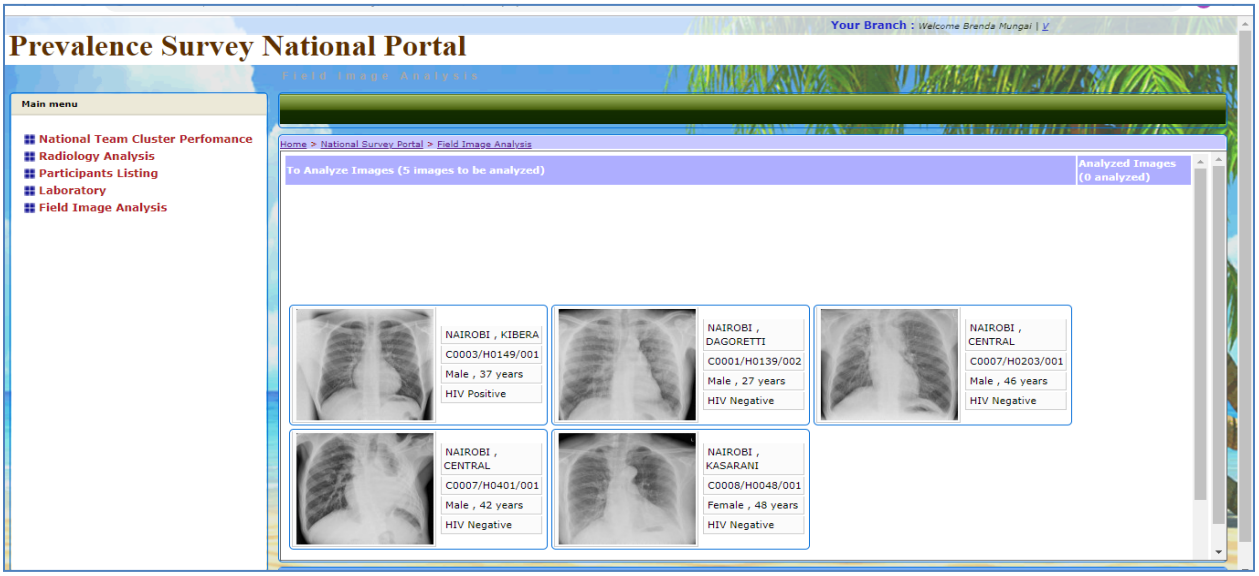


Figure 3.5: Snapshot of the reporting interface of the CXR reporting system

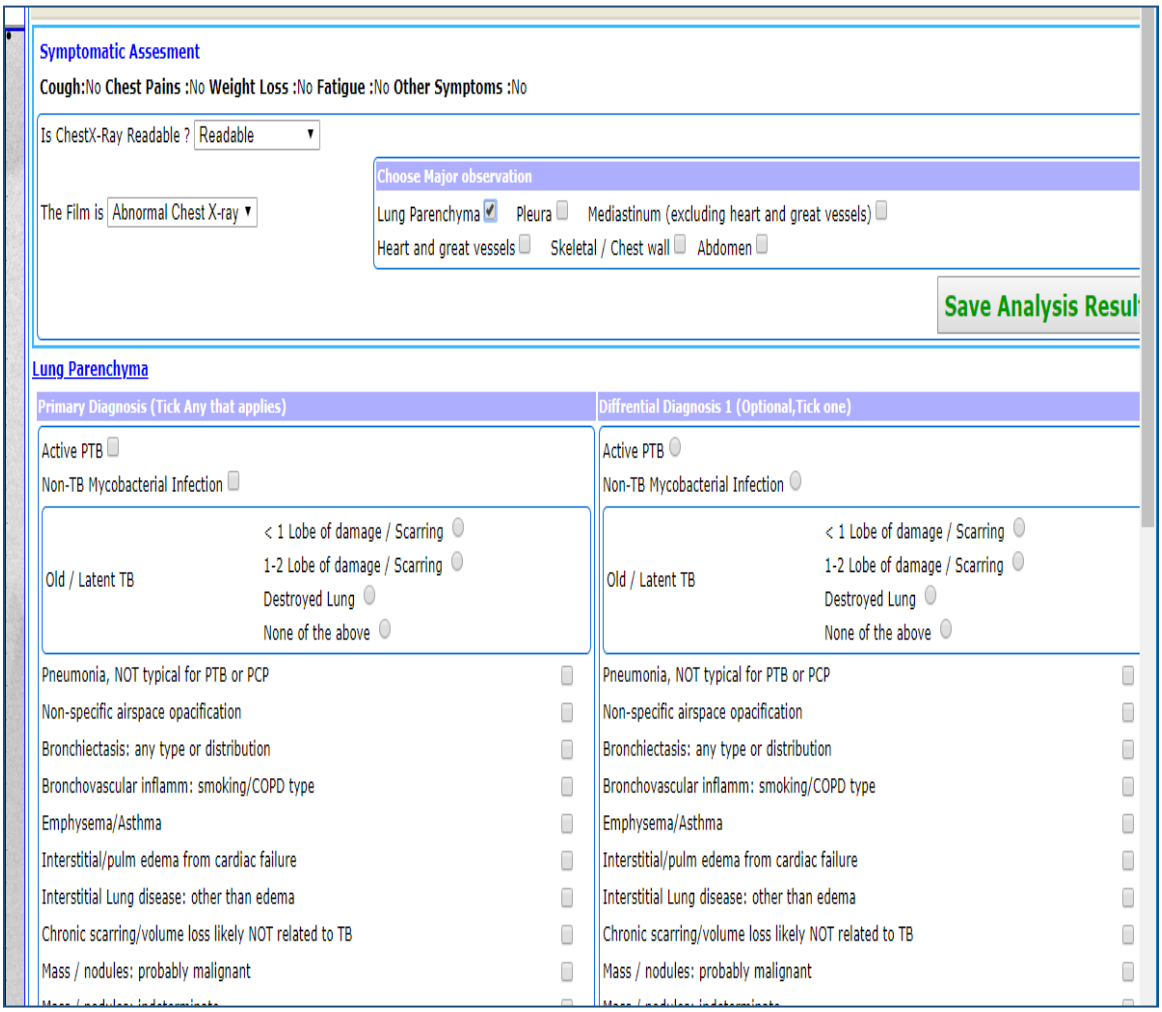


Table 3.1: Summary of study radiologists' qualifications, years of experience in TB imaging, country of residence and the part of the study they participated in.

Radiologist	Qualifications	Experience in TB imaging	Country	Reported
A	Consultant radiologist	19 years	Kenya	Pilot study, Main study
B	Consultant radiologist Fellowship in radio-oncology	15 years	Kenya	Pilot study, Main study
C	Consultant radiologist	10 years	Kenya	Main study
D	Thoracic radiologist	10 years	United Kingdom	Main study
E	Specialist chest radiologist	20 years	United Kingdom	Pilot study, Main study
F	Consultant radiologist	10 years	Kenya	Main study
G	General Body Imaging Radiologist	1 year	United Kingdom	Main study
H	Consultant Radiologist: Chest and Oncological Imaging	30 years	United Kingdom	Main study
I	Chest, Head and Neck radiologist	3 years	United Kingdom	Main study
J	Consultant radiologist	16 years	Kenya	Pilot study, Main study
K	Consultant radiologist	15 years	United Kingdom	Pilot study, Main study-Third reader
L	Thoracic radiologist	12 years	United Kingdom	Main study-Third reader

Table 3.2: List of selected differential diagnostic options for CXR reporting and definitions developed for our study*

	Primary diagnosis	Definition
Lung parenchyma	**Active PTB**	Features of active PTB https://pubs.rsna.org/doi/full/10.1148/rg.275065176
	Non-tuberculous Mycobacterial infection	Features overlap with PTB. Consider NTM in smaller cavities + midzone predominance
	Old / latent TB : < 1 lobe of damage / scarring	Features of latent/healed PTB with total scarring / damage less than 1 lobe equivalent
	Old / latent TB : 1-2 lobes of damage / scarring	Features of latent/healed PTB with total scarring / damage equal to 1-2 lobe equivalent
	Old / latent TB : destroyed lung	Complete destruction of 1 whole lung equivalent due to PTB
	Pneumonia, not typical for PTB	Suspected pneumonia, but without typical TB or PCP features
	Non-specific airspace opacification	Any airspace opacification that cannot be classified under any of the above
	Bronchiectasis: any type or distribution	Localized or diffuse bronchial dilatation: tramline appearances +/- wall thickening
	Broncho vascular inflammation: smoking / COPD type	Coarse, thickened broncho-vascular bundles in peri-hilar distribution.
	Suspected Emphysema / Asthma	Hyper expansion +/- flattening of diaphragm +/- bullous changes. Select only if unequivocal.
	Interstitial pattern / pulmonary oedema from cardiac failure	Classic features of congestive cardiac failure with interstitial +/- pulmonary oedema

	Interstitial pattern, other than oedema	Any interstitial patterns, including miliary. No further specification required.
	Primary diagnosis	**Definition**
	Chronic scarring/volume loss, likely not related to TB	Chronic parenchymal banding/architectural distortion, pattern unlikely to be the result of PTB
	Mass/nodules: probably malignant	Malignant features: e.g. spiculation, lymphadenopathy, and/or lung metastases
	Mass / nodules: indeterminate	Indeterminate: no definite malignant or benign features
	Mass / nodules: probably benign	Benign features: calcified granulomas, hamartomas, association with old TB scarring.
	Mycetoma	Fungal ball in a pre-existing cavity
	Suspected Kaposi sarcoma	"Flame like" opacities in peri-bronchial distribution +/- large effusions
Pleura	**Pleural effusion/ thickening / calcification: insignificant**	Small and likely potentially clinically irrelevant.
	Pleural effusion: significant	Size that is potentially clinically relevant, including in cardiac failure
	Pleural thickening / calcification: likely benign	Post-infectious / hemothorax (commonly unilateral) or pleural plaques (bilateral)
	Pleural thickening / calcification: potentially malignant	More than 10 mm thickness, mediastinal pleura involved +/- associated pleural plaques.
Mediastinum (excluding heart and great vessels)	**Mass, indeterminate**	Any mediastinal mass, other than suspected lymphoma/EPTB or goitre
	Suspected Lymphoma	Large volume adenopathy (+/- lung pathology), including bilateral hilar and extensive
	Suspected EPTB	Unilateral hilar adenopathy and mediastinal adenopathy (+/- lung pathology)
	Goitre	Superior mediastinal mass, extending to the neck with tracheal deviation

	Spinal/para-spinal pathology	Spinal/paraspinal mass or destruction
	Primary diagnosis	**Definition**
Heart & great vessels	**Cardiomegaly**	Cardiothoracic ratio > 0.5
	Cardiac pathology: Other	Any classic features, other than enlargement.
	Pericardial effusion	Globular enlargement of cardiac shadow
	Aorta atherosclerosis / elongation	Subjective elongation/calcification of aorta
	Pulmonary arterial hypertension (PAH)	Elevated cardiac apex, enlarged right atrium and pulmonary arteries, pruning of peripheral vessels
	Aortic/Pulmonary artery pathology: other	Any other than atherosclerotic / PAH
Chest wall	**Free text**	Any abnormalities of bones and chest wall

***Adapted from Fleischner Society guidelines [81]**

Ten specialist radiologists (five Kenyan, five from the United Kingdom) with median experience of 12·5 years in TB/chest radiology were recruited (Table 3.1). A one-to-one training was conducted for the radiologists in Kenya on the online reporting tool and diagnostic case definitions.[81] For the UK based radiologists, online sessions were conducted. CXR reporting portal instructions (Appendix 7) were shared for reference.

An anonymised line list of all the participants from the prevalence survey database was obtained; the sampling frame included all CXRs classified as "abnormal, suggestive of TB" or "abnormal other" by the survey field readers. Images selected for inclusion in this study were uploaded to a web-based picture archiving and communication system.

Each radiologist was randomly assigned 114 CXRs for review through the online system. After completion of each reading, the image was released into a pool for second reading. The readers were blinded to each other's report, but not to clinical information (sex, age, HIV status and symptoms). Finally, 10% of images were re-allocated to the original readers, for assessment of intra-observer variation.

Discordancy resolution

After the reading of the films by the ten radiologists, an initial analysis was carried out to identify discordances in the CXR readings. Discordancy was defined as discrepant primary diagnoses by the radiologists' pair. One of two additional radiologists (LJ and AA) undertook a "tie-break'" read, with knowledge of the first two radiologists' classification. The two readers were blinded to the first two readers' identity to ensure there was no bias.

3.3.6 Data management and analysis

Sampling

The most common diagnoses in the pilot study were cardiomegaly, at 36% among the "abnormal other" group (Figure 3.2), and old/latent TB at 14% among the "abnormal, suggestive of TB" group (Figure 3.3). To estimate prevalence of cardiomegaly and old/latent TB within 3.5% percentage points of the true value with 95% confidence among the "abnormal other" group and "Abnormal, suggestive of TB" group respectively, a total sample size of 1140 images was calculated. This comprised 390 "abnormal, suggestive of TB" and 750 "abnormal other" images.

For the main study, images classified as either "abnormal, suggestive of TB" and "abnormal other", were included except for those sampled in the pilot study. These images were grouped into 99 strata as per the prevalence survey clusters, and sampled without replacement from each stratum.

Analysis

Dr Peter MacPherson a Wellcome Trust Fellow & Reader in Population Health assisted in the statistical analysis. Statistical analysis used R v3.6.2 (The R Foundation for Statistical Computing, Vienna). Inter- and intra-reader agreement was calculated using the Cohens Kappa statistic. Study participant characteristics were calculated as medians or percentages. The prevalence of primary diagnoses was calculated as the number of CXRs depicting the abnormality divided by the total number of images that were readable; 95% confidence intervals were estimated using the binomial exact method. A number of final diagnoses were combined or removed before analysis, based on their prevalence and likelihood of clinical relevance. The 1140 CXRs were among those analysed using CAD4TB v6.0 (Delft Imaging Systems, Netherlands) as outlined in section 2.3.3.[78] Median scores and interquartile ranges (IQR) were calculated for each primary diagnostic group.

3.3.7 Ethical approval

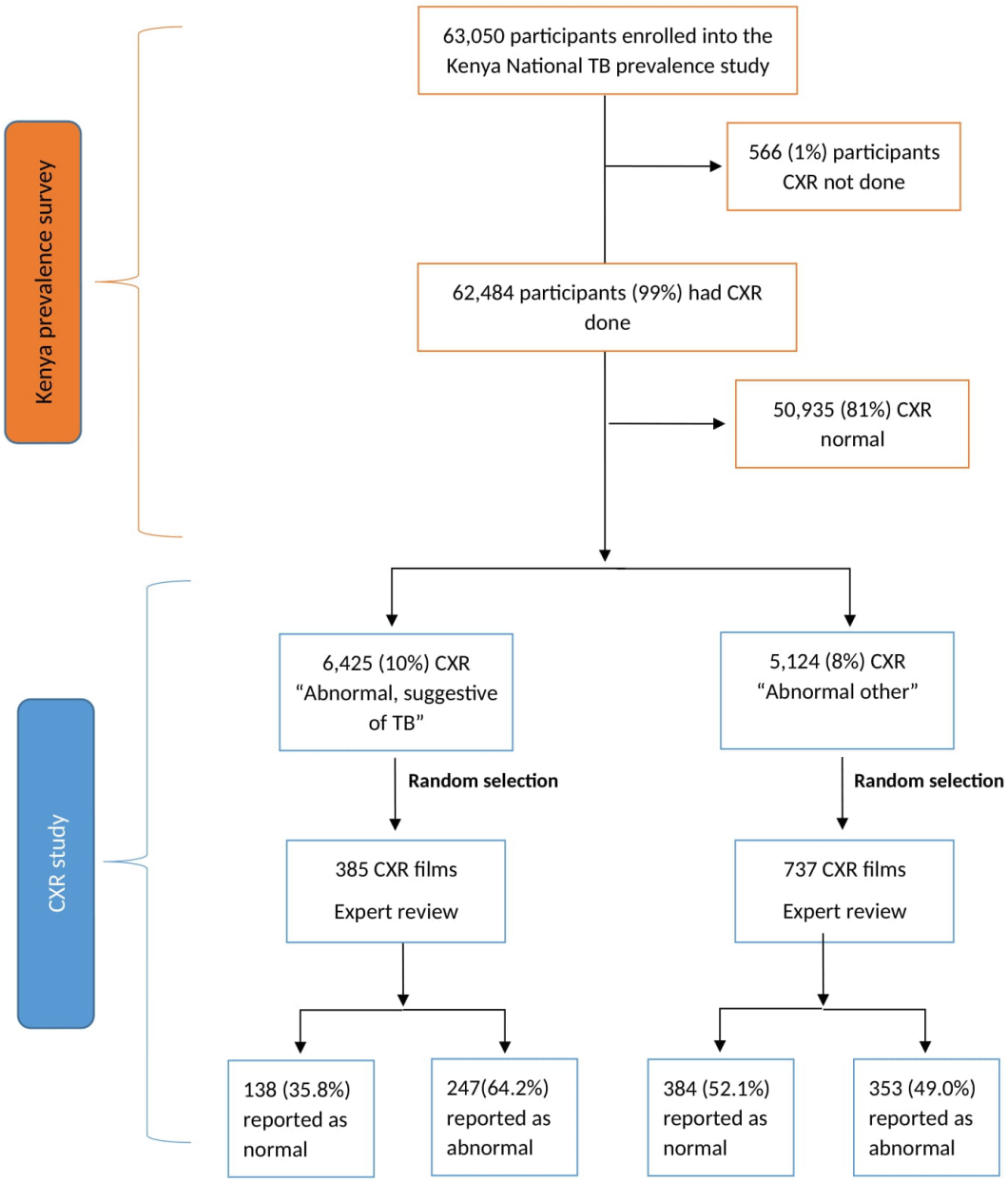
This study was conducted as part of the Kenya Prevalence survey ethics approval reference number SSC 2094 by Kenya Medical Research Institute. The CXR study used anonymized prevalence survey database and individual consent to participate in this secondary analysis was not required.

3.4 Results

3.4.1 Participant characteristics

Out of 63,050 participants in the Prevalence Survey, 62,484 (99%) underwent CXR, with 50,935 (81.5%) reported as normal by survey field staff, 6,425 (10.3%) as “abnormal, suggestive of TB”, and 5,124 (8.2%) as “abnormal other” (Figure 3.7).

Figure 3.6: CONSORT Flow Diagram showing participant flow from the Kenya National TB Prevalence Survey, and this nested CXR study



Out of 1140 images included in the main study, 1123 (98·5%) were read by two radiologists and 17 (1·5%) were classified as unreadable. The median patient age was 51·0 years (IQR 36·5–66·0) and 720 (64·2%) were female. Two-hundred and fifty (22·3%) had reported cough of any duration, 40 (3·6%) chest pain and 42 (3·7%) self-reported HIV positive status. Six (0·5%) reported current and 34 (3·0%) reported previous TB treatment. GeneXpert and/or culture results were positive for 27/456 (5·9%) of those that had sputum tested (Table 3.3).

Table 3.3: Characteristics and sputum microbiology results of study participants, stratified by the original survey classification of the chest X-rays as "abnormal, suggestive of TB", versus "abnormal other" by field clinical officers

	Abnormal, suggestive of TB (N=385)	Abnormal, other (N=737)	Total (N=1123)	P-value
Sex				< 0.001
Missing	0	1	1	
Female	198 (51·4%)	570 (70·8%)	720 (64·2%)	
Male	187 (48·6%)	239 (29·2%)	402 (35·8%)	
Age (years)				< 0.001
Median (Q1, Q3)	45·0 (33·0, 64·0)	54·0 (38·0, 67·0)	51.0 (36.2, 66.0)	
CAD4TB score				< 0.001
Median (Q1, Q3)	54.0 (47.0, 65.0)	49.0 (45.0, 53.0)	50.0 (45.0, 56.8)	
Study consensus				<0.001
Abnormal CXR	247 (64·2%)	353 (49·0%)	600 (53·4%)	
Normal CXR	138 (35·8%)	384 (52·1%)	522 (46·6%)	
Missing			1	
Cough of any duration				0.002
Missing	0	1	1	
No	278 (72·2%)	594 (80·6%)	872 (77·7%)	
Yes	107 (27·8%)	143 (19·4%)	250 (22·3%)	
Reported Weight loss				0.674
No	324 (84.2%)	613 (83.2%)	937 (83.5%)	
Yes	61 (15.8%)	124 (16.8%)	185 (16.5%)	
Reported Fever				0.385
No	320 (83.1%)	597 (81.0%)	917 (81.7%)	
Yes	65 (16.9%)	140 (19.0%)	205 (18.3%)	
Reported Night sweats				0.001
No	278 (72.2%)	594 (80.6%)	872 (77.7%)	
Yes	107 (27.8%)	143 (19.4%)	250 (22.3%)	
Self-reported HIV status				0.005
Missing	183	389	572	
HIV-negative	180 (89·1%)	328 (94·3%)	508 (92·4%)	
HIV-positive	22 (10·9%)	20 (5·7%)	42 (7·6%)	
Taking TB treatment				0.069
Missing	182	340	522	
No	199 (98·0%)	395 (99·5%)	594 (99·0%)	
Yes	4 (2·0%)	2 (0·5%)	6 (1·0%)	
Previously treated for TB				< 0.001
Missing	182	403	522	
No	175 (86·2%)	391 (98·5%)	566 (94·3%)	
Yes	28 (13·8%)	6 (1·5%)	34 (5·7%)	
Sputum GeneXpert/Culture				0.001
Missing	66	600	666	
Negative	293 (91·8%)	185 (99·3%)	429 (94·1%)	
Positive	26 (8·2%)	1 (0·7%)	27 (5·9%)	

3.4.2 Inter-reader and intra-reader variability

The overall agreement between pairs of readers was moderate with kappa = 0·41 (Table 3.4 below). There was perfect intra-reader agreement at kappa=1. The median time between intra-observer reliability assessments was 22 days.

Table 3.4: Cohen`s Kappa scores for the expert radiologists inter-and intra-reader variability

Radiologists	A	B	C	D	E	F	G	H	I	J
A	1.000	0.372	0.178	0.000	-0.421	0.623	0.438	0.292	-0.429	0.016
B	0.372	1.000	0.659	0.322	0.459	0.700	0.475	0.114	0.503	0.214
C	0.178	0.659	1.000	0.046	0.409	0.814	0.215	0.204	0.298	0.224
D	0.000	0.322	0.046	1.000	0.765	0.500	0.488	0.678	0.232	0.500
E	-0.421	0.459	0.409	0.765	1.000	0.698	0.576	0.487	0.422	0.688
F	0.623	0.700	0.814	0.500	0.698	1.000	0.036	-0.227	0.529	0.800
G	0.438	0.475	0.215	0.488	0.576	0.036	1.000	0.175	0.455	0.500
H	0.292	0.114	0.204	0.678	0.487	-0.227	0.175	1.000	0.427	0.157
I	-0.429	0.503	0.298	0.232	0.422	0.529	0.455	0.427	1.000	0.620
J	0.016	0.214	0.224	0.500	0.688	0.800	0.500	0.157	0.620	1.000

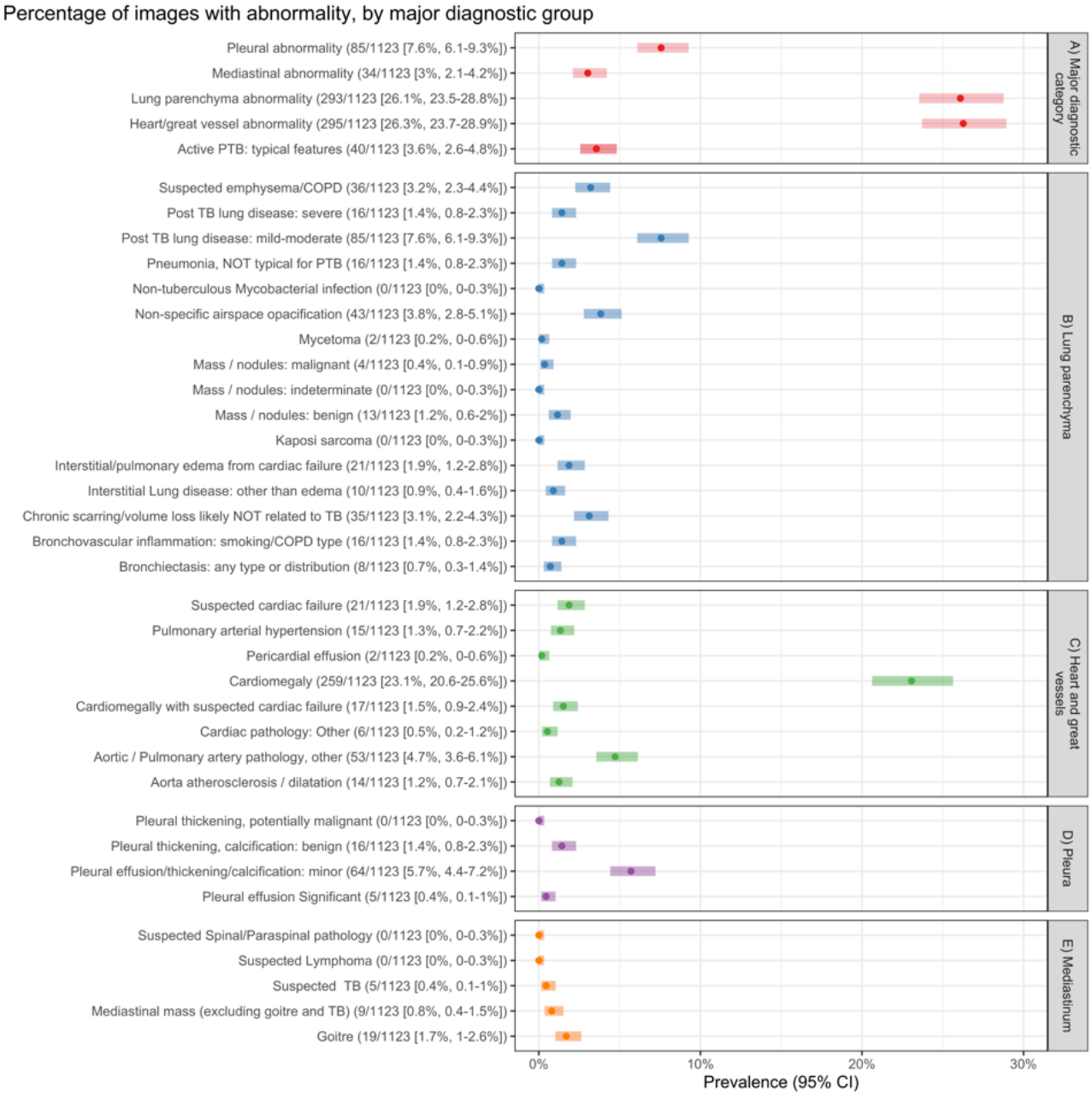
This table captures Cohen`s Kappa scores for the ten main study radiologists matched per reading pair. The green highlight shows the intra-reader score which was perfect for all re-reads.

3.4.3 Prevalence of CXR abnormalities

Overall, out of the 1123 readable images that were abnormal through field clinical officers reporting, only 600 (53·4%) were classified by study radiologists as having an abnormality. Of the images classified as “abnormal, suggestive of TB” by field interpretation in the survey, 203 (64·9%) were classed by expert reviewers as abnormal, whereas among the “abnormal other” category 397 (49·0%) were abnormal by expert radiologist read (Table 3.3).

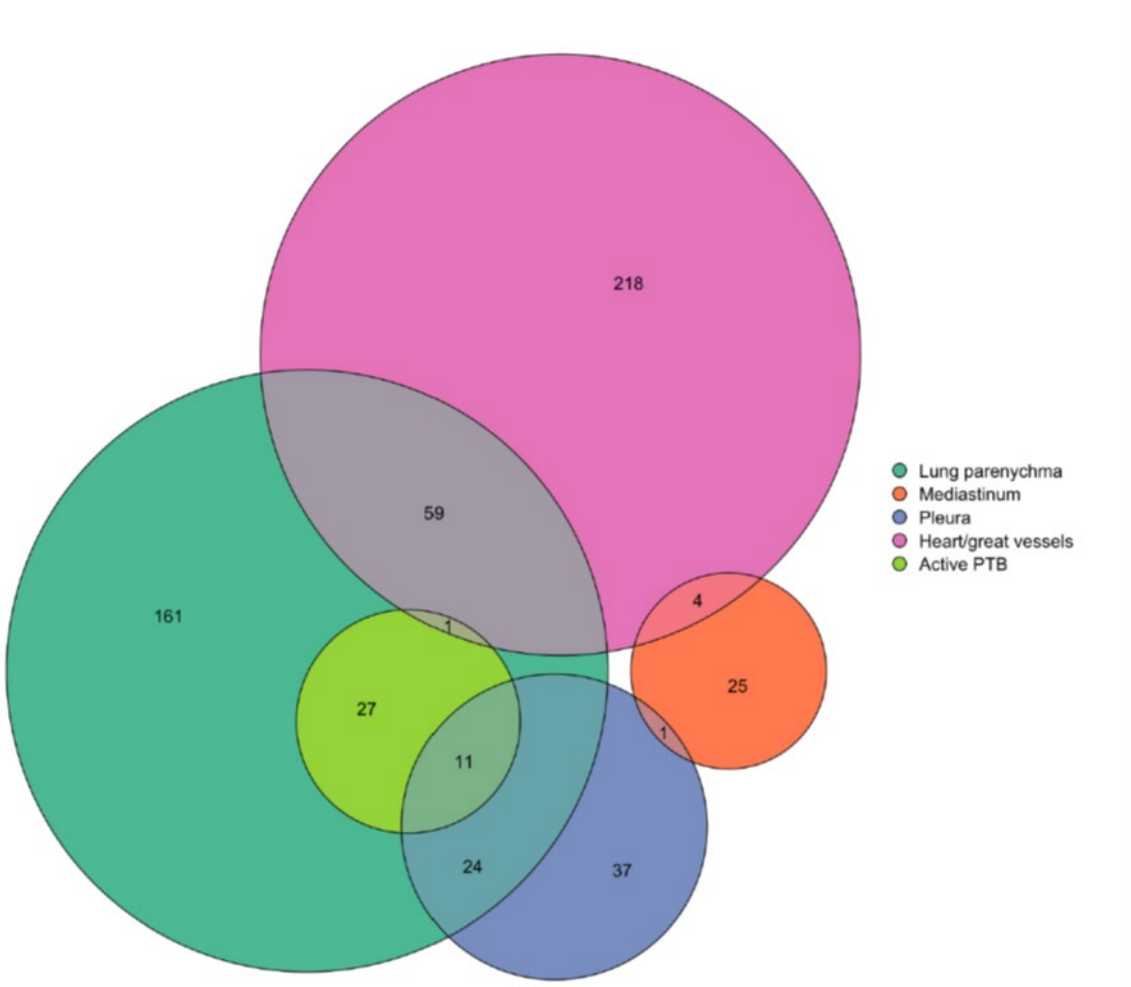
Overall prevalence of abnormalities in the major anatomical categories were: heart and/or great vessels 26·3% (95% CI 23·7%-28·9%), lung parenchyma 26·1% (95% CI 23·5%-28·8%), pleura 7·6% (95% CI 6·1%-9·3%) and the mediastinum 3% (95% CI 2·1%-4·2%) (Figure 3.8). Among the 600 abnormal images, 21% (127/600) had multiple abnormalities, cardiomegaly accounted for 259/600, 43·2% (39·2%-47·2%) followed by mild/moderate post-TB lung changes at 85/600, 14·2% (11·5%-17·2%) (Figure 3.9).

Figure 3.7: Prevalence of CXR abnormalities reported by major diagnostic categories for our main study



A) Captures prevalence of abnormalities in the major diagnostic categories. Active PTB was captured in the major diagnostic category (A) as this is the key diagnosis in any TB screening program. B), C), D), E) capture abnormalities by the specific anatomical groups.

Figure 3.8: Euler diagram of abnormalities identified during the CXR study



This Euler diagram shows the distribution of abnormalities among the 600 CXRs identified as abnormal by the radiologists. 21% (127/600) had multiple abnormalities.

Among the potentially relevant non-TB abnormalities, cardiomegaly was the most prevalent at 23·1% (95% CI 20·6%-25·6%), while cardiomegaly combined with features of cardiac failure occurred in 1·5% (95% CI 0·9%- 2·4%). Non-specific patterns were noted in 4·6% (95% CI 3·5%- 6·0%), while suspected chronic obstructive pulmonary disease (COPD), including emphysema, was present in 3·2% (95% CI 2·3%- 4·4%). Mediastinal masses, excluding goitres, occurred in 0·8% (95% CI 0·4%-1·5%).

For presumed TB related abnormalities, prevalence of minor post-TB lung changes, such as old/latent TB involving fewer than two lobes of damage/scarring was 7·6% (95% CI 6·1%- 9·3%), active-TB was 3·6% (95% CI 2·6%- 4·8%) and severe post-TB lung changes, i.e. bronchiectasis and/or destroyed lung, 1·4% (95% CI 0·8%- 2·3%).

Between a quarter and a third of females had cardiomegaly (29%). For males 11·7% had cardiomegaly and 11·2% mild/moderate post TB lung changes. History of cough was a common feature across all diagnosis types with 69/250 (27·6%) of coughers having cardiomegaly. Out of the 40 participants with chest pain, 22·5 % (10·8-38·5%) had cardiomegaly and 20% (9·1-35·6%) had minor post-TB lung changes. Bacteriological confirmation of TB was found in all categories of reported TB-related lung abnormalities and 4/27, (14·8%, 4·2%-33·7%) of images reported as non-specific patterns (Table 3.5). Out of the 34 participants with a history of previous TB treatment, features consistent with minor post-TB lung changes were reported in 11(32·4%, 95% CI 17·4%-50·5%), active PTB in 6 (17·6%, 95% CI 6·8%-34·5%) and severe post-TB lung changes in 4 (11·8%, 95% CI 3·3%-27·5%).

Table 3.5: Prevalence of potentially relevant radiological findings characterized by sex, age, history of cough, chest pain and microbiological confirmation of TB

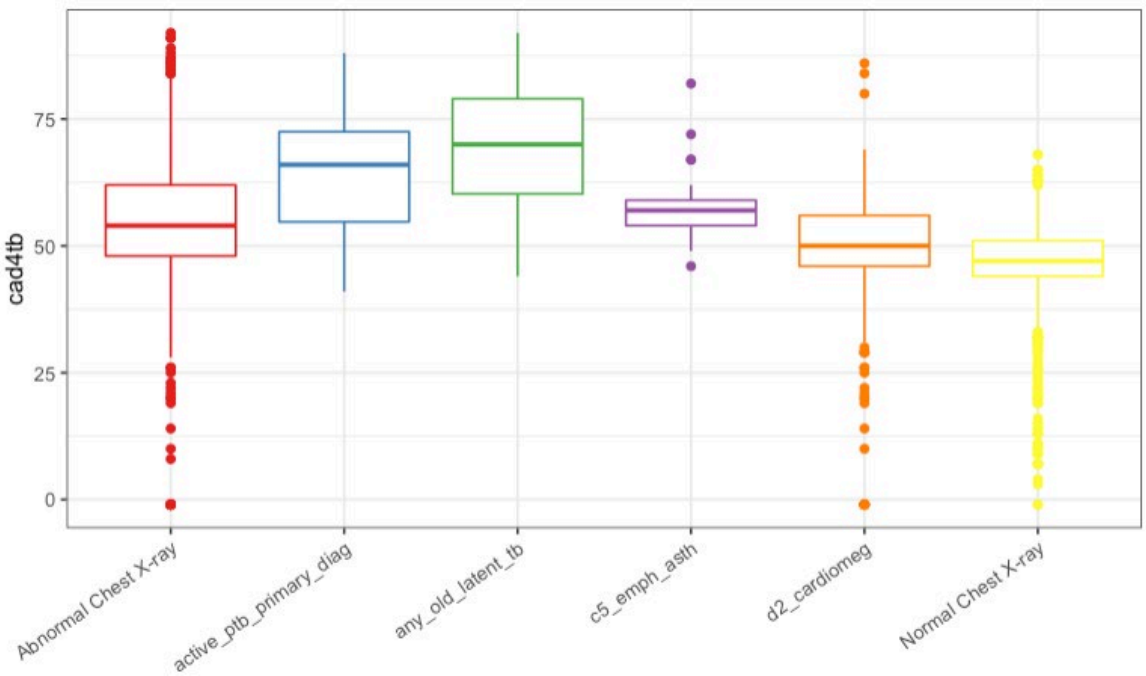
RADIOLOGICAL FINDINGS	Prevalence		Sex		Age	History of cough of any duration	History of chest pain	Bacteriological TB confirmation (GeneXpert/Culture)
	n=1123	%, 95% CI	Female N=721, % (95%CI)	Male N=402,% (95%CI)	Median, IQR	N=250,% (95%CI)	N=40,% (95%CI)	N=27, % (95%CI)
Cardiomegaly	259	23·1% (20·6%-25·6%)	212/721, 29.4% (26.1%-32.9%)	47/402, 11.7% (8.7%-15.2%)	59(45-70)	69/250, 27.6% (22.2%-33.6%)	9/40, 22.5% (10.8%-38.5%)	0/27, 0.0% (0.0%-12.8%)
Cardiomegaly with heart failure	17	1.5% (0.9%-2.4%)	12/721,1.7% (0.9%- 2.9%)	5/402,1.2 % (0.4%-2.9%)	77(68-83)	7/250, 2.8% (1.1%- 5.7%)	0/40, 0.0% (0.0%- 8.8%)	0/27, 0.0% (0.0%-12.8%)
Suspected cardiac failure	21	1.9% (1.2%-2.8%)	16/721, 2.2% (1.3%- 3.6%)	5/402, 1.2% (0.4%-2.9%)	75(67-83)	8/250, 3.2% (1.4%- 6.2%)	0/40, 0.0% (0.0%- 8.8%)	0/27, 0.0% (0.0%-12.8%)
Mild/moderate post-TB lung disease *(Old/latent TB with =< 2 lobe damage)*	85	7.6% (6.1%-9.3%)	40/721, 5.5% (4.0%- 7.5%)	45/402,11.2% (8.3%-14.7%)	48(37-66)	18/250, 7.2% (4.3%-11.1%)	8/40, 20.0% (9.1%-35.6%)	6/27, 22.2% (8.6%-42.3%)
Non-specific opacification/interstitial pattern	52	4.6% (3.5%-6.0%)	28/721, 3.9%	24/402, 6.0%	59(46-76)	16/250, 6.4% (3.7%-10.2%)	1/40, 2.5% (0.1%-13.2%)	4/27, 14.8% (4.2%-33.7%)

			(2.6%- 5.6%)	(3.9%- 8.8%)				
Active PTB	40	3.6% (2.6%- 4.8%)	15/721, 2.1% (1.2%- 3.4%)	25/402, 6.2% (4.1%- 9.0%)	36 (26- 51)	21/250, 8.4% (5.3%-12.6%)	4/40, 10.0% (2.8%-23.7%)	11/27, 40.7% (22.4%-61.2%)
Suspected emphysema/COPD	36	3.2% (2.3%- 4.4%)	16/721, 2.2% (1.3%- 3.6%)	20/402, 5.0% (3.1%- 7.6%)	68(50- 73)	11/250, 4.4% (2.2%- 7.7%)	0/40, 0.0% (0.0%- 8.8%)	0/27, 0.0% (0.0%-12.8%)
Severe post-TB lung disease *(Bronchiectasis and or destroyed lung)*	16	1.4% (0.8%- 2.3%)	10/721, 1.4% (0.7%- 2.5%)	6/402, 1.5% (0.5%- 3.2%)	60(34- 72)	7/250, 2.8% (1.1%- 5.7%)	0/40, 0.0% (0.0%- 8.8%)	2/27, 7.4% (0.9%-24.3%)
Mediastinal mass (excluding goitre /TB)	9	0.8% (0.4%- 1.5%)	7/721, 1.0% (0.4%- 2.0%)	0/402, 0.5% (0.1%- 1.8%)	61(56- 71)	2/250, 0.8% (0.1%- 2.9%)	0/40, 0.0% (0.0%- 8.8%)	0/27, 0.0% (0.0%-12.8%)

3.4.4 CAD4TB analysis

The median score for all study CXRs was 50 (IQR 45-56.75) while for images classified as normal and abnormal by expert radiologists scores were 47 (IQR44-51) and 54 (IQR48-62) respectively (Figure 3.10 below). There was no difference between the sexes. The score for severe post-TB lung changes was highest at 76 (IQR 71-81). Active-TB and minor post-TB change scores were similar at 66 (IQR 55-73) and 67 (IQR58-79) respectively. The GeneXpert positive participants' images had scores of 72 (IQR63-80). Abnormalities with lower scores included suspected COPD at 57 (IQR 52-61), non-specific patterns at 56 (IQR 50-61), mediastinal mass, excluding goitres, at 52 (IQR 47-59), cardiomegaly alone at 50 (IQR 46-56), and cardiomegaly with features of cardiac failure at 57 (IQR55-60).

Figure 3.9: Box plot of CAD4TB scores for overall normal, abnormal and the clinically relevant diagnosis



3.5 Discussion

The main finding from this analysis of X-ray images from the 2016 Kenya TB prevalence survey was that the use of CXR for TB population-based studies identified a large number of patients with non-TB related abnormalities. Cardiac and pulmonary diseases accounted for 66% of the non-TB abnormalities in our setting. The radiological findings were consistent with complications of potential underlying NCDs. To our knowledge, this is the first study in sub-Saharan Africa to describe and quantify non-TB CXR findings among participants who underwent mass screening as part of a population-based TB prevalence survey. TB prevalence surveys and active case finding (ACF) activities using mass CXR offer an opportunity to identify other potential diseases, however, as currently structured, when TB is not confirmed, there is limited further diagnosis and management of these other conditions.[82] The findings of our study are also timely in the wake of disruption in the health system caused by coronavirus disease (COVID-19).[83] As countries accelerate ACF activities using CXR screening to make up for reductions in TB case-notification rates due to COVID-19, they could plan systems to manage other findings.

Cardiac abnormalities were the most prevalent abnormality

At the outset of the study, we expected abnormalities to be primarily related to non-TB pulmonary disease. However, the most prevalent findings were cardiac abnormalities with cardiomegaly at 23·1% (95% CI 20·6%-25·6%). A hospital based pilot study in The Gambia reports a similar finding of cardiac abnormalities being prevalent among non-TB patients (n=108). [82] The prevalence of cardiac abnormalities in our study is higher than in The Gambia (26.3% vs 20%) whose participants also had a lower median age (40 vs 51 years).[82] Our study analysed images which had all originally been classified as abnormal. This, together with higher median age and diagnostic criteria could explain our higher observed prevalence.

Calculation of the cardio-thoracic ratio (CTR) on CXR read by humans is a well-described affordable and reproducible screening method for cardiomegaly.[79, 84]

However, current studies, including our own, use CTR cut off values developed in Caucasian populations and there will be a need for robust validation of baseline CTR values for healthy populations in sub-Saharan Africa.[85] CAD for detection of CTR is under development.[86]

In sub-Saharan Africa, the commonest causes of cardiomegaly are conditions of significant public health importance associated with premature mortality, including: hypertensive heart disease; cardiomyopathies; cor pulmonale; chronic rheumatic heart diseases; and ischaemic heart diseases. [84, 87] Cardiomegaly has been associated with both higher body mass index (BMI) and higher median systolic blood pressure (BP).[79] The high prevalence of cardiomegaly in our study supports exploration of the benefits of CVD screening during TB CXR screening as a potentially affordable public health intervention.[13, 84] This could include adding relevant questions about previous hypertension diagnosis and treatment, measurement of BP and calculation of BMI. We recognize that a single BP reading is not diagnostic, but it could serve as an indicator for further follow-up.[88] Health messaging on prevention of NCDs through recommendations on diet, such as reduction of commercial sugar and high salt diet, could be considered for integration in such programmes.[84]

Chronic respiratory diseases requiring further investigation were detected

Non-TB related respiratory pathology, including chronic respiratory diseases (CRD) were another significant finding in our cohort. In a Vancouver study in 1960s, three cases of significant previously unknown non-TB lung disease were identified for every new TB case; in our study, this figure was approximately 2:1.[14] It should be noted that CXR alone has limited specificity for many of these conditions, especially in this cohort where very limited clinical information was available. The diagnoses of "non-specific airspace opacification" and "interstitial pattern" cover a range of possible pathologies, varying from incidental acute or chronic infective changes, not typical of TB, to non-infective pathology. COPD and emphysema cannot be diagnosed reliably on CXR alone, requiring spirometry and referral for further confirmation. However, CRD morbidity and mortality is on the rise, with the prevalence of COPD shown to range between 4%-25% in one systematic review in

sub-Saharan Africa comparable to 3·6% (2·3%-4·4%) in our study.[89] As expected, our study confirmed that screening for TB will detect alternative lung abnormalities in a significant number of non-TB cases and spirometry as well as expert clinical review for example pulmonologists will be required for a subset of these patients.

Post TB lung changes

Forty-four percent of the participants in our study with reported post-TB lung changes had a history of TB treatment. Among those, CXR revealed bronchiectasis and/or destroyed lung in 11% (95% CI 3·3%-27·5%), which is lower than reported in a prospective study in Malawi, that used computed tomography and reported >40% bronchiectasis and 10% lobar destruction post-TB treatment.[5] Bronchiectasis has a lower detection rate on CXR than CT, and will likely have been underestimated in our study. PTB is a risk factor for CRD and in the Malawi study ongoing clinical symptoms were associated with damage of three or more lobes, [5, 90] which is comparable to the "destroyed lung" category in our CXR study. Unfortunately, patients with post TB lung disease (PTLD) and chronic symptoms are likely to be treated empirically for recurrent TB.[91] We therefore recommend that TB screening programs look into developing the area of PTLD further. Latent TB infection treatment should be offered to eligible PTLD patients.[92] Our study also identified other less common findings for which interventions may be costly. For example, mediastinal and lung masses/nodules (0.4%) that may represent lymphoma/ malignancy and would need referral for definitive diagnosis and management.

Inter- and intra-reader agreement

In our study, half the images reported as abnormal by the field clinical officers were subsequently reported by our radiologists as normal. This finding is not surprising as TB prevalence surveys by design encourage high sensitivity with field officers having a low threshold for identification of abnormalities and referral for sputum-based testing to maximize sensitivity in the initial prevalence survey screening stage. [17] CAD software has been shown to have a role in TB screening activities especially prevalence surveys with diagnostic accuracy higher than clinical officers and comparable to expert radiologists. [52, 93] Inter-reader variability of CXR reporting is an

acknowledged limitation and was also the case in our study with inter reader agreement moderate at 0.41. CAD software seeks to address the limitation of inter reader variability.[52, 55] The moderate agreement in our study additionally can be explained by the limited clinical information available to our reporting radiologists.

Chest X-ray holds a valued position and is a primary diagnostic tool for many medical conditions because of its ease of use and low cost. Good clinical information is important in aiding radiologists to make an impression. A systematic review by Castillo et al concluded that clinical information improved interpretation accuracy, clinical relevance and reporting confidence.[94] In our study, clinical information could have helped improve inter reader agreement, additionally, avenues for dialogue between radiologists and clinicians would have led to optimum interpretation of chest x-rays. Further specialisation in radiology, for example chest radiology would in addition lead to better agreement.

In studies looking at CXR interpretation, inclusion of extensive clinical history, avenues for dialogue with clinicians and supportive investigations for example spirometry, may lead to specificity and better agreement. Feedback offered to the radiologists as to the final diagnosis once all supportive and diagnostic tests are done can also lead to specificity of reporting by radiologists.

Though CAD for TB software has an accuracy equal to expert readers, the software provides TB risk scores only. To characterise non-TB findings, once TB has been excluded, a human reader remains the only current solution available. CAD for cardiomegaly[86] is under development and may provide an automated solution for the detection of cardiomegaly in the future.

Further refinement of CAD software is required to identify non-TB lung pathology

CAD4TB has been developed to rapidly identify people with CXR abnormalities indicative of TB.[80] Our study had high median CAD4TB scores for all active PTB images at 66 (IQR 55-73) as defined by radiologist interpretation, as well as by bacteriological confirmation. Images with lower scores, including those with cardiomegaly (50, IQR 46-56) require review to ensure important non-TB pathology

is detected. Analysis and modelling of the non-TB abnormalities CAD4TB scores is required. This will enable quantification of patients with non-TB pathology who would be flagged depending on various threshold cut-offs. This will translate to the numbers of patients with controllable NCDs missed per 100 000 population hence justifying further refinement of CAD algorithms to include non-TB diagnoses.

Study strengths and limitations

Our study used population-based national prevalence data and an explicit sampling approach to select images for review. Each image was read by two expert radiologists. Moderate inter-reader variability was mitigated by applying a third reader to resolve discrepancies. However, low specificity is an acknowledged issue with radiological classification. This was a retrospective study and we had limited clinical information available. HIV results were self-reported. Important information such as smoking history and pre-existing medical conditions were not collected during the survey. We were therefore not able to adequately correlate clinical symptoms or HIV serostatus with our findings. Though the prevalence survey protocol required those with other CXR abnormalities to be linked to a health facility within the cluster, we had no way of ascertaining if this was done, or obtaining data on final diagnosis and clinical outcome. Our study engaged radiologists with variable years of experience from 1-30 years`, representative of what would be found in an actual implementation setting. Radiologists reporting in this PhD study used a collaboratively developed structured reporting tool to help standardize the approach and mitigate variability due to factors for example experience or geographical background. Mammography studies that compared association between radiologists' experience and accuracy in interpreting screening mammograms, show a positive association between reading volume and sensitivity as well as specificity.[95, 96] Extrapolation from these studies would suggest that accuracy is more related to frequency of CXR reading than total years of radiology experience. Further analysis, beyond the scope of this PhD, is required to determine if the varied years of

experience of the radiologists in our study may have had implications on sensitivity and specificity of the radiology reporting.

3.6 Conclusion and recommendations

Our findings are strikingly similar to those of the 1940s study in Europe; that mass radiography can be used to tackle "fundamental problems of disease in the chest, both of the respiratory system and also of the heart" and "aid in detection of early and treatable non-TB disease".[13] Currently, TB screening activities using CXR and CAD software are focused on finding abnormalities consistent with TB.[26] As countries like Kenya embark on TB ACF activities, they need to be aware that other respiratory and non-respiratory pathologies are likely to be as, or more prevalent, than active TB. Mass screening with CXR therefore offers opportunity to plan for and address multiple important diseases.[13, 14] Even though the algorithms or protocols for example in TB prevalence surveys do recommend that co-existent abnormalities should be referred as appropriate, there is no structured system for the detection and referral of such patients.[10, 17] Clear referral pathways, diagnostics and follow-up plans for non-TB pathology should be developed during the planning of TB prevalence surveys and ACF activities.[14] Prospective data collection about non-TB conditions identified during TB screening, characterisation of these patients, exploration of individual and health systems implications of these diseases could assist with further planning. Our findings were consistent with complications of potential underlying NCDs, including chronic respiratory disease in the population. We recommend a patient-centred approach incorporating NCDs screening and health promotion during TB screening activities. At primary care health facilities, prevention efforts for NCDs could be strengthened including health messaging.

3.7 Key policy implications

According to the World health report 2000, the fundamental objectives of health systems are; “improving health of the population they serve, responding to people`s expectations and financial protection from costs of ill health”. [97] Based on our study findings, and in line with the health system building blocks, the following policy recommendations should be considered.

3.7.1 Immediate recommendations- Service delivery

3.7.1.1 CXR TB integrated screening packages

TB service delivery in LMICs has largely been a vertical and disease specific program. Integration has been documented in a few instances for example TB HIV integration, TB and maternal child health. [98] Our findings highlight a potential missed opportunity for integration of TB and other diseases screening for example cardiac and chronic respiratory diseases.

There is a global momentum to find the missing persons with TB, especially with the slowed progress due to the COVID pandemic.[83] Funding agencies like The Global Fund are encouraging high impact TB interventions in the 30 high burden countries. [99] Digital X-rays feature prominently as the innovative tools to accelerate TB progress and there is funding to scale up CXR TB screening.

With focus being on identifying presumptive TB patients, there is a risk of neglecting the non-TB pathologies. From our findings, the high prevalence of cardiomegaly supports exploration of the benefits of CVD screening during TB CXR screening as a potentially affordable public health intervention. We recommend that national TB programs develop improved packages of care during TB screening including BP and BMI measurement. In addition, clear referral plans for the non-TB pathology for further investigation and management should be included in these screening packages.

During my PhD, I had an opportunity to engage with the Kenya NTLD-Program on this recommendation during the writing of the 2020-2022 Global Fund allocation

cycle grant. The quick win identified was having digital BP machines during the community screening activities. However, the funding to procure this was unavailable at the time and hence this was not actualized. This highlights the importance of funders as key stake holders to ensure allocation for an integrated package of care.

3.7.1.2 Strengthen referral systems for specialist care

"Integrated health services means different things to different people". [98] Well functioning clear referral pathways, diagnostics and follow-up plans for non-TB pathology ensure a form of integrated care for patients. From our findings, there will be need for further investigation and expert clinical review for a subset of these patients. These will include investigations like spirometry, echocardiogram as well as specialists review for example; physicians, pulmonologists and cardiologists. These may not be available at all levels of care and a referral mechanism is needed.

Kenya has a referral strategy inclusive of an implementation framework.[100] TB program should tap on to this strategy and strengthen the health system integrated referral system.

3.7.1.3 Focus on primary prevention of NCDs

Our findings were consistent with complications of potential underlying NCDs, including cardiac and chronic respiratory disease in the population. At primary care health facilities, prevention efforts for NCDs should be strengthened including health messaging on diet, exercise, salt and sugar intake, smoking and alcohol. Screening for these conditions and early management should be prioritised to avoid complications.

As captured in section 3.7.1.1, a patient-centred approach incorporating NCDs screening and health promotion during TB screening activities by the national and county health teams is also recommended.

3.7.2 Intermediate recommendations- Leadership and governance

3.7.2.1 Development of CXR TB screening policy in an integrated manner

Most LMICs like Kenya are currently planning for how to implement the CXR TB screening intervention. Our findings are timely and there is an opportunity for national TB programs and donors supporting the CXR policy to plan for the non-TB conditions. At this point, key stakeholders like the Division of Non-communicable diseases should be part of the planning committees.

Countries should develop integrated CXR TB screening policies that outlines how patients with TB and non-TB conditions are managed with clear pathways of care.

3.7.2.2 Post TB lung Disease programming

National TB programs mandate of managing TB begins with screening, diagnosis and ends with treatment. From our study, Post TB lung changes were present and it is likely that the burden is under estimated. Patients with post TB lung changes have chronic respiratory disease and unfortunately end up being treated as recurrent TB.[91]

We recommend that TB programs develop policies on post TB lung disease and monitor the burden of this. During the period of this PhD, I was involved in developing a chapter on post TB lung disease management in the Kenya integrated guidelines.[101] I presented on the preliminary findings of this study and evidence on the need to program for PTLD. To the best of my knowledge, Kenya is among the first country to have guidance on PTLD.

In addition, government and global funders will be required to fund the interventions for the management of PTLD. This will ensure improved quality of life for patients beyond TB treatment completion.

3.7.2.3 Intermediate recommendations- Health Information

3.7.2.4 Generation of health information on non-TB conditions during CXR TB screening

Our study provides important baseline information on prevalence of non-TB conditions identified during CXR screening. There is need for prospective data collection about non-TB conditions identified during TB screening by national TB programs. This will help in characterisation of the patients and obtaining of sub national data on prevalence per region. This will help with granular planning of individual and health systems implications of these diseases.

A recommended quick win is collection of the data on electronic systems that are already developed for TB indicators. In countries like Kenya where District Health Information Software 2 (DHIS 2) is in use, I recommend review of the current indicators and capture screening data in the platform.

4 Operational modelling as a means of assessing policy options for the placement of chest X-ray in the patient TB screening pathway for Kenya

4.1 Introduction

As outlined in Section 1.1.2, WHO recommended CXR and CAD for systematic TB screening.[9, 30] This chapter firstly presents a review of literature on operational modelling use in TB. It further details a mixed methods study conducted to assess the placement options of CXR and CAD in the patient screening and diagnostic pathway in Kenya, and the policy implications of the findings. In addition to literature sources, the operational modelling detailed in this chapter uses the findings from Chapter 2 which demonstrated high accuracy of CAD software in community-based screening, along with those in Chapter 3 concerning non-TB abnormalities that CXR can identify.

4.1.1 Aim and objectives

The overall aim of the study was to assess policy options for the placement of CXR in the TB screening and diagnostic patient pathway in Kenya.

Objectives:

a) To determine feasible CXR placement options in the TB screening and diagnostic algorithms.
b) To build an operational model, simulating the feasible strategies from a), and then to use this to project the expected health and cost outcomes.
   This will be split into quantifying and understanding:
   i. Each strategy's impact from a TB programmatic and cost perspective
   ii. The non-TB pathology that implementing each strategy will detect
c) To use the model developed in b) to assess the impact of implementing CAD in place of standard chest X-ray readers

4.1.2 Policy implications

The findings of this study will help guide the Ministry of Health (MoH) and NTLD-program on the outcomes of various policy options during the CXR-CAD TB screening policy formulation. Additionally, projection of the estimated burden of non-TB conditions and other health system effects that the CXR-CAD roll out may have will be done. This will guide the integrated health system approach to a CXR TB screening policy as recommended in Section 3.7.2.1. Finally, the findings would guide CAD software and digital X-ray machines developers as they make further enhancements to their tools to aid in TB case finding.

4.2 Literature review

WHO provides global guidance for adoption of new tools and algorithms aimed at reducing TB incidence and mortality.[6] Countries then contextualise this guidance and determine what should be incorporated into policy. An example of this guidance is the WHO TB systematic screening recommendations.[9, 30] Policy-makers have competing priorities and thus clear evidence which demonstrates potential impact on resources, patients, health systems and the wider population is crucial.[38]

Over the last century computers have revolutionised the process of modelling, allowing us to understand and analyse complex systems. The advent of health systems modelling enabled more complex simulation of interventions/policies, allowing better understanding of their impact on health system resources. [102, 103] One type of operational model, a 'Virtual Health System Model', has been demonstrated as a tool to aid policymakers in deciding which policy alternative(s) to implement by comparing the impact of different options. [40, 42, 43, 104]

As outlined in Chapter 1, Kenya NTLD-program is currently considering adoption of CXR and CAD in their TB screening algorithm. The WHO operational handbook for systematic TB screening 2021 has recommended various screening option algorithms for the general population as well as the high-risk populations.[30] In Kenya, as outlined in Section 1.3, the questions that policy-makers were seeking answers to

included: *What is the optimal CXR placement in the Kenya TB screening and diagnostic pathway? What would be the projected impacts of scale up? What would be the health system effects of adopting CXR in the pathway?*

This study aimed to assess policy options for the placement of CXR in the TB patient screening and diagnostic pathway for Kenya. Operational modelling was used to predict the impact of three alternative TB screening and diagnostic algorithms. The outcomes of these algorithms were compared to the 2018 base case algorithm which used: the four symptom questionnaire for TB screening, bacteriological testing through GeneXpert and sputum smear microscopy (when GeneXpert was not available), and subsequently CXR to aid clinical diagnosis in patients who tested GeneXpert or smear negative.

4.3 Methods

4.3.1 Study design

This was a mixed methods study, with qualitative and quantitative studies used to obtain model inputs, and quantitative methodology then used to build the model.

4.3.2 Study setting

This is covered in detail Section 1.2.

4.3.3 Data sources and methods of collection

The study was conducted between June 2018 and May 2021.

The following were key data sources that yielded both quantitative and qualitative data to inform model construction. Quantitative data was obtained from:

- The Kenya National TB prevalence survey detailed in Sections 1.2.2 and 2.3.2, [2, 3]
- Analysis of CAD software in CXR screening for TB (Chapter 2)
- New analyses of non-TB pathologies identified by CXR in the Kenya National TB Prevalence Survey 2016 (Chapter 3)

- Literature search

Qualitative data sources:

- Key informant interviews
- Observation and note-taking during the operational modelling meetings

4.3.3.1 Kenya National TB prevalence survey

This is detailed in section 1.2.2 and 2.3.2. [2, 3]

4.3.3.2 Analysis of CAD software in CXR screening for TB

The findings from Chapter 2 provided sensitivity and specificity data for CAD for TB software.

4.3.3.3 New analyses of non-TB pathologies

Data on prevalence of non-TB pathologies obtained from findings in Chapter 3 were applied in the model.

4.3.3.4 Literature search

WHO systematic TB screening operation handbook,[30] Kenya TB annual report,[105] Kenya`s TB catastrophic cost survey,[106] active case finding program data and NTLD-program diagnostic algorithms, and other published literature as captured in Table 4.2 below, provided inputs for the model.

4.3.3.5 Key informant interviews

The key informant interviews were conducted as detailed in Section 5.4.4.3. For this modelling chapter, the focus was on interviewees' thoughts on the role of CXR in the TB screening and diagnostic algorithm. The interviews helped in determining feasible options for CXR placement in the TB screening and diagnostic algorithms strategies to be modelled in Section 4.3.5 below.

4.3.3.6 Observation and note-taking during the operational modelling meetings

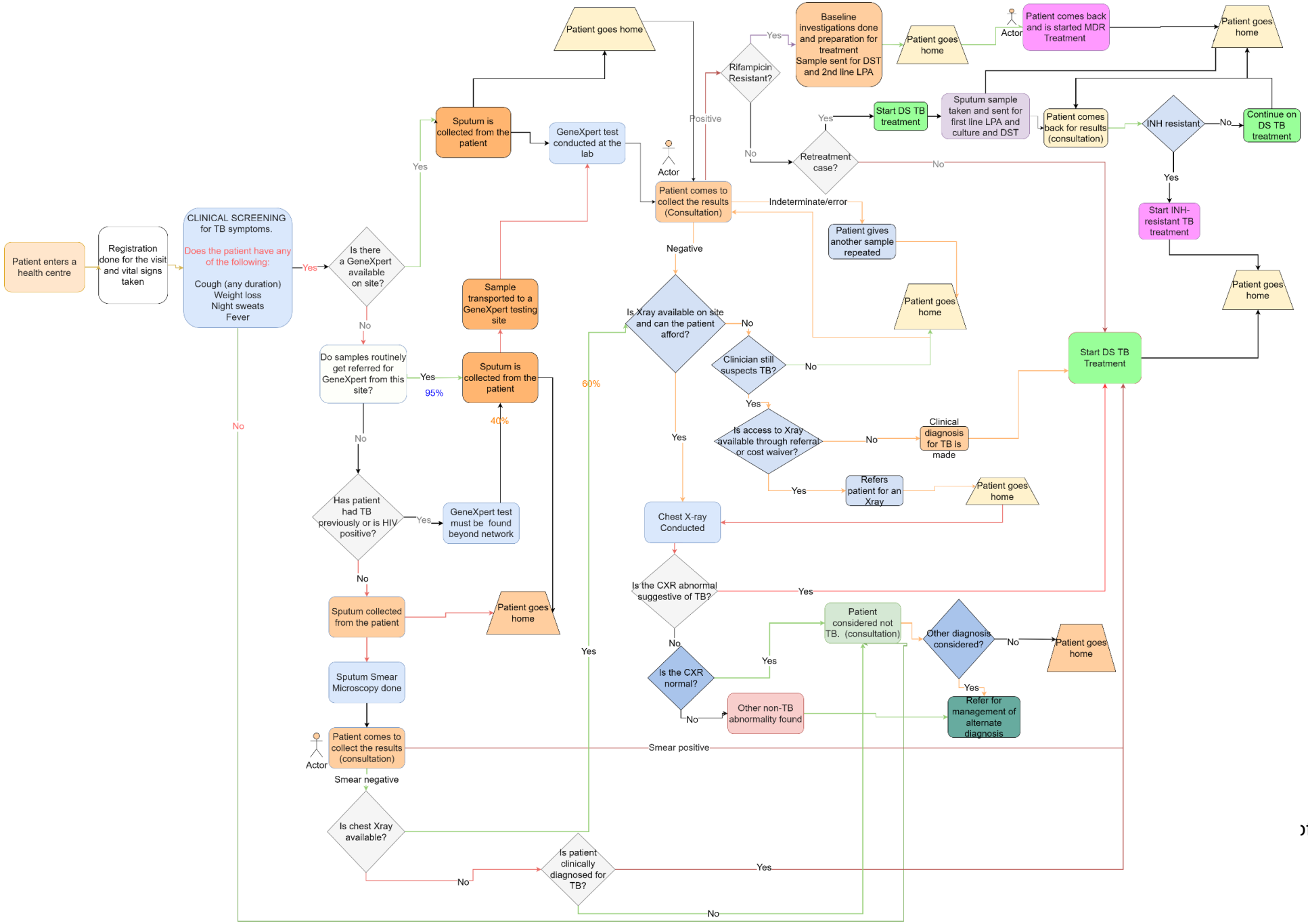
As part of the operational modelling introduction and model development, three workshops were conducted. The operational modelling meetings are described in more detail in Chapter 6. I facilitated the meetings, with the research assistant taking notes during the sessions. These meetings enabled building mutual understanding and consensus around diagnostic pathways and validation of model assumptions.

A validation meeting with NTLD-program officers and partners involved in TB work in Kenya was held in May 2021. I also attended the dissemination session for Kenya's TB patient cost survey and incorporated some of the findings in the costing part of the model.

4.3.4 TB patient pathway

The current TB patient pathway to diagnosis in Kenya was mapped out using draw.io[107] flow chart to cover the screening, triaging and the diagnostic process (Figure 4.1). Alternate screening, triaging and diagnostic algorithms to be modelled were identified (see section 4.3.5 below). This process was ongoing and consent to document the discussions during attendance of these meetings was sought.

Figure 4.1: Kenya TB screening and diagnostic pathway 2018



4.3.5 Strategies to be modelled- Patient management algorithms

Four approaches with CXR at different points in the algorithm were identified from the literature search and key informant interviews. These approaches are summarised as strategies inTable 4.1.

Strategy 0, the base case, uses standard symptom screening followed by microbiological testing (smear microscopy or GeneXpert), then CXR for microbiologically negative cases.

Strategy 1 is the same as Strategy 0 (the base case) except that an extended, seven-point symptom screening process is used instead of the standard screen.

Strategy 2 uses the extended symptom screening followed by CXR, with microbiological testing for those with CXRs suggestive of TB. Three different sub-strategies are assessed; a) with Clinical Officer interpretation of CXR, b) with the CAD4TB threshold set at 55 and c) with CAD4TB threshold set at 61.

Strategy 3 uses CXR as the initial screening process instead of symptom screening with microbiological testing being used for those with CXRs suggestive of TB. Once again three different sub strategies are assessed; a) with Clinical Officer interpretation of CXR, b) with the CAD4TB threshold set at 55 and c) with CAD4TB threshold set at 61.

Figure 4.2 and Figure 4.3are schematic outlines of the four strategies which were then modelled.

The sensitivity and specificity of the different modes of CXR interpretation were obtained from the findings in Chapter 2:

a) Clinical officers` interpretation

b) CAD4TB software at a threshold of 55 to achieve a sensitivity of 95% and specificity of 80%

c) CAD4TB software at a threshold of 61 to achieve a sensitivity of 90% and specificity of 83.2%

Table 4.1: Modelled CXR TB screening and triaging strategies

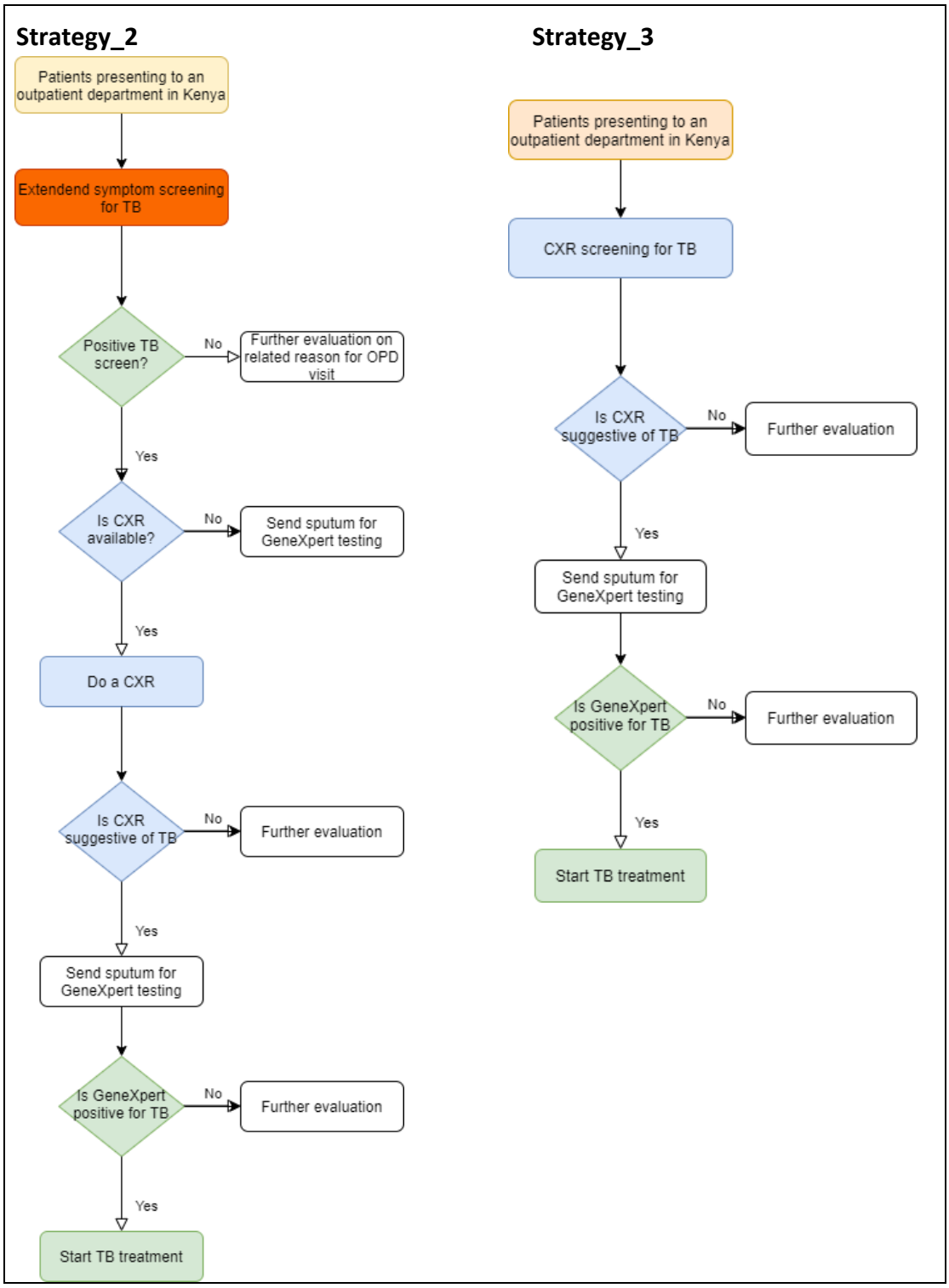
Strategy 0 (Base case)	0	Base case strategy using standard symptoms screening then bacteriological testing (GeneXpert/ Microscopy*) then CXR for the GeneXpert Negative presumptive TB **Standard symptom screen (Any of the following symptoms)** 1. Cough of any duration 2. Night sweats 3. Loss of weight 4. Fever
Strategy 1	1	Extended seven symptom screening, then bacteriological testing (GeneXpert/ Microscopy) then CXR (Clinical Officer interpretation) for the GeneXpert Negative presumptive TB **Extended symptom screen (Any of the following symptoms/signs)** 1. Cough of any duration 2. Night sweats 3. Loss of weight 4. Hotness of body 5. Chest pain 6. Low weight (Body Mass Index < 18.5) 7. High temperature (>37.5 degrees centigrade)
Strategy 2	2a 2b 2c	Extended seven symptom screening, then CXR (Clinical officer interpretation) then GeneXpert testing Extended seven symptom screening, then CXR (CAD software threshold of 55) then GeneXpert testing Extended seven symptom screening, then CXR (CAD software threshold of 61) then GeneXpert testing
Strategy 3	3a 3b 3c	CXR screening (Clinical officer interpretation) for all then GeneXpert testing CXR screening (CAD software threshold of 55) for all then GeneXpert testing CXR screening (CAD software threshold of 61) for all then GeneXpert testing

**When GeneXpert testing is not available, microscopy is used*

Figure 4.2: Schematic outline of Strategy_0 and Strategy_1

The difference between Strategy_0 and Strategy_1, is the use of additional symptoms during TB screening. In both strategies, CXR is used to aid clinical diagnosis after microbiological testing.

Figure 4.3: Schematic outline of Strategy_2 and Strategy_3



For strategy_2, CXR is used to triage patients after extended symptomatic screening but before microbiologic testing. In Strategy_3, CXR is used for screening all patients regardless of symptoms.

4.3.6 Operational modelling using the Witness package

An operational model of the TB patient pathway was built using the discrete event simulation (DES) package –WITNESS®.[39] There are five key elements in the WITNESS® model: entities, attributes, resources, queues, and activities.[39, 40] A patient (entity) visiting a health facility in Kenya was the entry point to the model. The health facilities were Sub-county (Level 4), County (Level 5) or National hospitals (Level 6) that had a CXR machine and GeneXpert machine on site.

The patient going into the model was assigned attributes i.e. Sex, TB status, HIV status. The patient then travelled through the model activities which included: TB screening, clinician consultation, microbiological testing and chest radiography. The resources included human resources- clinicians, lab technologists, radiographers, digital CXRs, GeneXpert machines, microscopes etc. Queues were generated when entities competed for resources.

Collation of data for the base case scenario (Strategy_0) including assumptions was carried out. Validation of the model using the current process and current outputs was conducted and the model configured for the revised process. The model then incorporated alternative strategies. GeneXpert was the bacteriological confirmation test for TB but when not available, the probability of using microscopy was also modelled. The model was then run with the alternative algorithms and analysis of the outcomes and sensitivity of each strategy conducted as outlined in Sections 4.6.3.2 and 4.6.3.3 below. The model produced a visual representation of the patient pathways being modelled which was beneficial for engagement and validation.[108]

4.3.6.1 Input parameters

The starting point of the model was the Kenya TB screening and diagnostic pathway 2018 (Strategy 1 in Figure 4.1 above). The input parameters included patient volumes, patient types, diagnostic accuracies (sensitivities and specificities), facility levels and costs (Table 2). Sensitivities and specificities applied for the different triaging and diagnostic tools were from program data, prevalence survey and the literature review.

Table 4.2: Model input parameters

Parameter	Value (95% CI)	Source	Year
Number of outpatient attendees modelled	**20,000**		
TB prevalence among outpatient attendees-New	13.82%	NTLD program data	2019
TB prevalence among outpatient attendees	38.16%		
HIV prevalence (general)			
HIV prevalence (Adults all)	4.9% (4.5%-5.3%)	National AIDS and STI Control Programme[71]	2020
Male	3.1% (2.7%-3.5%)		
Female	6.6% (6.0%-7.1%)		
HIV prevalence in TB and no TB cases			
HIV prevalence in TB cases-Public	Male 20.1%, Female 31.9%	NTLD program data	2019
HIV prevalence in DR TB cases-Public	Male 31.4%, Female 49.7%		2019
HIV prevalence in TB cases-Private	Male 28.1%, Female 39.7%		2019
HIV prevalence in DR TB cases-Private	Male 46.7%, Female 57.9%		2019
HIV prevalence in no TB cases	4.9% (4.5%-5.3%)	NASCOP[71]	2020
Proportion of TB that is Drug resistant TB			
New cases-public facilities	1.3%	NTLD program data	2019
New cases-private facilities	0.5% Female, 0.7% Male)		2019
Retreatment cases-public facilities	4.6%	WHO global report[6]	2020
Retreatment cases-private facilities	4.6%	WHO global report[6]	2020
Microscopy			
Sensitivity - ZN Microscopy for HIV-negative	57(50-64%)	Van Cleeff, M., Kivihya-Ndugga, L., Meme et al[109]	2005
Specificity- ZN Microscopy for HIV-negative	98(97-100)%		
Sensitivity- Light-emitting diode fluorescence microscopy (LED-FM)for HIV-negative	84(79-89%)		
Specificity-Microscopy LED-FM for HIV-negative	98(95-100)%		
Sensitivity- ZN Microscopy for HIV-positive	36(28-44)%		
Specificity- ZN Microscopy for HIV-positive	100(100-100)%		
Sensitivity-Microscopy LED-FM for HIV-positive	73(65-80)%		
Specificity-Microscopy LED-FM for HIV-positive	100(100-100)%		
GeneXpert			

Sensitivity- GeneXpert as a first test pooled	88(84-92)%	WHO Xpert MTB/RIF implementation manual Technical and operational 'how-to': practical considerations [70]	2014
Specificity- GeneXpert as a first test pooled	99(98-99)%		
Sensitivity- GeneXpert in smear negative	68(61-74)%		
Specificity- GeneXpert in smear negative	99(98-99)%		
Sensitivity- GeneXpert in smear positive culture positive	98(97-99)%		
Specificity-GeneXpert in smear positive culture positive	99(98-99)%		
Sensitivity- GeneXpert for HIV-negative	86(76-92)%		
Specificity-GeneXpert for HIV-negative	99(98-99)%		
Sensitivity-GeneXpert HIV-positive	79(70-86)%		
Specificity-GeneXpert HIV-positive	99(98-99)%		
Sensitivity-GeneXpert identifying Rif resistance	95(90-97)%		
Specificity-GeneXpert identifying Rif resistance	98(97-99)%		
Sensitivity- GeneXpert ultra in smear pos culture pos	88(85-91)%	Dorman SE, Schumacher SG, Alland D, et al.[110]	2018
Specificity-GeneXpert ultra in smear pos culture pos	96(94-97)%		
Sensitivity- GeneXpert ultra for HIV-negative	91(86-95)%		
Specificity-GeneXpert Ultra for HIV-negative	96(94-97)%		
Sensitivity-GeneXpert Ultra HIV-positive	90 (83-95)%		
Specificity- GeneXpert Ultra HIV-positive	96(94-97)%		
Sensitivity-GeneXpert Ultra identifying Rif resistance	95(91-98)%		
Specificity-GeneXpert Ultra identifying Rif resistance	98(97-99)%		
Chest X-ray			
Sensitivity of bacteriological diagnosis with X-ray	77%	A H Van't Hoog , H K Meme, H van Deutekom et al[111]	2012
Specificity of bacteriological diagnosis with X-ray	83%		
Sensitivity of Clinical diagnosis with X-ray	80 (74–85)%	van Cleeff MR, Kivihya-Ndugga LE, Meme H et al[109]	2005
Specificity of Clinical diagnosis with X-ray	67% (62–71%)		
Sensitivity of CAD4TB bacteriological confirmed TB (Minimum TPP)	90%	Mungai B, Ong'angò J, Ku CC, et al. [44]	2021
Specificity of CAD4TB bacteriological confirmed TB	90.4 (88.1-92.6)%		

Sensitivity of CAD4TB bacteriological confirmed TB (Optimal TPP)	95%		
Specificity of CAD4TB bacteriological confirmed TB	83.2 (79.9-86.6)%		
Clinical symptoms questionnaire			
Sensitivity of Extended symptom screening (Any TB symptom-cough, hemoptysis, fever, night sweats, weight loss)	71%	WHO operational handbook on tuberculosis [30]	2021
Specificity of Extended symptom screening (Any TB symptom-cough, haemoptysis, fever, night sweats, weight loss)	64%	Kenya prevalence survey data[3]	2016
Sensitivity of Extended symptom screening (Any symptom including BMI)	90(84-95)%	van't Hoog AH, Meme HK, Laserson KF et al[111]	2012
Specificity of Extended symptom screening (Any symptom including BMI)	32(30-34)%		
Individual combination of symptoms from prevalence survey data			
COSTS			
Estimated unit cost per test-ZN Microscopy	UDS 1.3	NTLD program data	2020
Estimated unit cost per test- LED FM	USD 1.6		
Estimated unit cost per test- Standard GeneXpert	USD 25 (20-30)	Hsiang E et al [112]	2016
Estimated unit cost per test- Ultra	USD 21	Sarah Wood Pallas et al[113]	2018
Estimated unit cost per test- Chest X-ray	USD 11	Puri, Lekha et al[114]	2016
Estimated unit cost per test- CAD4TB	USD 1	Delft[59]	
Estimated cost of Clinical officer CXR read	USD 0.5	NTLD program data	2020

This table captures model input parameters from various sources as referenced in the source column.

4.3.6.2 Outcomes of interest

The model outputs were compared to the base case Strategy_0, these included; the number of presumptive TB patients identified tested with GeneXpert, number of patients diagnosed with bacteriologically confirmed TB (drug-sensitive and drug-resistant), number with clinically diagnosed TB and those with non-TB abnormalities identified. In addition, overall health system costs per strategy were analysed and Incremental cost-effectiveness ratio (ICERs) per strategy were calculated.

Sensitivity analysis for the different strategies was conducted. For each strategy, true positive, true negative, false negative and false positives were calculated. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were also computed.

4.3.7 Ethical approval

Ethical clearance from Kenya Medical Research Institute scientific ethics review unit (Non KEMRI Protocol no. 616) and Liverpool School of Tropical Medicine Research Ethics Committee (18-052) was obtained to carry out the study. Written informed consent was obtained from each participant as per the approved protocol. (See full details section 5.4.7).

4.3.8 Data storage and management

All the data (including recordings and transcripts) were stored in a two-step password protected laptop and external hard disk only accessible to the researcher. Additionally, we backed up data in a password-protected Microsoft OneDrive cloud solution.

4.3.9 Data analysis

After the data collection, the research assistant transcribed the recorded interviews verbatim and I reviewed all the transcripts. The transcripts were read multiple times to promote familiarization with the content. Themes and sub-themes emerging from the data were categorized as follows; the utility of CXR, CXR strategies, barriers and enablers to CXR use and factors to consider during roll out. Guided qualitative content analysis was carried out and QSR Nvivo 12 Pro was used to code the data in themes.

4.4 Results

4.4.1 Objective 1: To determine feasible CXR placement options in the TB screening and diagnostic algorithms.

4.4.1.1 CXR is a useful tool in TB case-finding activities

Most of the respondents made reference to the prevalence survey findings of CXR identifying 88% of the prevalent cases, performing much better than symptom screening.[2, 3] There was general agreement that CXR was a sensitive tool and should be incorporated in ACF activities to aid in finding all persons with TB early, even the asymptomatic as captured in the quote below.

> *"I actually think if we were to make progress; two things finding all TB patients and finding them early, chest x-ray is key as a tool because if you identify people that need to be an X-ray and you X-ray them early, you will pick up lesions of TB long before those people become symptomatic. So, I think chest x ray is a key."* ***KII 009***

In addition, use of CXR would identify other non-TB conditions that were noted to be prevalent in Chapter 3. The biggest challenge for use of CXR is feasibility as captured in the quote below, which will be further presented in Section 4.4.1.4.

> *"I think generally there is push, […] of incorporating more sensitive tools in diagnosis of TB based on the fact that there are many people with TB who are missed yet these people are already presenting in the health facilities. One such tool is deployment of chest X-ray, but what generally holds it, […] is more about the feasibility of where and how do we incorporate it in the screening approach so as to inform scale up."* ***KII 019***

4.4.1.2 Suggested CXR strategies during the key informant interviews

Though there was general consensus among the respondents that CXR was important, there were varied ideas on where in the algorithm it should be placed. The feasibility of use of CXR due to barriers highlighted in 4.4.1.3 below resulted in

diverse views. The three main strategies suggested were: use of CXR for screening, triaging and clinical diagnosis.

a) CXR as a primary TB screening tool

For community-based TB case finding activities (including at institutions such as schools, prisons etc.), there was consensus that CXR TB screening strategy would likely be preferable as the prevalence of asymptomatic TB would be higher.

Relating to facility-based ACF, there were diverse views on CXR TB screening for all patients attending the out-patient department (OPD) regardless of symptoms. Some respondents felt CXR was preferable as it was a more sensitive screening tool ensuring identification of TB among all persons including the asymptomatic who would be visiting the facility for other reasons. However, acceptability for those with no respiratory symptoms was likely to be difficult, placing an unnecessary health system burden on clinicians, facility managers and patients as captured below.

> *"For me, active case finding is really an outpatient exercise, everyone who goes to the OPD should really be screened for TB. Now if patients have gone to a health care facility and they don't have respiratory symptoms that is where the trick is. Do you want to X-ray all those people or do you want not to X-ray those people? Remember, if you are going to X-ray everybody, if I have gone with an abdominal pain and you are telling me to get a chest x ray, you will have a lot of push backs from clinicians who might think that is not a good practice, you may have a lot of pushbacks from health facility managers who think you are over loading your chest x ray unit and stuff like that. So, there I think for chest X-ray within health care settings, it would probably be directed mostly at those who have symptoms or those with certain conditions. If you go to a health care facility, you have none specific symptoms and your BMI is very low, and I have no idea what is happening to you, a chest x ray can be part and parcel of that investigation process […]. This is where operational research is needed to see how best to position chest X-ray in the different scenarios."* ***KII 009***

Similar to the WHO systematic TB screening guidelines,[30] for high-risk populations (e.g. people living with HIV, TB contacts, children) the respondents recommended CXR to be used as a screening tool at first point of contact. Finally, it was suggested to use CXRs for baseline TB screening in high-risk settings such as quarries and cement factories, and among high-risk populations such as health care-workers and workers handling silicone.

b) CXR for triaging in facility based active case-finding

For predominantly patient-initiated pathways (e.g. facility-based screening at OPD), there was consensus on CXR use for triaging those with symptoms. Use of CXR would aid in patient-centred care reducing patient anxiety caused by waiting long periods for test results, as well as reduce the demand on the laboratory system. CXR triaging was likely to be cost-effective and enable rapid feedback and clinical decision, however, for it to be beneficial, timely CXR results would be required.

> *"As they come in, they get a chest X-ray, if a chest X-ray is available to the clinician not two days later but within an hour or so, an hour or two. If you really want to do a good program, for [private sector] you have access to an X-ray within half an hour, so if you could say in a public health care setting or rather within a public health program you had the ability to get a chest radiograph within an hour or two then you can then request your sputum test. Why is that important? What we are seeing in this country is we are overloading the laboratory system with specimens, sputum [tests] that are not needed."* ***KII 009***

c) CXR for clinical diagnosis

Other suggested CXR placement options included using more sensitive symptoms questionnaire but leaving CXR for clinical diagnosis. Another proposal, though noted to be resource intensive, was the parallel use of CXR and GeneXpert during ACF or targeted screening.

4.4.1.3 Barriers and enablers to CXR use in screening and triaging

The identified barriers and enablers to the roll out of CXR for screening and triaging in line with the health system strengthening blocks are captured in Box 4.1 below.[97]

Box 4.1: Barriers and proposed solutions for roll out of CXR for screening/triaging

Health system building blocks	Barriers	Proposed Solution/enablers
Service delivery	Kenya has approximately 100 digital X-ray machines in the public facilities. Their availability is limited to the sub-county, county and national hospitals. CXR TB screening would therefore be limited to these facilities. An X-ray machine in a health facility serves a whole range of clients and is not exclusive for lung conditions. Therefore an increased demand for CXR for TB screening may cause a disruption in the health system as well as cause a long wait time for those being screened for TB. *" then x ray machines are busy, they are used for other things so it is very discouraging for me to wait*	Availability of ultra-portable CXRs present an opportunity for community-based TB screening as well as mobile screening activities in lower level health facilities, and to supplement increased demand in OPDs with high workload.

	for twelve hours for an x ray that there are people with fracture, there are some people who need to be X-rayed I don't know for what, there is only one radiologists, there is no radiologists at all, there are some facilities with x ray but no radiologist at all or there are radiologists but they are not trained on the new like the digital ones, they may not be able to use, availability of consumables." **KII 016**	
Health workforce **Medical products, vaccines and technologies**	Scale up in use of CXR for screening and triaging will lead to overstretching of the available X-ray machines as well as the human resource especially radiographers, radiologists to do the X-ray and also interpret these.	CAD software (as detailed in Chapter 2) *"And artificial intelligence has been found to be as good as human readers and can therefore facilitate increasing access to decision making and prompt decision making and therefore find it, a lot of filling that space. That decentralized setting a decision is made quickly that at this cut off point this person requires to have further TB testing in the lab rather than sending her to a doctor who is held up*

	Acceptability of CXR TB screening among HCWS and capacity building required. There is also a risk of over-diagnosis of clinical TB as clinicians may fail to do lab confirmation and/or start TB treatment even with negative microbiological result.	*somewhere to read it and the decision is made the following day."* A network mechanism would require setting up to assist clinicians with interpretation and management plan for persons with abnormal CXR and negative microbiologic testing. A quality assurance system should be set up.
Financing	Cost of the chest X-ray currently at 500-700 Kenya shillings ($ 5-7). This out of pocket expenditure will be a barrier to access by the clients.	This cost should be borne by the NTLD-program or through the National Health Insurance Fund. The newer digital CXRs have lower operational costs so the cost per CXR is likely to be less.

	Indirect cost of accessing CXRs for example transport costs in case of referral to another facility	Investing in mobile outreaches to ensure clients have more accessible CXR services will mitigate this risk.
Information	Misinformation on CXR safety among patients *"The biggest threat to implementation of chest X-ray is understanding that a chest X-ray is safe, as in the community must see the chest x ray as safe because for a long time, it was portrayed as exposure to x rays can lead to cancer and with the fear of cancer we must first demystify that."* **KII 003**	Adoption of newer digital X-ray machines with less radiation exposure may help to allay these fears.
Leadership/Governance	The NTLD-program had started planning for a stand-alone CXR TB screening policy. Involvement and engagement of other sectors for example Ministry of Finance, NHIF, community services etc. would be required for a comprehensive policy.	During the formulation of the CXR policy, health system integration and involvement of diverse actors must be key.

4.4.1.4 Factors to consider when rolling out CXR TB screening and triaging algorithm

a) Health system integration

Ensuring the inclusion of all stakeholders using an approach that integrates TB screening and triaging in the health system from policy formulation, through implementation, to evaluation.

> *"It's TB that needs to integrate with the health system completely for it to make sense to use x ray in health facilities. So, the TB program [should] be part of the health system and not to be a parallel program so that way we will be able to see the benefits of X-ray reduce TB transmission, assistance in the ACF, eventually I mean we get more patients to the system, and they reduce these missed cases.* ***KII 006***

b) Feasibility

CXR and CAD have been shown to be accurate tools, however, feasibility of the roll-out needs to be carefully considered. Among the questions that need to be answered include: Which facilities will this be conducted at? Who will bear the cost of CXR? Which stakeholders need to be involved? Which human resources need to be engaged and how will they be capacitated? What will be the role of the CAD software? How will non-TB abnormalities be linked or referred? The respondents felt if roll-out is done for facility case-finding, the facilities engaged should have digital CXRs and GeneXpert on site (these are sub-county-Level 4, County-Level 5 and National-Level 5 facilities). For community-based screening, additional mobile X-ray machines will be required.

c) Cost-effectiveness analysis

To assess what strategy to scale up, cost-effectiveness analysis is required. One respondent felt it was likely that triaging with CXR then doing GeneXpert is likely to be more cost-effective with a faster turnaround than the base case of GeneXpert then CXR.

d) Pilot or full roll out of CXR for TB screening

The respondents felt that CXR implementation should be done as pilot and not full scale up as there were lots of factors to be considered. The suggestion was also for the pilot to be conducted in two types of facilities- in a high-burden and a low-burden TB County.

4.4.2 Objective 2: To build an operational model, simulating the feasible strategies from objective 1, and then using this to project the expected health and cost outcomes.

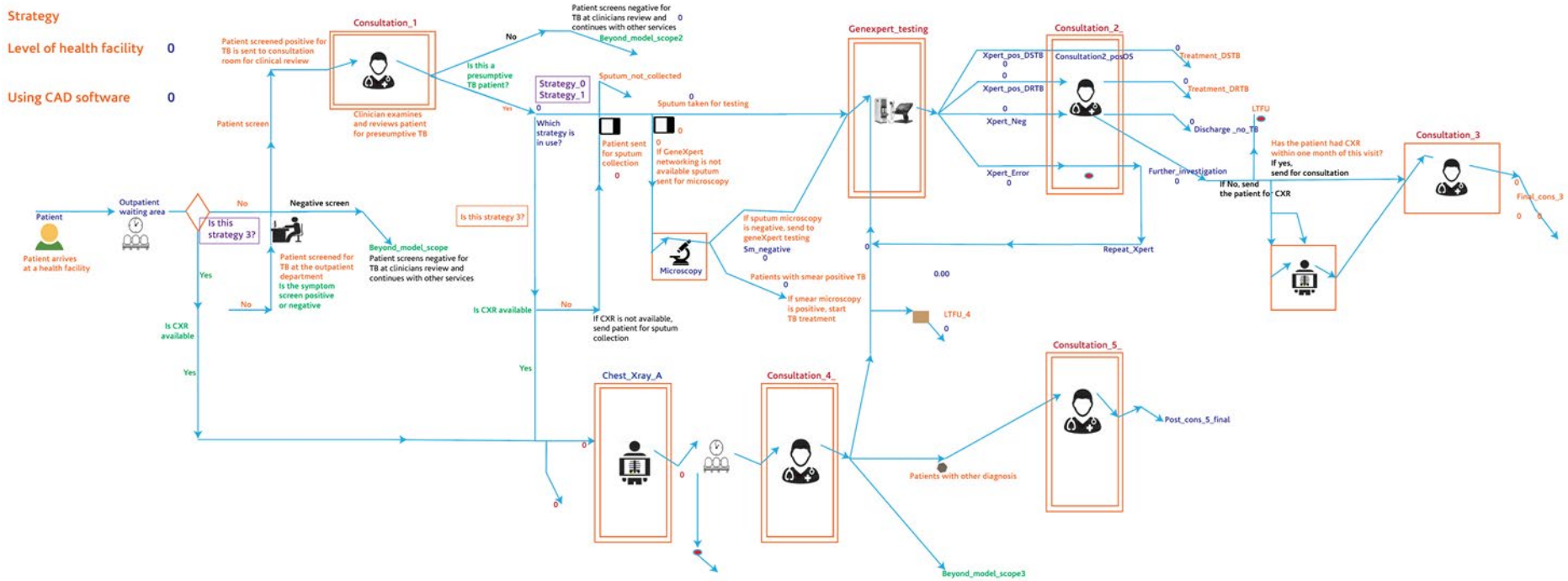
The strategies were modelled with 20,000 patients entering a health facility at the outpatient department and exiting either at point of diagnosis (TB or non-TB), discharge from the model (i.e. not a TB patient) or lost to follow up as depicted on the operational model in Figure 4.4 below.

Programmatic impact

The summary projections for the programmatic impact of CXR in different positions (Table 4.3) show that Strategy 3b (CXR screening for all with CAD interpretation at threshold of 55 – to achieve a sensitivity of 95% and specificity of 80%- then GeneXpert testing), had the highest absolute total (2248) drug-sensitive and drug-resistant cases identified, as well as proportion of true TB cases identified of 77.5%, and an additional 663 true positive cases compared to the base case. Strategy 3c (CXR screening for all with CAD interpretation at threshold of 61 – to achieve a sensitivity of 90% and specificity of 83%- then GeneXpert testing) followed closely with the next highest absolute total (2093) drug-sensitive and drug-resistant cases identified, a proportion of true TB cases identified of 72.2% and 508 additional true cases identified compared with the base case. Strategy 2a (extended symptom screening, CXR with clinical officers' interpretation then GeneXpert testing) had the least additional true TB cases (+100) and the highest cost per additional TB case. The strategies with CXR for screening (3a, 3b, 3c) or triaging (2a, 2b, 2c) had the lowest number needed to test one bacteriological confirmed case of (2), compared to (4) in

the base case, and (6) in Strategy 1. Strategy 1 (Extended symptom screening followed by GeneXpert screening) also had the highest false positive cases projected.

Figure 4.4: Operational model snapshot



This image captures the CXR for TB screening model showing the different strategies and the service points the patient passes through till they exit the model. Points of model exit are a) diagnosed to have TB, b) other non-TB diagnosis c) discharged from the model/other unrelated pathology d) Lost to follow-up

Table 4.3: Projections of programmatic impact of the various modelled strategies.

Modelled strategy	Presumptive TB patients receiving GeneXpert testing	Total drug-sensitive (DS TB)TB cases identified	Total drug-resistant TB (DR TB)cases identified	True TB cases identified (DS and DRTB)	Percentage true positive identified	False TB cases identified	Percentage false positive identified	Missed true TB cases	Percentage missed true TB cases	Number needed to test to get one bacteriological confirmed true TB	Additional True TB cases compared with base case (Strategy_0)
Strategy_0	6615	1603	59	1585	57.6%	90	0.6%	1168	42.4%	4.2	0
Strategy_1	11361	2060	76	1961	75.3%	188	1.3%	643	24.7%	5.8	+376
Strategy_2a	3650	1651	67	1685	57.4%	33	0.2%	1253	42.6%	2.2	+100
Strategy_2b	4063	1978	69	2012	68.5%	35	0.2%	926	31.5%	2.0	+427
Strategy_2c	3287	1842	70	1897	64.6%	15	0.1%	1041	35.4%	1.7	+312
Strategy_3a	4568	1793	69	1810	62.4%	52	0.3%	1089	37.6%	2.5	+225
Strategy_3b	5065	2205	91	2248	77.5%	48	0.3%	651	22.5%	2.3	+663
Strategy_3c	3960	2047	79	2093	72.2%	33	0.2%	806	27.8%	1.9	+508

This table shows the programmatic impact of various strategies on the number of presumptive TB cases requiring a diagnostic test, number of TB cases identified and comparison to the base case (Strategy 0) additional true TB cases.

**The identified cases are all bacteriologically confirmed. Clinically diagnosed TB cases have been excluded from this table*

Cost-effectiveness

The CXR for triaging after extended symptom screening with CAD interpretation (Strategies 2b and 2c) had the lowest incremental cost effectiveness ratios (ICERs) (i.e. lowest cost per additional true case identified) and were therefore, the most cost-effective strategies (Table 4.4). Use of clinical officers for CXR interpretation in triaging was the least cost-effective with ICERs of 715 and 705 for strategies 2a and 2b respectively. Figure 4.5 shows modelled strategies all had better programmatic performance with higher TB cases identified than the base case though at higher additional costs.

Table 4.4: Projections of cost impact of the various modelled strategies.

Modelled strategy	Additional True TB cases	Total incremental Cost compared to base case (USD)	Incremental cost-effectiveness ratio (ICER)
Strategy_0	0	-	-
Strategy_1	+376	133,030	354
Strategy_2a	+100	71,508	715
Strategy_2b	+427	89,049	209
Strategy_2c	+312	69,649	223
Strategy_3a	+225	158,649	705
Strategy_3b	+663	181,181	273
Strategy_3c	+508	153,556	302

This table captures the additional true TB cases, total incremental costs compared to the base case. Further, the incremental cost effectiveness ratio for each strategy is calculated. The lower the ICER the more cost effective a strategy is.

Figure 4.5: Comparison of the incremental costs of modelled strategies versus additional true TB cases

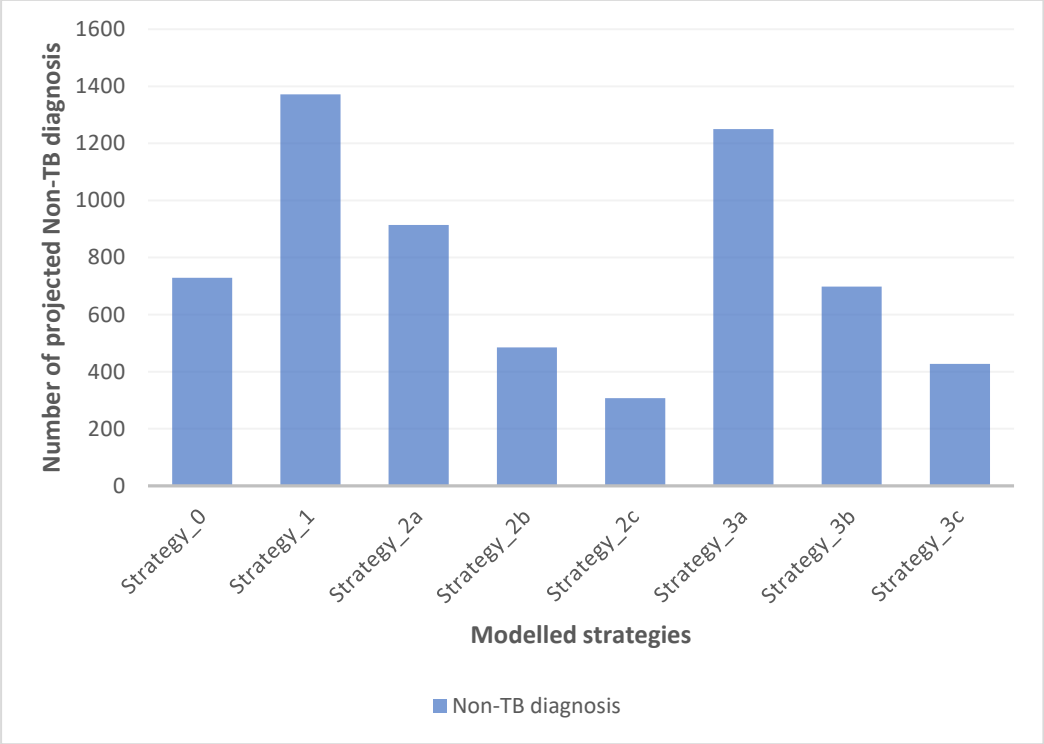
Use of CAD in place of standard chest X-ray readers increased the sensitivity of the strategies (Table 4.5) and the additional true TB cases identified (Table 4.4). A lower CAD threshold of 55, had a higher total number of persons with presumptive TB undergoing GeneXpert testing due to the increased sensitivity, but had a lower cost per additional TB case detected than a higher CAD threshold score of 61.

Projected non-TB pathology

All the strategies are projected to detect non-TB pathology during CXR examination at screening, triaging or diagnosis. These pathologies include cardiac, pulmonary, mediastinal or pleural abnormalities.[45] The highest prevalence of the abnormalities was cardiac as presented in Chapter 3. The chart on Figure 4.6 below shows the aggregate non-TB pathology per strategy. Use of CAD depicted the lowest non-TB abnormality because the cut-off threshold only classified CXRs as normal and abnormal suggestive of TB. This is therefore and under-representation and is not a

true reflection of reality as the CAD4TB software modelled does not have a cut-off for other abnormalities.

Figure 4.6: Non-TB abnormalities projected per modelled strategy



Sensitivity, specificity, PPV and NPV analyses

The sensitivities and specificities for the modelled strategies varied from 57% (Strategy 2a) to 75% (Strategy 1), and 99-100% respectively as shown on Table 4.5 below. The PPV was lowest for Strategy 1 (91%) and highest where CXR was used for screening or triaging.

Table 4.5: Sensitivity, specificity, PPV and NPV of the modelled strategies

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Strategy_0	57.6%	99.4%	94.6%	93.0%
Strategy_1	75.3%	98.7%	91.3%	95.6%
Strategy_2a	57.4%	99.8%	98.1%	92.6%
Strategy_2b	68.5%	99.8%	98.3%	94.4%
Strategy_2c	64.6%	99.9%	99.2%	93.8%
Strategy_3a	62.4%	99.7%	97.2%	93.2%
Strategy_3b	77.5%	99.7%	97.9%	95.9%
Strategy_3c	72.2%	99.8%	98.4%	94.9%

4.5 Discussion

Operational modelling was used to predict the impact of alternative TB screening and diagnostic algorithms with CXR placed at different points compared with the 2018 base case algorithm of CXR for diagnosis. This operational model of a patient initiated health care pathway used sequential screening and confirmatory testing as parallel algorithms common in TB prevalence surveys had little benefit for active case-finding activties.[30, 115] The sequential screening tests were symptom screening and/or CXR followed by GeneXpert as a confirmatory test. A strategy using CXR-CAD screening for all, then GeneXpert though the most expensive, demonstrated the ability to identify more persons with TB. Enhanced symptom screening, including signs like BMI and temperature >37.5 °C, followed by CXR-CAD triaging and diagnosis by GeneXpert offered the most cost-effective combination optimising case-finding while maintaining efficiency. [111] The availability of new technology including -ultra-portable CXRs has the potential to make CXR TB screening and triaging feasible. For screening at health facilities, CXR for triage after enhanced symptom screen was recommended while CXR screening for all was noted to be more feasible and acceptable during community-based screening of high-risk populations.

Kenya has an estimated overall national TB prevalence of 426 per 100,000, i.e. 0.426%.[3] This model was health facility-based and therefore a higher prevalence

from the NTLD-program prevalence data was applied - 13.82% among the new TB cases, and 38.16% among the previously treated. The PPV for most of the strategies modelled was therefore high due to the high prevalence, however, we did not include the clinical diagnosis in this sensitivity analysis which could have had an effect on PPV. Using a highly sensitive symptom screen with low specificity (Strategy 1) has the lowest PPV and therefore a high number of people with false positive TB would be put on treatment.

CXR as a triage test

Adding more symptoms to the clinical questionnaire increased sensitivity but with low specificity.[111] A triage test i.e. CXR in strategy 2 optimized case-finding while maintaining efficiency especially when CAD software which had a higher sensitivity than clinical officers` interpretation was used. This balance is important to avoid health systems being overwhelmed. For example GeneXpert for all symptom screen positive patients in Strategy 1 required 11361 samples (56% of the 20,000 patients entering the model) to be tested compared to Strategy 2a`s 3,650 (18%). The use of CXR for triaging cut down the GeneXpert tests and lab resources required by approximately 70%. Previous studies have similar findings showing that a triage test strategy improves the affordability of GeneXpert for TB diagnosis by reducing costs by up to 40%.[115, 116]

CXR for TB screening

A study by Frascella et al estimated approximately 50% of prevalent TB cases are sub-clinical and ignoring this burden will undermine TB control and elimination strategies.[21] Regardless of how sensitive a symptom screening is, it will always miss the asymptomatic patients with TB. The ability of a CXR screening algorithm to identify subclinical TB that would likely be missed by the symptom screening pathway contributes to the increased case-finding of Strategy 3b.[21] This finding is similar to other studies among household TB contacts and HIV-positive patients that found CXR screening increased case-finding with earlier diagnosis.[56, 117]However, this

strategy is resource intensive and respondents felt it would be less feasible and acceptable, to both the health care-workers and patients.

Additional benefits of a CXR TB screening/triage strategy

Use of CXR identifies persons with CXRs highly suggestive of TB who may be bacteriologically negative who may be at increased risk of developing active disease in future. [118] However, there is a potential risk of clinical over-diagnosis and care must be taken for the GeneXpert negative, abnormal CXRs diagnosis.[26] As demonstrated in Chapter 3, it may be difficult to distinguish between old/latent TB and post TB lung disease and these may be subjected to recurrent TB treatment.[45, 91] TB programs should be aware of this as CXR for TB screening is rolled out and plan for a second level review or support clinicians for the CXR images abnormal suggestive of TB with negative molecular WHO-recommended rapid diagnostic tests (mWRDs).

Secondly, this modelling has shown that the use of CXR for screening/triage will lead to identification of non-TB pathology (Figure 4.6) that will need to be planned for.[45] However, the specific CAD4TBv6 software in this study did not have capability of identifying other non-TB abnormalities. Though some of the currently available CAD software have some capability of identifying some non-TB abnormalities,[25] this is still limited and proper coordination and planning to identify images requiring further evaluation is needed. In Chapter 3, most of the non-TB abnormalities had lower scores, for example cardiomegaly CAD score was at 50 (IQR 46-56). With a threshold score of 61, these images would have been missed completely. Countries should consider having images with scores about 50 and above having an expert radiologist read.

Health system effects

CAD software as demonstrated in Chapter 2, can ease the human resource requirement for CXR interpretation providing faster interpretation, less human resource need while delivering high sensitivity and specificity for abnormalities

suggestive for TB.[44, 52, 55] The use of CXR-CAD either in screening and triage reduced the number of GeneXpert tests required to diagnose a TB case by approximately 15%. Though our percentage of GeneXpert tests saved was lower, this was comparable to other studies that showed a 50% saving of GeneXpert tests when CAD software was used compared to human readers.[55] The operational model has enabled demonstration of CADs flexibility of varying thresholds (55 vs 61) showing the impact on number of tests done versus the number diagnosed. As highlighted in Chapter 2, by varying the CAD screening threshold, the number of TB cases deemed acceptable to be missed can be balanced against how much money is available to spend on expensive confirmatory sputum investigation given the limited resources.[55] It is important to note that even with use of CAD, human readers, for example, will outperform CAD for interpretation of complex non-TB CXR abnormalities, or even in deciding on management plans for TB patients with complex and or extensive lung damage.

Operational modelling usefulness

The operational model used in this study enabled involvement of the policymakers who were able to visualise the movement of patients along the pathway. In addition, adjusting sensitivities and specificities of various process within the model is possible with prospective country or facility specific data. WHO has developed an accompanying operational guideline and the screenTB tool to aid countries calculate impact of various algorithms. The screenTB online tool aims to help TB programs and their partners plan TB screening activities by modelling the potential outcomes, similar to what the operational modelling in this study set out to achieve. [119] Though the screenTB is a useful tool, it has been calibrated with aggregate data from various populations and contexts and is still a “black box”. Due to this, we recommend prospective data collection and comparison of the screenTB tool and the virtual implementation models to inform country planning, including feedback from policymakers on utility.

Strengths of the study

The use of a mixed methods study enabled choice of strategies, inputs and assumptions based on the model users' views. It also helped the understanding of what strategies were feasible and acceptable, triangulated with the programmatic and cost implications. Data from local context especially prevalence survey and facility level records ensured the model fully reflects the country specific context.

Limitations

A model is as good as its assumptions. There were some decision points that were difficult to model for example, clinical officers` decision for the GeneXpert negative to say discharge from pathway or not, or clinical suspicion of TB. Clinical decisions are very individual and hard to model with certainty. The costing conducted in the study is high level health system costs. Patient related costs (direct and indirect) would be important to analyse to see what strategy would have less catastrophic costs to the patient.[106]

4.6 Conclusion

"The ideal algorithm does not exist."[115] As we have demonstrated, the choice of a screening or diagnostic algorithm is setting specific and depends on many considerations. From this study findings, the policies may be heterogeneous varying by level of health facility, availability of digital CXRs, CAD, and mWRDs on site. CXR for TB while an important tool for screening and rapid advancements making it accessible through the decades, still has many health systems consideration for roll out. With the available infrastructure, it is recommended to national TB programs, that the roll out of a CXR screening and triage strategy be limited to health facilities with CXR on site and even then, additional X-ray capacity would be required. For CXR screening for all, this would be considered for community based screening of high-risk populations. Development of national policies are required to guide the use of CXR in TB screening.[120]

4.7 Key policy implications

Based on the findings of this study and the release of the WHO systematic TB screening guidelines 2021, the following policy recommendations should be considered.

4.7.1 Operational modelling is a useful tool to aid in policy-making and should be considered for adoption

The use of operational modelling in this study enabled projection of programmatic and cost implications for the various algorithms modelled. This virtual modelling was interactive and policymakers were able to appreciate the impact of the policy alternatives. Though there are tools like the screenTB that can help project impact, the model built in this study is context specific and offers flexibility of adjusting different parameters prospectively during implementation.

This model can be adjusted by level of facility, patient types, and sensitivities, specificities at different decision points. The outcomes projected will enable Kenya make initial decisions on what strategy to prioritise and what level of facility, prospectively, data can be adjusted in the model during implementation to improve on the accuracy. Further in Chapter 6, I recommend a framework on adoption of operational modelling as a policy engagement tool.

4.7.2 CXR is useful for TB triage and screening and should be adopted where feasible

From the study findings, the Kenya NTLD-Program should consider adopting CXR as a triage tool in OPD settings where there is availability of a digital CXR and GeneXpert on site. Currently, Kenya has the extended symptom screening followed by GeneXpert that has led to laboratory commodities and human resources being strained. This modelling projects cost effectiveness when digital CXR- CAD is used for triaging.

Though CXR TB screening is ideal to identify persons with subclinical TB disease, this study findings show that feasibility of this at facility level is still limited in LMICs. CXR TB screening should be prioritised for special populations i.e. children, household contacts, people living with HIV and community screening activities.

Prospective data on CXR for TB screening or triaging should be collected to help refine scale up and implementation. In addition, other parameters like patient costs, time to diagnosis, health system needs for roll out should be collected during the pilot implementation.

Over diagnosis of clinical TB is a risk when using CXR for screening and triaging therefore countries should have clear protocols on how to manage GeneXpert negative CXR suggestive of TB patients. Prospective data on this cohort of patients should be collected and analysed regularly.

4.7.3 CAD software is an important tool to aid in CXR TB screening and triaging

CAD software can ease the human resource requirement for CXR interpretation providing faster interpretation, less manpower need while delivering high sensitivity and specificity for abnormalities suggestive for TB.[44, 52, 55] The use of CXR-CAD either in screening or triaging reduced the number of GeneXpert tests required to diagnose a TB case in this model. In addition, the varying of thresholds shows the effect on sensitivity, specificity versus programmatic outcomes and cost. Adoption of CAD software offers countries faster interpretation with flexibility of resources they can engage. Countries however should be aware of the other non-TB abnormalities and plan for this as outlined in Chapter 3. The choice of CAD software to use should also consider ability to detect other non-TB conditions that may be more prevalent.

5 The tuberculosis policymaking pathway in Kenya

5.1 Introduction

This chapter seeks to advance the understanding of lung health policymaking analysis in a lower-middle-income country (LMIC), Kenya. A review of literature and the policy framework and theories used in health policy analysis are presented in this chapter.

Subsequently detailed is a qualitative study that was conducted to map out the lung health policymaking pathway, and identify the actors involved in the process. The understanding of the pathway was important to inform the development of a framework to guide the adoption of an operational modelling approach (as described in Chapter 6) in the Kenya TB policymaking process.

5.1.1 Aims and Objectives

The aim of the study was to understand the lung health policymaking pathway, from agenda setting through to policy formulation, policy implementation, monitoring and evaluation. Focus was given to the agenda setting and policy formulation stages.

The objectives were:

1) To map out the pathway of lung health policymaking in Kenya from agenda setting, through to policy formulation, policy implementation, monitoring and evaluation.
2) To identify the key actors in the policy process and understand their roles.

5.2 Literature review

Health policy analysis focuses on the policy cycle from how a problem is defined, to agenda setting, policy is formulation, implementation and evaluation.[121-123] Understanding the policy process as well as the interests and power of actors offers insights on how to actively engage with the process and how to influence it. [124-126] In LMICs, health policy analysis remains an important yet underdeveloped area.[127]

Policymaking is a complex and iterative process.[121, 128] Multiple actors with varied degrees of interests, values and power are involved in the policymaking process.[128] The critical influences of policymaking in LMICs are power, national context and global health actors.[128] LMICs' policymaking takes place in a different context to high income countries (HICs), characterised by weaker regulatory authorities, modest government financing and disproportionate external influence.[122] Political authority, financial resources and technical resources are power tools influencing policy.[129] Global health policies shape national health policy processes and outcomes in LMICs considerably. [128, 130, 131]

TB is an old disease that re-emerged as a global priority in the 1990s, in part due to the HIV pandemic which fuelled its increased incidence.[49, 132] In order to achieve the goal of ending the TB epidemic globally, optimization of the current and new tools in TB control is necessary to accelerate the decline of the TB incidence.[49] There have been new developments in TB screening and diagnostics, safer and shorter treatment regimens, as well as preventive therapies.[49] As LMICs consider adoption of the new tools into policy, multiple questions arise. What guides policymakers when drafting TB policies for introduction of new tools or algorithms? How do the global policies shape the national policies? What factors influence this adoption? What is the process from agenda setting to evaluation? Who are the actors involved in the process and what is their level of influence?

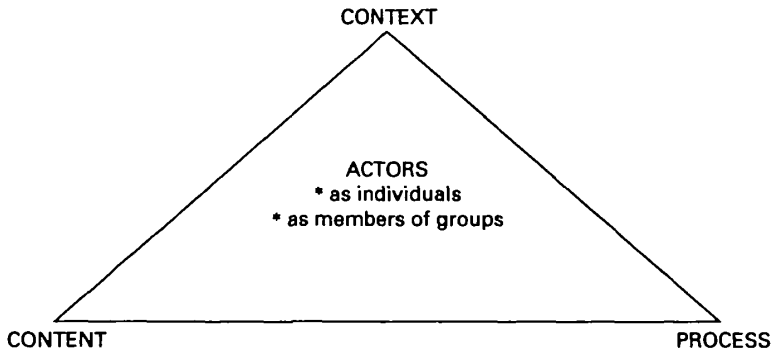
To answer these questions, we conducted a qualitative study to map out the TB policy pathway in Kenya and identify the actors involved.

5.2.1 Descriptive Policy frameworks

Descriptive frameworks identify key variables and their interactions in the policymaking process and are key to a reliable policy analysis.[122] This section presents two frameworks; the policy triangle and stages heuristic, which are commonly used in health policymaking.

The policy triangle, proposed by Walt and Gilson in 1994, is the most used framework in LMICs.[127, 133] This framework shifts from the traditional thinking of content only in policymaking to the interactions of context and actors who then shape policy processes and ultimately, content.[126] Though simplified as depicted in Figure 5.1 below, there is a complex interrelationship between all the dimensions. For a successful policymaking process, the actors are central in influencing the agenda to be set and the content of the policy. Their position, power, interests and values are key in the policy process.[126]

Figure 5.1: Policy triangle theoretical framework showing the interaction of context, content and policy process and the central role of actors.



The stages heuristic is the oldest and best known public policy framework introduced by Laswell in 1956.[121, 134] It depicts policymaking as a progressive cycle and was initially

presented in seven stages.[121] However, these have been reformulated over time to four to five stages; agenda setting, formulation, legitimation, implementation, and evaluation.[121, 135] Agenda setting is the first stage where the problem gains the attention of policymakers. The time period may differ with long periods in some instances and short in others, for example in the case of COVID-19, where the global disruption led to rapid development of policies.[136] The second stage is the formulation where policy options are generated and process of narrowing down to the preferred alternatives is carried out.[137] The policies are then executed during the implementation phase and evaluated in the final stage. The major criticism of the stages heuristic is that it depicts policymaking as a linear process with clear stage demarcations while in reality it is a more complex and iterative process.[134, 138]

This study employed a hybrid of the stages heuristic framework and policy triangle. The stages heuristic framework was used to describe the policy process and offer a sequential view of the policy process.[121, 134, 139] This enabled a simple way of exploring the stages in the policy process while acknowledging the iterative nature of policymaking. The four stages; agenda setting, formulation, implementation, and evaluation were used in the development of the key informant topic guides and in the analysis.[122, 138] For the policy triangle, though the focus of this study was not about the content, there was exploration of the actors and their roles at each stage of the policy process, as well as the context. This combined approach enabled deeper exploration of processes and actors.

5.2.2 Analytic policy frameworks/theories

There are theories of public policymaking which attempt to explain the policy process and enhance the understanding of causality.[122] The theories include multiple streams (Kingdon), rationality, incrementalism, punctuated-equilibrium, and top-down and bottom up implementation as described below.[122, 132, 140-144]

The multiple streams theory postulates that policymaking is random with three independent streams constantly flowing, namely problems, policies and politics streams.[140] The problems stream represents the broad problems and public issues facing the community that need to be addressed. The policy stream contains the available policy alternatives and solutions to the problems- these include research findings or new interventions that could solve the problems. The politics stream represents the government or leadership changes as well as the national priorities of the country. Once in a while the three streams overlap and this creates a window of opportunity when policy development or change occurs.[140]

The rationality theory presumes that policymakers define the problem, propose solutions and review them objectively to choose the best alternative for implementation. [132, 145] The assumption is that policymakers will inject resources into the most cost-effective interventions that will maximize the total reduction of disability-adjusted life years (DALYs).[132] The incrementalism theory, on the other hand, states that policymakers maintain status quo and only make small changes over time. [146] The punctuated-equilibrium theory suggests that policymaking is actually not rational or incremental and instead it is characterized by periods of stability when minimal or no new policy changes occur interrupted with instances of rapid changes.[132, 141] This theory has two components; policy image and policy venue. The policy image is how the problems and solutions are viewed. This may be constant and predominant over time, but could change as new information about the problems and solutions emerges. The policy venue relates to actors that make decisions regarding certain issues. When policy image and venue shift, then disruption occurs, leading to a period of change. [141, 142]

The top-down and bottom-up theory views implementation of policies from two perspectives. The first one, top-down, postulates that policies are designed by central actors with no input from the local actors/implementers.[143] Described as a prescriptive approach, this theory is criticized for not taking into consideration the local actors and context. It is argued that the approach can be useful where a workable solution already

exists and needs to be implemented. Public health programs, for example eradication of smallpox, followed a top-down approach similar to the COVID-19 pandemic response in some countries. [147-149] The second approach is bottom-up, where the local actors at service delivery level generate the policy issues to be brought to the policymakers.[143] Proponents for a bottom-up approach say the local service deliverers have expertise and a better understanding of the problems at implementation level, hence are therefore able to propose purposeful policies.[147] The criticism of a bottom-up approach is that flexibility and autonomy of the local actors may lead to performance which does not meet targets.

Combining the two approaches (top-down and bottom-up) has been suggested as a way to draw on the strengths of the two while minimizing the weaknesses. [144, 147] To understand implementation and which of the two approaches suit different scenarios, an ambiguity/conflict model was developed. [147] In public health situations like eradication of smallpox or elimination of TB, which are low conflict and low ambiguity, administrative implementation is applied. This is typically a top-down implementation with central actors developing the policies with clarity for those who implement them. [147] Bottom-up approaches are most useful in high ambiguity situations.

For this study, the findings helped identify the predominant theories as outlined in the results and discussion sections.

5.3 Reflexivity

As a qualitative researcher, I recognize that my position and views have a potential to directly or indirectly influence the research design, execution and interpretation of the research data findings.[1] I have reflected on this in the Reflexivity and positionality statement on Page 2 of this thesis.

5.4 Methods

5.4.1 Study design

This was a quantitative and qualitative, retrospective, and prospective analysis of lung health policy in Kenya employing the stages heuristic and the policy triangle framework.

5.4.2 Kenyan context

As covered in section1.2.3, health is a fully devolved function in Kenya with implementation and provision of health services being a responsibility of the county government. The national government - in the case of health- Ministry of Health (MOH) is responsible for national health policy formulation, health regulation, capacity building, technical assistance to counties and management of national referral health facilities.[36] The NTLD-program is responsible for TB and lung health functions at national level.[37]

5.4.3 Rationale for qualitative study

Qualitative methods are useful in the inquiry of processes and for understanding why things are the way they are from peoples' perspectives. [150] In this study, the use of qualitative methods enabled us to understand the complexities of the policy process, and which actors are involved, as well as their roles.

5.4.4 Data collection

The data collection was conducted between July 2019 and August 2020.

The methods used for both study objectives were:

a) A desk review of policies in lung health from January 2013- March 2020
b) Key informant interviews with actors who are involved in the policy process from agenda setting, through to formulation, implementation and evaluation

FGDs with TB/Lung technical working group (TWG) member representatives were planned. Focus group discussions (FGDs) with at least two technical working groups had

initially been planned It was intended that these FGDs would generate their collective views on the policy process, to gather information on their experiences of the process and triangulate the information from desk reviews and key informant interviews. However, due to COVID-19 pandemic restrictions, this was not possible. The validation meeting described on section 4.3.3.6 replaced the FGDs and helped triangulate interview data.

5.4.4.1 Desk review

This focused on all policies concerned with lung health developed between January 2013 and March 2020. The data sources were the National TB, Leprosy and Lung Disease webpage[151] and Ministry of Health website.[152] The desk reviews were conducted from July 2019 to October 2019. A data collection sheet (Appendix 8) was used to capture the details of the policies. The focus was on the title of the policy, document date and actors acknowledged in the development of the document. The desk review informed the mapping out of the actors to be interviewed and also helped identify the actors who are left out of the policy processes.

5.4.4.2 Study participants

The study participants were TB stakeholders at national and county levels. Purposive sampling was completed with a representation of different actors identified from the desk review and from the literature search. Representation was from the; public sector (national and county), private sector, civil society organisations, academia, professional societies, technical agencies, funders and research institutions (Table 5.1). During the interviews, snowballing was used to identify additional interview respondents. This ensured the obtainment of rich information with good representation from all those involved in the policy process.

To ensure country wide representation, representative counties from the six regional blocs were identified. The council of governors, which is a governing body made up of the 47 county governors, divided the counties into 6 regional blocs: 1) North Rift

Economic Bloc, 2) Frontier Counties Development Council, 3) Lake Region Economic Bloc 4) Mt. Kenya and Aberdare region 5) South eastern Kenya Economic Bloc 6) *Jumuiya ya Kaunti za Pwani (Coastal region)*. One county from each bloc was chosen for a key informant interview to provide their perspective of implementation and evaluation of policies.

5.4.4.3 Key informant interviews

The interviews were useful to explore the views and experiences of the key stakeholders in the policy process, and to provide useful insights as to how policies are prioritized and formulated. Additionally, the interviews explored the roles of individual actors in the process.

The interviews were conducted between October 2019 and August 2020. Invitation letters (Appendix 9) were emailed to the identified participants that included brief study information describing the study objectives and benefits (Appendix 10). Informed consent was sought once the participants reviewed the study information sheet (Appendix 10). Follow up phone calls were made to set the interview date, time and venue. For the interviewees in country, face-to-face interviews were prioritized except during the COVID-19 pandemic when online interviews were conducted on Zoom or Skype.

Each key informant was interviewed individually except in two counties where joint interviews were conducted at the participants' request. Semi-structured topic guides were developed and used for the interviews (Appendix 11). The researcher conducted all the interviews herself with the research assistant taking notes and audio recording the sessions with consent. All the interviews were conducted in English.

Table 5.1: Stakeholders listed for the interviews categorized into broad groupings

Category	Planned List of stakeholders to be interviewed
Public sector	Ministry of Health- Director of Medical services National TB, Leprosy and Lung Disease Program- Head of Program Paediatric, Core TB, GeneXpert, MDR TB TWGs- Chair/ appointed representative Laboratory regulators, Pharmacy and Poisons Board Kenya Medical Supplies Agency County government – TB, Leprosy and Lung coordinator, County Director of Health
Private sector	Clinical Director Private for profit hospital/Private not for profit
Civil Society	Local NGOs- AMREF Health Africa, Centre for Health Solutions Kenya International NGOs Advocacy groups- STOP TB partnership Kenya
Funders	Global Fund USAID
Technical agencies	WHO country office, WHO Global CDC
Academia	University of Nairobi
Research institutions	Kenya Medical Research Institute
Professional Societies	Kenya Medical Association Kenya Paediatric Association, Respiratory Society of Kenya

In total, 24 key informants were interviewed with representation as follows: 7 policymakers at national level, 6 county officials, 3 Civil society representatives, 3 technical partners/donors, 3 professional societies, 1 academia, and 1 research institution.

After the desk review and the key informant interviews, findings from the interviews were shared with select individuals who had been interviewed previously for validation. Additionally, during key informant interviews, we also asked about the policies

developed during the said period to triangulate further. This aided validation as well as data triangulation.

5.4.5 Data storage and management

All the data (recordings and transcripts) were stored in a two-step password protected laptop and external hard disk only accessible to the researcher. Additionally, data was backed up in a password-protected Microsoft OneDrive cloud solution.

5.4.6 Data analysis

After the data collection, the research assistant transcribed the recorded interviews verbatim and I reviewed all the transcripts. The transcripts were read multiple times to promote familiarization with the content. Preconceived categories from the heuristic conceptual framework following broad stages: Agenda setting, Policy formulation, implementation and evaluation were used. Themes and sub-themes emerging from the data were added on to this framework.

Qualitative content analysis was carried out and QSR Nvivo 12 Pro was used to code the data in themes. In addition to mapping out the policy stages, analysis of the findings focusing on both `what happened, how and why it happened' was completed as shown in the results section. The role of actors was also analysed with further identification of those who were left out and why.

5.4.7 Ethical issues

Ethical clearance from Kenya Medical Research Institute scientific ethics review unit (Non KEMRI Protocol no. 616) and Liverpool School of Tropical Medicine Research Ethics Committee (18-052) was obtained to carry out the study. Written informed consent was obtained from each participant as per the approved protocol. Participants were pseudo-anonymized to ensure anonymity. Names, institutions, or positions were not used in identifying quotes.

The interviews were audio recorded with participant consent, transcribed and analysed. To ensure confidentiality and security, all audio recordings and information collected during the study were stored on a secure password-protected electronic computer with access restricted to the researcher. The audio recordings and interview transcripts will be held securely for seven years as stipulated by Kenya data protection act, then disposed of. None of the stored material will contain any details that would breach confidentiality or anonymity of participants.

5.5 Results

5.5.1 Objective 1: To map out the pathway of lung health policymaking in Kenya from agenda setting, through to policy formulation, policy implementation, monitoring and evaluation

A total of 27 policies were developed in the period 2013-2020. Twelve (44%) were guidelines, seven (26%) were standard operating procedures, five (19%) were policy documents and three (11%) were national strategic plans (Appendix 12).

It was evident that the bulk of the 27 policies available were TB focused with only four (15%) having non-TB lung health content. Though included in the NTLD strategic plans, the burden of other non-TB lung diseases is unknown and hence not prioritized. The reasons offered by respondents for the lack of prioritization included:

Overlap of the mandate of NTLD and NCD programs

The respondents noted an overlap between the mandates of NTLD-program and division of non-communicable diseases (NCDs) in terms of lung health. However, the current NCD strategy captures Chronic Obstructive Pulmonary Disease (COPD) and lung cancer only;[153]

> *"I mean lack of clear, what is it called? Governance or leadership or what entity really runs the show. Like in Kenya, we had the national TB program, then we had*

the NCD department and who does what? There is a lot of slippage in those kinds of scenarios." ***KII 019***

Lack of expertise and policy champions

Lack of funding and expertise to implement other lung health activities was also cited as a barrier to their prioritization;

"So, two things for me, one is funding but the other thing is …, these are TB experts so there is no expertise within the unit to handle lung health." ***KII 007***

Additionally, one respondent felt that lung health lacks a policy champion. Though the TB program occasionally engages lung specialists, they have a clinical inclination and lack programmatic experience. In addition to expertise, a policy champion is required;

"The resource, the human resource part is so important, the staffing part of it. As I told you it is an area which, other than, yes you may have the skill but you may also have the passion. It is a job area that requires that passion. Most of the people who could push this agenda forward are, are clinical but they don't know the programmatic way of doing it. So, it needs two forces; a good clinical person and a good programmatic person, combined." **KII 021**

Lack of political will to invest in the management of lung health

Lung health service delivery other than TB is mostly done by the private sector and spearheaded by organizations like the Respiratory Society of Kenya (RESOK) formerly Kenya Association for Prevention of Tuberculosis and Lung Diseases (KAPTLD). It was noted that there has not been a high-level push nor funding by the ministry to manage other lung health conditions;

"It is not such a big agenda in the higher levels of the ministries so nobody is taken to account. So, really if there is high level push and look at what has happened to cancer, and eventually establishment of the national cancer control

program, it is because there was much higher-level push at the highest level of the MOH. So, once there is that push then it will happen. Then of course the MOH has to allocate resources because I don't think there is going to be a donor who is going to allocate resources for non-communicable diseases, you have to sort it out" **KII 019**

Other non-TB lung conditions are not a priority intervention area for global partners/donors

TB is a global agenda and is funded majorly by international donors. This is not the case for the other lung conditions. The quote below notes that since these conditions are not communicable, the donor funding streams are unlikely to cater for them and therefore the MOH must budget for this;

"…there is unlikely to be funding for non-infectious conditions, I don't know, the landscape the way it looks is the guys who fund are keeping the infections from reaching them so for other lung health […] I think there has to be considerable interest at the country level in terms of MOH and all that.." **KII 019**

There was a period when the practical approach to lung health (PAL) was in the WHO guideline and Kenya also incorporated this into the guideline. During this period, one respondent notes there was funding to invest in some spirometers, but the output was not well documented;

"yea, for me, I think we invested when we bought spirometers, peak flowmeters with Global Fund money as part of the grant, but then we did not put the same effort in terms of even recording and generating, tracking the.., generating of what we call the evidence." **KII 007**

Opportunities noted to bring focus on lung health matters

One respondent noted that the planned policy and roll out of CXR for TB screening presents an opportunity to bring lung health to the agenda;

> *"… with a chest x ray policy you will have to do lung health policy because, the people who did an x ray and don't have TB but had something that put them there, will need to be figured out."* **KII 003**

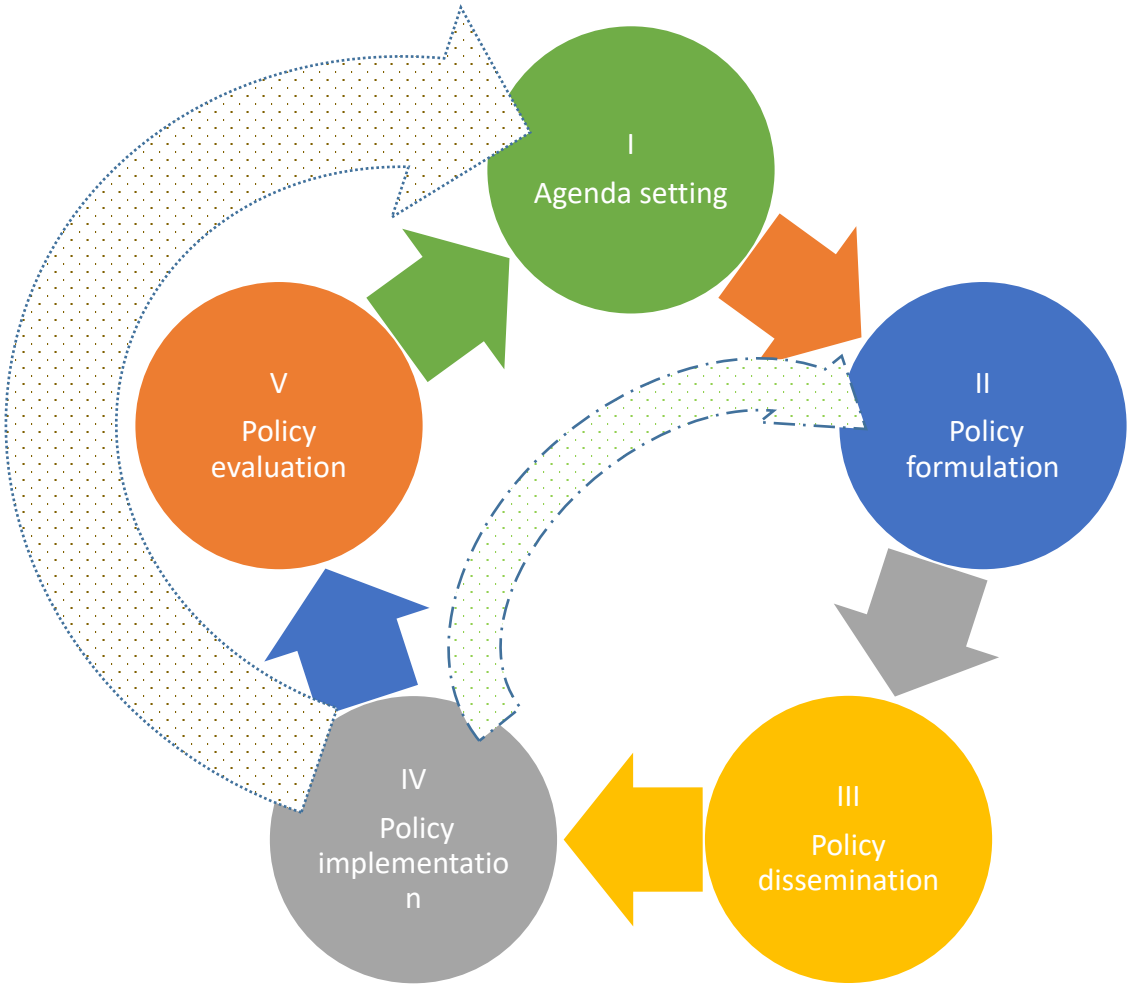
Another opportunity mentioned is the post-TB lung disease agenda and occupational health in general;

> *"There should be a deliberate effort to establish people with the necessary expertise to really look at lung health as bigger than tuberculosis because lung health goes beyond even just the health sector or the health itself. There are issues to do with pollution, work place related issues and there are a lot of these that is happening. If you go to the cement factories, there are a lot of chest screening, you know and lung functions, those ones are being done but is there a linkage between the[TB] program and those ones…."***KII 007**

5.5.1.1 Pathway of TB policymaking in Kenya

The initial protocol of the study was to review lung health policy in general, however, we shifted our focus to TB because of the paucity of policies on lung health. The findings of the study showed that in Kenya, the TB policymaking pathway is an iterative process with five stages (Figure 5.2). The reality was that steps in TB policymaking were complex and non-systematic. In some situations, implementation preceded agenda setting and policy formulation as was the case of introduction of GeneXpert technology as discussed in more detail in the role of funders in policymaking. In general, our finding was that the agenda setting, policy formulation, dissemination and evaluation occurs at national level while policy implementation was predominantly at county level.

Figure 5.2: TB policymaking cycle in Kenya



* *The broken arrows show alternate pathways during the cycle where some policy pathways start with implementation before policy formulation and agenda setting*

I. Agenda setting

What triggers development of TB policies in Kenya?

The initiator of the TB policy development is most often a government officer. From the findings, the main triggers for the development of TB policy in Kenya are evidence, global targets and availability of funding. In a few cases, legal and political factors have led to the development of policy. In addition, policies, for example strategic plans and guidelines, have a time period after which they need revision; five years for the strategic plans and two to three years for guidelines.

a) Evidence- Global policies especially WHO guidance

All the respondents raised global policies, especially WHO normative guidance as a major trigger in policy development or change. WHO guidelines are formulated through review of evidence from various sources, an example being the WHO guidance on use of CXR for TB screening as outlined in Chapter 1.[9, 154] Additionally, if WHO guidelines are used, funding for the policies would not be a challenge as captured by a quote below;

> *"So, you realize we are a member state of WHO and whenever there are new recommendations or guidelines from WHO, they are key influence to a country to decide on whether to adopt or not. Largely we have adopted a number of most of the recent WHO recommendations; chest x-ray, LTBI [Latent TB Infection], PMDT and others. So, yea WHO is quite an influence and of course we are largely funded by Global Fund, again for continued funding we have to be in line with what is best for the country and again with the WHO recommendations. It is good to get new things on board things that will be funded by our main donor who is Global Fund. Again at MOH level, when you are going to request for funding for anything that is new, the question will be, so where did this come from, where is the recommendation? So the WHO recommendation and guidelines go a long way in helping us push our agenda within the ministry for funding."* **KII 014**

Once the global guidelines are published, the policy transfer methods engaged include:

i. Learning

WHO and other international organizations invite the NTLD-program focal persons and partners to a meeting to gain more in-depth understanding of the guidance. The countries then align to take up normative guidance by looking at their local context pros and cons, availability of resources and the best way to roll this out. This process takes varied lengths of time and can sometimes last for years;

> *"I think it is basically […] a country level decision on what to take and what not to take but it is more about how to take it. So most of the countries will take it but it is how you adopt it to align with your context but the key issues usually the length of time that adaptation of global guidance take and I think very good example of IPT and the years it has taken…"* **KII 019**

ii. Enabling transfer of policies through funding

Donors or funding agencies for example the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and PEPFAR/USAID have a key role in agenda setting. If WHO releases a new guideline and there is a funder push to have this rolled out at country level, then this influences the agenda. An example in our study was the roll out of GeneXpert technology as captured in the quote below;

> *"Yea, they (funders) play [the] biggest role. I remember before we even thought of GeneXpert the plan then was to expand Line probe assay but a meeting in Geneva happened and Kenya was going to implement GeneXpert. GeneXpert [machines] were procured, we had five GeneXpert [machines] in the county without a policy."* **KII 003**

iii. Socialization

It was noted that global targets set the agenda leading to policy transfer as countries want to conform to global trends. An example that was given was the "*First WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era: A Multisectoral Response*".[155] The permanent secretary of health attended this and committed that Kenya would conform to the declarations. The subsequent year in 2018, there was a United Nations High Level Meeting on TB (UNHLM), the president was in attendance and committed to the targets set for high burden TB countries.[156] Though the targets are yet to be achieved, there were policies adopted like the latent TB Infection (LTBI) policy to fast track this;

> *"There have been meetings which have graduated to finally us saying let us develop these guidelines and again there is also something that is pushing this issue for LTBI; this UN meeting. Our president signed some commitments and we have targets as a country that we should put at least one million, almost one million people on LTBI by […] 2022."* **KII 001**

Sometimes global guidance has to be piloted before being adopted

When there is new global guidance, at the country level the NTLD-program and stakeholders decide whether to adopt it or not. In the case of the Isoniazid preventive therapy (IPT), though WHO offered global guidance and IPT proved beneficial in preventing TB in certain population groups, there were fears among health care workers and policymakers on toxicity and resistance. Due to the fears and lack of implementation experience, Kenya delayed development of policy as pilot implementation was conducted. The availability of implementation experience and renewed political will from the highest level of MOH as a result of change of leadership, acted as an important trigger to policy formulation in 2015. This was followed by rapid roll out of IPT country-wide between 2015 and 2016;

"So, the availability of the actual proof of concept for actual implementation. Two, also now the convergence of I think political will available from the highest level of MOH, and from both the TB and HIV program were an important trigger and that enabled bringing all the other stakeholders together. So, the political will […] became like the coalescing point for these other stakeholders and they were then brought on board. I think to me, those were the most important triggers to the policy now being made and implemented" **KII 019**

b) Evidence- Country level research

Most respondents noted that local research is likely to influence policy if it is wide scale, commissioned by or in conjunction with the government, for example, national surveys. Individual or other research according to the respondents was unlikely to influence policy on its own. This would be useful in the policy formulation when looking for evidence to support a given agenda;

"… we had the prevalence survey in 2014-2015, which was actually a game changer for the country because a number of new interventions came from the prevalence survey, the active case finding and the groups that we target for finding missing cases, […] it also informed how we use chest x-ray in our TB detection. In as much as we did not implement some of the recommendations that came from the study because of the implementation challenges, that was one key use of important information. Another local research that happened that informed some policy, guidelines or planning for us is the DRS that showed us prevalence of resistance among our TB patients." **KII 014**

Routine national data is also used by the TB program to guide policymaking as captured below;

"…Routine data and surveillance analysis, we are looking at trends, looking at performances, looking at experiences; programmatic experiences and practices so it informs policies and decisions." **KII 004**

Other research projects that are small scale often do not influence TB policy decisions as the NTLD-program is less likely to be aware of the projects, and the channel for feedback or dissemination is not well established;

> *"I think research within TB programs across the world is suffering quite a lot in my view. I don't see any of the country that I have been to that research really drives policy formulation in countries. That research eventually is picked up by WHO and eventually it lands in countries based on assimilation of those research projects done in the countries, but in the countries themselves I don't see a lot of people focusing on research results and using those local research results to formulate policy. There is a big gap in TB program in my view."* **KII 009**

The respondents agreed that having a platform for presentation of Lung/TB research, would ensure that findings from local studies are incorporated into the policy discussions as captured by two respondents below;

> *"You know most of the research bodies here have no forum with the TB program. Like I know the university they do a lot of research but rarely does that research reach the TB control program for discussion. The university doesn't communicate to the TB control program, the research they do, they do a lot of research but rarely do they communicate with them."* **KII 015**

> *"In our country for example which started research taskforce many years ago we have one or two meetings and then it died off because it didn't receive as much, maybe because of financing or whatever and everybody was too busy for that kind of thing, that research task force, I am not even sure if there is one existing, I don't think there is one existing right now."* **KII 009**

One respondent noted, however, that in programs dealing with neglected tropical diseases, e.g. filariasis, trachoma, local research does indeed inform policy directly as there is no universal standard of handling these diseases.

c) Other influences- CSO push, medical legal, political

Other factors, though rare, may influence agenda setting. During the interviews, respondents gave an example of the TB Isolation policy that was developed due to CSO pressure.[157] Members from the CSO community took the government to court over the section 27 of the Public Health Act, CAP 242 to ensure detention of non-adherent patients, if required, occurs at health facility and not in prisons. The court then barred prison-based detention and ordered the MOH to develop a policy to ensure patient-centred approach during the entire treatment course and articulate procedures and factors to be considered before enforcement of isolation. [157, 158]

Politics or personal interests, for example, were noted to have a role in purchase and use of Interferon Gamma Release Assay (IGRA) for latent TB testing while it was noted to be more expensive than doing a tuberculin skin test (TST).

> *"Politics does play a big, big role. As much as there is a lot of drive towards evidence-based policy, sometimes there are also certain interests that as a country and as people who work in the lung health space you cannot run away from and so you have to sort of balance both sides so yes. A good example is the use of IGRA, yea in diagnosis of latent TB infection. [….] Our country being a resource limited country and especially because evidence shows that IGRA is not superior to TST in terms of diagnosis of LTBI but also the fact that IGRA is so expensive, as an individual [I think] it is not the most prudent way to diagnose people with latent TB infection, especially in sub Saharan Africa where we know that 30% of us are already infected. I feel this is one area there has been a lot of push from sources that I am not sure about, to use IGRA in testing for latent TB infection and so I know already there is a process in place towards the use of you*

know Quantiferon and all that so that we have this as part of the guidelines. Personally, I don't feel very convinced that this is the way we should be moving but it's one of those cases where you can tell that this is, there is a lot of politics behind this." **KII 002**

Another respondent felt that so far, politics has not affected policymaking but has the potential to as per the quote below;

"however, there are people in power who can start to say no, I think you need to do this and that can be an issue so can that make it turn out to be a policy at the end of the business, if there are people in power who are pushing a particular agenda, sometimes that would affect but so far it has not happened but I know there are chances." ***KII 003***

II. Policy formulation

The respondents described the policy formulation stage in six steps as illustrated in Figure 5.3.

[Step 1] Policy champion identification and planning

Once the agenda is set and there is consensus within the NTLD-program and stakeholders that the topic is a priority, the head of program identifies a responsible officer to drive the policy formulation. Additionally, a team of technical experts are identified to be part of the policy formulation process – they are representative of various stakeholders including MOH program, funding agencies, learning institutions, non-governmental organizations, private sector, research institutions, and CSOs. Further description of the actors is captured in section 5.5.3. The technical experts include programmatic experts at the national level, specialists, for example if it is a paediatric policy, paediatricians are looped in. This team forms a committee which then prepares a presentation covering the justification and road map for the development of policy.

The focal person at NTLD-program then presents the plan and road map to the TB Inter Agency Coordination Committee (TB-ICC) who approves the process. The TB-ICC is a committee set up by the country as part of the GFATM funding mechanism to bring together all the major players in TB in Kenya quarterly to deliberate on TB control activities and funding.

[Step 2] Policy alternatives assessed and zero draft produced

The technical experts committee holds a data synthesis meeting to review the evidence to support the drafting of the policy. This meeting involves bringing stakeholders on board to discuss the evidence, the suggested policy and the implications it would have on programming. This is also the step where respondents noted modelling of scenarios would be best placed.

At this stage, the policy options are considered and various factors for example; cost, cost effectiveness, patient side effects in case of new regimen, operational or logistical requirements as well as overall impact, determine which alternative will be adopted. An example of the roll out of bedaquline- a new TB medication- that was offered to the country free of charge, considerations made in selecting the policy option are captured below;

> *"…now if you think about a drug like bedaquiline adoption takes forever, this time there was no cost, because at that time it was free. But with side effects on the patients, are you sure whether the patients can manage, the monitoring tests that are required, are you able to do that? And that is another question that was not taken care of, but you are also thinking about the patients, the side effects and the quality of care and the care expected. So there are a lot of ways to look at that cost."* ***KII 003***

In the process of weighing different policy options, patient advocacy for example by CSOs can also determine the choices. An example on the TB preventive therapy (TPT) roll out and the choice of regimen is quoted below;

> *"Now there are a lot of decisions, one; cost. Isoniazid is cheap, is cheap so we go for it yeah of course there are better regimens, there is 3HP, there is 1HP I think is being tried. [….] It is the cost of the commodity in our setting, not cost effectiveness, most of those drugs have been shown to have similar or less [effectiveness] with this one this regimen being an inferior to the other, meaning that they are more or less the same. But now the issue of getting the drug to the patient unfortunately we don't consider this. You know the cost that pertains to the patient accessing the services. So, if a patient has to come so many times to the facility those are things that are not accounted for in the cost and decision making but I think there is pressure from civil society organizations to push for indemnity and dosing and drugs that have been shown to be, to have less [Adverse Drug Reactions] ADRs."* **KII 005**

The participants noted that in two cases, modelling was used to help in making decisions on what policy option to adopt during this stage. Modelling was used during the writing of the current strategic plan as well as GeneXpert scale up on the number of equipment needed. More details of knowledge of modelling and where operational modelling may be applied in the policy process are captured in the discussion section.

The operational requirements for certain policies are also discussed at this stage. County representatives offer insight on the actual situation at facility level to enable the team to adopt workable policy options;

> *"So, the counties [involvement] is from the initial steps of the committee of experts' meetings. For example, when we recently had our diagnostic committee*

of experts, we were discussing about using TB LAM and we were discussing about ultra-cartridge […]. So, we had nearby counties like Nairobi and Kiambu who we sat with to learn if you want to roll out this, what is there on the ground and how can this be done?…, so we involve them in the planning process.." **KII 022**

At this stage, local evidence or operational research on the particular area is presented as part of the supporting evidence. The local evidence then guides the team on how to adopt the global policies in the country context as depicted in the TB lateral flow urine lipoaribomannan assay (LAM) example below;

"We gather our own in country evidence, we selected a few pilot counties and just do what we can, observe and come up with our own evidence that we now translate to policies, slightly different from what the WHO had recommended …that we use LAM to be specific LAM for PLHIV with CD4 count cells of a hundred or less. As a country we decided to use a cut off of two hundred" ***KII 021***

Though local research, especially small studies, did not seem to play a role in agenda setting, they were noted to be important during policy formulation stage. This quote captures more examples;

"When you are now writing the policy you have to figure out where do we have evidence? So the small [bits of] research is done here and there, you add. Like if you remember IPT we had a lot of small research done here and other researches done there. When we were looking at active case finding there was a lot of these things from research done in Kisumu. Use of bedaquiline we just started by working with the findings and then based on that we were able to expand till to adoption." **KII 003**

After all the considerations, drafting of the policy document is then done at this stage.

[Step 3] Technical consultations

The draft policy is presented to the TWG who give their feedback and input. It is then circulated by email to a team of experts who will review the policy document. The team of experts consist of professionals within the country who have high skills, knowledge and experience in TB and lung health. The writing team discusses and agrees on suitable members depending on the policy topic. Though some members overlap, some are chosen specifically, for example, if it is a paediatric document, the team would be predominantly made up of paediatricians engaged in TB and lung health. The team of experts are not remunerated hence offer their expertise on voluntary basis.

[Step 4] Review of the draft policy and consensus building

The draft policy is then presented to a wide group of stakeholders in a one- or two-day meeting. Discussions are held during this meeting and the way forward captured by the writing committee, who embark on revision of the policy document.

[Step 5] Stakeholder validation

A final stakeholders' meeting is convened and acts as a validation meeting to present the finished document. Feedback received from this meeting is then incorporated by the committee. Because stakeholders are involved through the process, this meeting serves as a concurrence by the stakeholders as most have been part of the process as noted by one of the respondents below;

> *"We take it back to the TWG, the TWG says okay this is what you have come up with, these are our inputs, and we endorse it for stakeholder review. During the stakeholder engagement, you share what the findings were or what the policy looks like. Then the stakeholder then either buys in or says no, yes, include this or remove this and that kind of thing […] but more often than not they don't have can I say major corrections if any .. Because they were engaged before they give their views."* ***KII 004***

[Step 6] Endorsement of the policy

The final policy document is then presented by NTLD-program at the TB-ICC who either endorse the policy or provide feedback for further refinement;

> *"After that it goes back to the TWG and they subsequently endorse it to go to the TB-ICC and the TB-ICC to adopt it and become policy. Once the ministry endorses the policy it is then cascaded downwards."* ***KII 004***

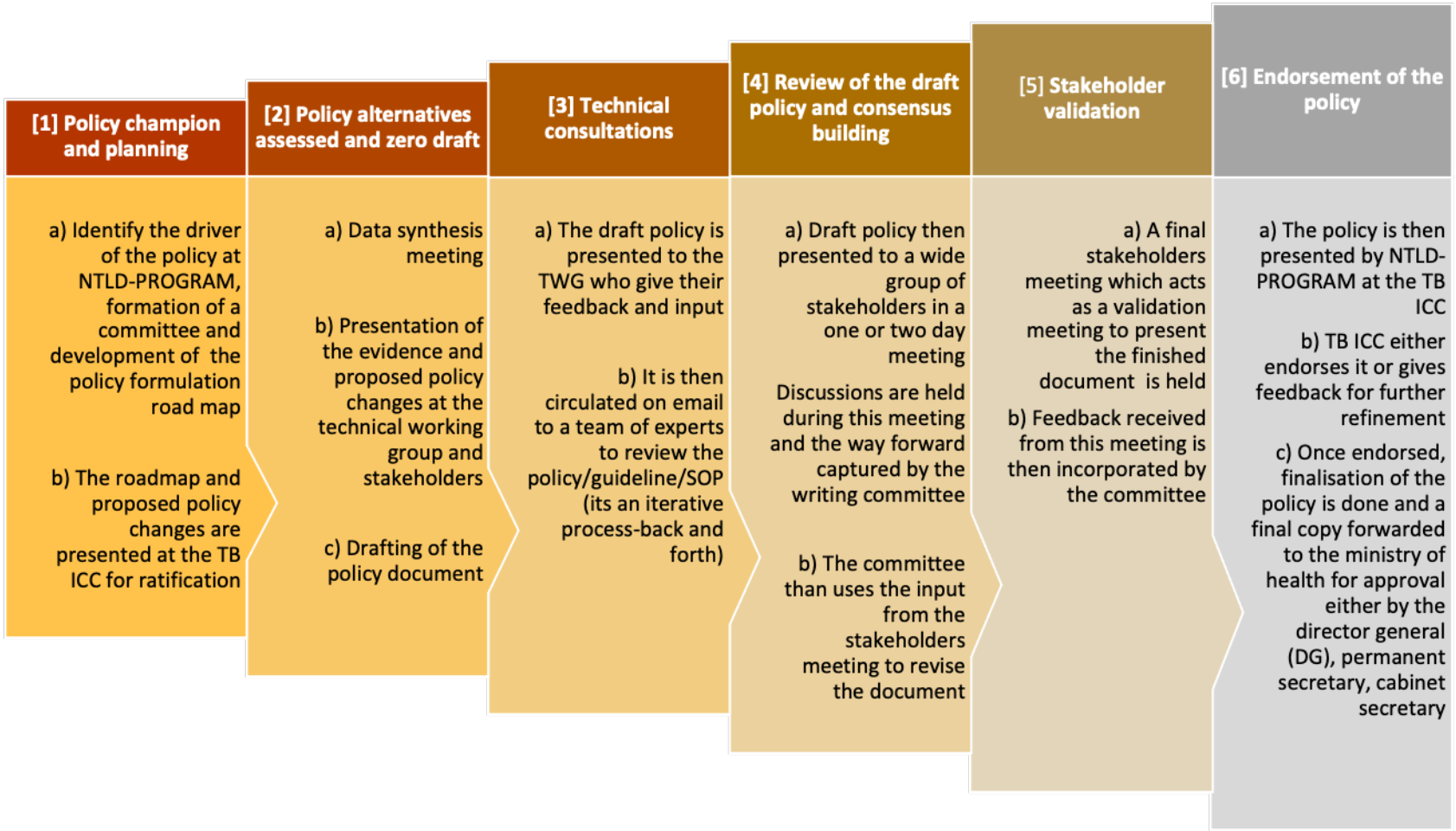
Once endorsed, finalization of the policy is done and a final copy forwarded to the MOH for approval either by the director general (DG), permanent secretary (PS) or cabinet secretary (CS). The office to give final approval is determined by the type of policy, if it is a technical report/ guideline the DG and head of program sign the document. If it is a policy direction involving wider range of stakeholders beyond health for example a national strategy, or financial re-allocation, this is endorsed by the PS and /or CS.

The policy formulation is an iterative process and on average takes 6 months. As respondents shared, some of the processes overlap and depending on the urgency, some processes take a shorter time. There is a common technical procedure manual developed that guides policy formulation and review within the MOH; [159]

> *"Yea so the steps ideally should be as that but sometimes you find that there are some steps that overlap and some come before the other depending on the particular policy that we are looking at."* ***KII 004***

Some of the challenges highlighted during the policy formulation process include questions on whether there is adequate evidence to support a certain policy, whether the country consider this a need/priority and feasibility studies on the economic impact, how much it will cost. There is also limited capacity to interpret the technical information into a language the policymakers can understand.

Figure 5.3 : The six stages of the TB policy formulation in Kenya



III. Policy dissemination

The role of dissemination is to ensure the policy reaches a wide audience of the relevant population and implementers. The mode of dissemination is dependent on the type of policy, the target audiences and the budget allocated for the dissemination activity. A launch is conducted for policies with wide impact or magnitude, with major financial implications or key changes to patient care, for example reduction in duration of DR treatment from 18 months to 9 months. This ensures reach of wide audiences- mainstream and social media coverage. The quote below aptly captures what determines the mode of dissemination;

> *"So, for launch there are particular things like a strategic plan needs a launch because you need the policymakers on board, you need the media, you need everybody to be part of and supportive of the new direction you have provided. The other thing is also, there are some things that bring in some hitch. If it is a MDR [Multi Drug Resistant] TB regimen and we are introducing a drug that is short term regimen for example, it is a big relief to everybody who has been taking this treatment for a long time. So, when they hear that now it is going to be shorter what are the chances that now you improve the acceptance? But now for dropping of CAT II [Category 2 treatment], the population you are targeting is small, it is not such a big, I don't think it was a big thing that needed a lot of media support. Then there is also what are you advocating for, if you look at the strategic plan, it draws in funding, there was the support for it, it brings in more partners on board to support the big drive […] So, there are a lot of things that determine, and of course the donor also, the donor who has funds for it [document to be launched] may also want to put in a big story. The other thing is also the ministry leadership, what do they want. If the ministry leadership wants to use that as an opportunity for something [else], they also will use a launch…"*
>
> **KII 003**

In cases where the policy is targeted, for example to health care workers, the DG, may write to the counties through the council of governors' office or through the county directors of health informing them about the policy. This ensures involvement of top county leadership and ownership. Another mode of dissemination cited was stepwise training and sensitization of the county leadership, followed by sub-county teams and finally to facility representatives. This was reported to help cascade the policy to the lowest level of the health system, in some cases to members of the community.

Some of the challenges highlighted were that dissemination was mostly seen as a onetime event while this should be continuous, and that the target audience were the same circle of people involved in the development process;

> *"You find that this is like a onetime thing, after it is done, who is meant to continue? Because dissemination is not one time, yea, so it is a bit left out, you find now the next time you are encountering this guideline implementation is maybe when you are doing a technical assistance."* **KII 001**

In addition, the target group for the dissemination must be right as a wrong target group then leads to implementation challenges;

> *"There are some that are done well but there are some where dissemination is done to the wrong audience so the people who are not hands on with that particular guideline. So, it is said to have been there but the target of the audience… is not the one doing implementation. Dissemination should actually reach the implementers and especially the care provider at the facilities and yes, we need the management to know but some of them they really don't have time to disseminate this to the people at the lower ground and they may not know the weight that it bears on the individual health care workers implementing this specific one on TB. So, we should try as much as possible to identify the right audience and specifically reaching the health care workers is key"* **KII 011**

IV. Policy Implementation

The national and county level roles overlap in the initial stages of policy implementation. The respondents highlighted that the national level ensures that the policies are developed and disseminated. The national team then works closely with the implementers, mostly county government and partners to translate the goals of the policies developed into action. In the process of dissemination the national level also supports the counties cascade sensitization and trainings to facility level as well as initial implementation. There is therefore overlap in the policy dissemination and implementation. This is important to ensure clear understanding of the policy and how to roll it out as captured by the respondent below;

> *" the how is an important, you see for a policy to be successfully implemented, the health care worker in a certain health centre must understand it the same way the program manager in Nairobi understands it and ensure there is no policy implementation gap. So, how you actually disseminate but also how you support the initial implementation becomes extremely important. […] The practical part of the how being clearly and explicitly mentioned and then also having how the health care workers will be, some form of hand holding in the initial phases to ensure that they are supported to fully implement."* **KII 019**

The national team continues supporting implementation through funding, technical advice and building capacity of county health care workers.

Funders have a key role in policy implementation

At county level, there are non-state actors mostly US government funded commonly referred to as implementing partners who work with the health management teams to help in successful roll out of the policies. In addition, GFATM is a key funder to the national level to ensure implementation of TB activities with targets attached to the funding;

"If the Global Fund, the major funder of TB programs in the world says we want to push LTBI, and countries get advice to say this year we want to LTBI well, you put in your application in the next grant, we would want to see you allocate sufficient grant on LTBI. Now because countries will require to report to the Global Fund on what they have done on their LTBI they will struggle to make it happen. So, it is all those things. Funders in my view are key, the program is key, the stakeholders are key. If funders say we want to see this reported to us then we all create the mechanisms to report on it and we do it […] because the funder will want to see this happen. It is a multi-duplicity way, it is a little complicated but at the end of the day it is whether people believe in that policy recommendation and whether there is money for it and whether the country is expected to report on that, not necessarily by WHO. Reporting by WHO is not the most important thing." **KII 009**

Implementation can either be a pilot or full roll out dependent on the type of policy and availability of resources

Implementation of policies can either be full roll out or pilot. According to the respondents, the desire of NTLD-program is always full roll out, however, certain factors determine the implementation mode for example availability of strong evidence, adequacy of resources etc. Full roll out occurs where the policy is an internationally recognized standard, if it offers superior patient care for example in the case of a better regimen with less side effects, or where it would be a human rights concern to offer a different model of care. Pilots are conducted if the NTLD-program requires more evidence of the intervention, to assess the yield, figure out the operationalization and if resources are inadequate;

"if you don't think you have adequate evidence and whether that can actually apply in a country it would be nicer to have a pilot, that way you know what are

the challenges you will experience, what is the yield you are going to get, assuming it is a test, what are the unforeseen gaps that you may need to fill. So those things make, like TB LAM for example, the number of people who have, who needed to get that test were very few, chances that you get them at disposal are very low, so can try in a bigger facility and see what is the number of patients that we are going to get, how many of them will not get DST, how many of them will get DST, how many of them truly have TB, […] you know before we scale up to evidence and do we really need to scale it up.[…] you don't want to start something and then after that say, no it has completely failed yet everybody has been trained." **KII 003**

The predominant implementation framework was top-down approach and this could have had an effect on implementation of policies

The participants at county and facility level felt that even though there was involvement of implementers at policymaking, most policies were top-down. They suggested a bottom-up approach to ensure greater involvement of facility level staff in development of guidelines. In addition, they noted that rapid change of guidelines would bring confusion for implementers;

" most of the decisions they are usually have been made from top down, the best approach that we need to have is a down top approach because the risk of the other one top down is once the policies are now disseminated to the facility level where we are doing the implementation a lot of revisions have to be made. And that for instance has affected most of the guidelines on HIV where we have a lot of sensitization very rapid before staffs can get acquainted with the current guidelines another one has come within three months or within six months. So you find there is a lot of confusion among the staff on which guidelines will be most appropriate to stick to. So, when you do a down top approach then at least you are able to pick what are the challenges that will inform decision making,

what suggestions do these people at the site level have so that that can help in the formulation of a finer policy." **KII 011**

An example of the GeneXpert algorithm development was quoted as a best practice where a bottom-up approach was used;

"… Looking at the GeneXpert algorithm [at country level] is a down up and […] they are only up grading as new things come and there is minimal confusion. So, that tells you that when it comes from down, we will always be upgrading as things change and confusion will be lesser." **KII 011**

Other reasons for non-optimal policy implementation

Lack of adequate sensitisation of the facility staff who carry out implementation activities as well as inadequate resources to support the policies, are the challenges leading to non-optimal implementation;

".. Sometimes we rush on dissemination of policy when we have not actually prepared the ground, the site level from top to down. So, occasionally you may find staff are interacting with policies that they themselves don't understand but they are required to implement. Then again number two, I would say that sometimes we don't consider the resources that are required during the implementation of the policy.[…] At the time of implementation you may drive a lot of demands in terms of resources; human resource, capital that are required plus all those other tools that may lead to collapse. I would say that most of the times the county team have tried to involve the facility staff though not fully because you may find just one or two involved in terms of dissemination of the policies but the other staff are not really engaged..." **KII 012**

In some cases, however, implementation did not go as planned, due to lack of supporting structures and assigned budget, as in the case of the TB isolation policy as

discussed above on page 154, and lack of advocacy, for example for the social protection policy.

V. Policy evaluation

Monitoring and evaluation is carried out through routine supervision via technical assistance (TA), TB program reviews, routine indicator monitoring and self-reporting of counties during quarterly review meetings. Most respondents noted that evaluation was weak, as evaluation activities were not always well articulated at policy formulation. Only guidelines that directly affect treatment indicators are measured routinely, leaving out other aspects for example how effective the policy is, how it is implemented, etc;

> *"One of the things that M&E, and I think we have not done very well is to monitor implementation of policy and the impact of course. Impacts are normally done through these reviews that we do in midterm reviews for evaluation and the rest but one of the other things that should happen is one, effectiveness of this policy in terms of dissemination, who has been reached, who is there, are they available where they are supposed to be." KII 016*

To improve policy evaluation, suggestions put forth included: inclusion of policy monitoring during the TA visits both by national and county teams, having a monitoring and evaluation plan as part of the developed policy and organizing regular reviews of policies;

> *"To facilitate evaluation we should come up, develop policies and their policy implementation package like if I go to a site this is what I expect to see in the short-term outputs of this. So that we gear our tools like for example M & E tools, the supervisory tools they are based on evaluating specific aspects of the policy that is on routine basis monitoring. We monitor policies implementation; we have something structured in such a way that we are able to collect data in a way that you can analyse."* **KII 005**

Though feedback on matters of policy can be provided from the counties and other implementers to the national level, there was no standardized way to do this. As one of the county respondent noted;

> *"I would say yes, to me yes, I don't know how the other counties do but the good thing with the national TB program at least they have focal people for different programmatic areas, for example like for ACF we know the focal person, so, for anything that I go there and find gaps, I do an email to the focal person or I make a call. I make a call and I follow up with an email so that the person is able to address that, for me that one has been working because the follow up and the feedback back to us usually comes back to us, so that is what we do"* **KII 010**

5.5.2 Objective 2: Mapping out the key actors and their roles in the policy cycle

The main actors in the development of TB policies from the desk review were: Ministry of Health (NTLD, NASCOP, counties) program, funding agencies (Centre for Disease Control, USAID, JICA), learning institutions (University of Nairobi, Moi Teaching and Referral Hospital), non-governmental organizations (Centre for Health Solutions-Kenya, ICAP, Amref Health Africa, Program for appropriate technology in health), private sector (The Kenya Association for the Prevention of Tuberculosis and Lung Diseases (KAPTLD)), research institution (KEMRI), civil society organizations (KELIN, STOP TB Partnership) (Figure 5.4).

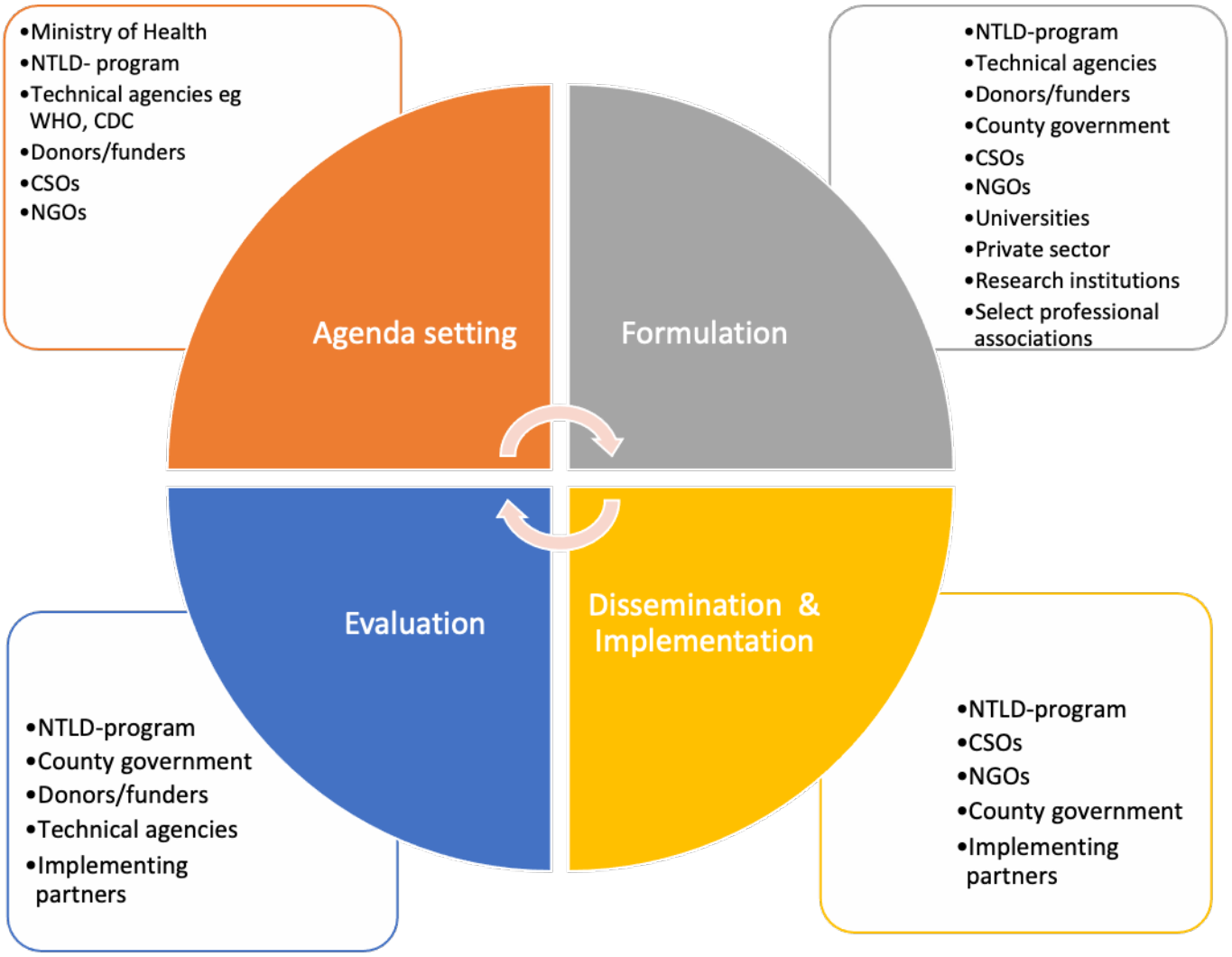
Figure 5.4: Word cloud from the desk review showing the stakeholders/actors involved in development of TB policies in Kenya

From the key informant interviews, the respondents felt that the process of TB policy formulation in Kenya was fairly advanced and inclusive of most stakeholders including the patient community, research institutions, and universities, among others;

> *"I think in this country we are doing pretty well, […] I see patients and communities involved, I see professional societies, I see academic institutions, I see donors there, I see implementing partners of various kinds. So, I think this country has a good mechanism for engaging people in policy formulation. There are very good mechanisms."* **KII 009**

Figure 5.5 shows at what stage of the policymaking the actors are involved.

Figure 5.5: Actors in the TB policymaking pathway and the stage at which they are involved.



5.5.2.1 What specific roles do the actors play?

This section outlines the actors' specific roles and highlights those noted to be missing from the policy process. Three classifications are used depending on the level of engagement in the entire process; fully engaged- those involved in all the steps from agenda setting to evaluation, partial engagement- those involved in one or two of the processes, and those who are completely left out of the process.

a) The actors that are fully engaged

Ministry of Health (NTLD-Program)

The TB program is instrumental in the full policy cycle from the agenda setting process as the initiator of the policy to evaluation stage. The head of the TB program either initiates the idea or receives a proposal to be discussed and steers this. The trigger of the agenda as covered in the agenda setting theme is varied, with WHO guidance being the predominant factor. Thereafter, the TB program calls for a technical working group to propose the idea. Subsequently a technical team is put together to start the policy formulation. The role of the head of TB program is well captured in the quote below;

> *"Always look at NTP as the fulcrum or the focal, the focus around which everything in TB will rotate, the partners, even the mainstream ministries still depends on, the NTP has to be the one to push an agenda for the senior guys at the ministry to take it up, for the partners to take it up, for the civil society to take it up. [….] the ability for the NTP to provide what we call technical and programmatic steer is extremely important in policy formulation especially in circumstances where you need to do policies, where you need to do programmatic technical, like you need some program change of course. You have survey results that show you for example you are not doing so well so you need to change course and with policies to support that change of course and new interventions, the NTP has to take leadership and then to rally all this together.."*
>
> **KII 019**

Various units within NTLD-program are involved in the policy process depending on the program area. However, the policy and planning, monitoring and evaluation (M&E) and health promotion sections play a supportive role in the entire policy processes. The policy and planning team help in the planning and budgeting, the M&E team with generating baseline data and target setting while the health promotion section which has the communications and advocacy team support in the packaging, editing and the final policy document layout.

World Health Organization

The WHO, as a body to set normative guidance, has a key role in generating the country TB agenda. New guidelines trigger discussions with countries regarding which guidance should be adopted, and how, as presented in the agenda setting section on page 149;

> *"Most of the time we have aligned country guidelines to WHO guidelines with just some tweaking of some of the recommendations. […].The government trusts WHO, so something that is coming from WHO is more likely to be adopted by government compared to other agencies like MSF […]. We people just look at WHO because of being a trusted source of policy direction. So, if WHO recommends that we are changing this indicator, we are changing this practice then countries are more like to take that up."* **KII 005**

At country level, WHO also has technical officers whose role includes starting the conversations and supporting countries in adoption of the policies. The WHO officers are important stakeholders in the entire policy cycle offering technical guidance;

> *"The first thing is to present to the country the intervention and be able to convince them that it is doable, the benefits, the merits and demerits and where it has been done. Overall, you must be able to demonstrate that it doesn't harm the population. You give them the way it has been done and if it is something*

which has not been done, you can do pilot in a country but of course with ethical considerations which must be passed by that host country." **KII 015**

Donors/ Funders

Donors play a critical role in the entire policy pathway and their role is outlined in section 5.5.2 above. The donors are involved (particularly GFATM, USAID and CDC) to varying extents. Some donors are involved in the agenda setting, policy formulation through to implementation for example CDC and USAID;

"We also have partners who are considered key partners. Basically I think USAID has been central to most of the policy formulation in terms of supporting that [the process], sitting on the table and guiding the direction. CDC and other players including USAID implementing partners are also involved in the process. […] There has been a move to be able to rally or support that was more like, I would call it up hazard not very structured, but now we are able to get all partners to push the TB agenda in a specific way. I think I have noticed the fact that we have been able to leverage TB/HIV money to support TB work case finding and retention." **KII 005**

GFATM, a big donor in TB, influences agenda setting by insisting on guidelines and practices in line with normative guidance. It is not involved in country level policy formulation but influences implementation through funding particular interventions. Donors facilitate implementation of the policies through providing resources and agreeing on performance framework targets with the country. Funders are therefore involved in monitoring the targets and, by extension, implementation of policy. If the country does not meet its performance framework targets, GFATM is then involved in discussions at the country level to identify the issues, and supports the country to be able to recalibrate and design policies that are addressing the gap. The quote below captures this role;

"For example implementation is going on and you think the results are not [good].., the country signed performance frameworks with Global Fund saying you will get these number of cases, you will put these number of people on TPT, you will get these amount of treatment success rate and then this coverage of services. Imagine, in circumstances when in a country the numbers that are in the performance framework are not being achieved, the coverage is not getting there, so Global Fund staff have to be involved in discussion at the country level and identify what are the problems. So they get engaged sometimes and […] and trigger a change of course. Though Global Fund will not be involved in policy formulation, they support the country to recalibrate, to design policies that are addressing their real need. So, they would be involved in all that, in supporting that process but leaving it to be country driven, yea." **KII 019**

County government

There is a challenge in involving all the 47 counties in formulation stage, so the NTLD-program identifies select county representatives during this process. However, views from the county are sought during formulation stage through meetings and email communication. The county governments are key actors in the dissemination and implementation of the policies. During the dissemination process, the NTLD-program targets the senior county leadership, County Executive Committee members of health (CEC), County Directors of Health (CDH), Chief Officers (CO) and County TB coordinators to ensure there is buy-in, county ownership, political goodwill and advocacy. Counties fully involved in the policy development process have better adoption of policies as noted by the respondent as below;

"yes, there are counties that are involved in a number of policies and those ones really benefit […], the counties that are fully involved in policies from inception to implementation, the way they pick up that intervention is different from a person who had no idea what is going on, because this other person who was totally

involved comes from a point of full information, full knowledge, full understanding of this intervention and is also excited to see it work in their county. Vis a vis this other person who feels this is another intervention that has been brought in my county, I have no idea how am going to do it but I am just going to follow the steps that they have been told, so first is to change that person's perception before that person can [implement]." **KII 010**

Implementation is spearheaded by the county though funding in most cases is provided at national level. The counties further assimilate the policies into their county level documents, but the way this is carried out varies by county. During evaluation of the performance indicators, counties are involved in the supervision and technical review missions. However as earlier reported, there are no standardized feedback mechanisms to give feedback on the policies. For some policies, quarterly or biannual review meetings offer an opportunity for feedback.

Civil Society Organizations and patient community groups

CSOs act on behalf of the patients and bring in patient experience during the policy cycle. They ensure human rights, gender and national or global provisions of patient centred care and right to health are factored in the developed policies. CSOs also help in dissemination of policies to the communities. Some of the CSOs are also engaged as representatives in the civil society task force at global level. The quote below captures what the CSO role in the policy process is;

"First of all is to look at some of the provisions that affect the patients, like the human right, issues of gender, to ensure that they have been taken into consideration. They also look at the national constitution; what does it say about provision of health? Is this policy coming to contribute to this broader agenda for the country? Of late, we have also been looking at the four agenda, so is this policy in any way contributing to the health target in the UHC and the president's commitment's, yes. We also look [at] things of pricing. If this is a policy that is

introducing a new drug, is it affordable to the country, is it affordable to the patient? If it is not affordable to the country then definitely, we do a lot of advocacy for the reduction of the prices, basically affordability and accessibility and if it is at the country level, if the cost is going to the patient then we would either advocate for the reduction or that the government takes up the cost. So, basically our issue is centred on the human person, ensuring that he is very comfortable in accessing TB services." **KII 013**

Non-Governmental organizations and Implementing partners

The NGOs and implementing partners support the program both at national and county levels. They are involved in evidence synthesis during the policy formulation process and support the policy development, implementation, monitoring, evaluation and feedback. They do this by offering technical input as well as funding some of the meetings;

"synthesizing evidence, policy formulation and then three policy implementation but then lastly it is monitoring in a sense to look and see, okay we said ACF must be you know conducted in these many counties, what are the results looking like? Why is it that some counties are doing very well while others are not? So that monitoring, evaluation and…, you know supporting that feedback mechanism of implementation and getting results." **KII 002**

b) Actors partially engaged:

Though the NTLD-program is fairly inclusive in the policy process, some actors felt they were not optimally involved and they highlighted opportunities for further engagement.

Research organisations including academic institutions

Research institutions are involved in the entire policy pathway. In the agenda setting, for example the Kenya prevalence survey, the study coordinator was from a research institution –KEMRI. The interviews highlighted that research institutions are involved in

the clinical aspects of guideline formulation, monitoring and evaluation, and operational research when required;

> *"we also have people from the research institution [….] in addition to the clinical aspect of it, element of monitoring and operational research which can go along with the work, elements of, I think I have mentioned public health"* **KII 001**

The NTLD-program has involved academic institutions from early on at the policy formulation stage and sometimes at the dissemination forum;

> *"I must say universities have been engaged in the past especially in policy development and even within the TB program I think when they are calling you, they are not calling you just because of your lung health expertise but as university faculty. Because of course one of the goals in a university is to you know create new knowledge, apart from just you know using people's knowledge that has been generated, one of the goals of universities for example the University of Nairobi whose vision has been you know a world class university and part of that is also being world class in terms of generating new knowledge"* **KII 023**

The academia, though, felt their early inclusion at the agenda setting stage would be beneficial for the research they conduct to contribute to the evidence base as well as address the gaps noted in the policy process. In addition, they noted an opportunity to be involved in the policy dissemination process. As noted by one of the respondents, though some dissemination occurs by the involvement of faculty in the policy process, there was no structured way to sensitize the entire team to ensure all students and faculty are reached. Other academic institutions such as the Kenya Medical Training Centre (KMTC), which trains the largest number of nurses and clinical officers, were missing from the list of engaged stakeholders.

Professional associations

NTLD-program engages professional associations in the policy formulation stage to varying degrees. The respiratory society of Kenya (RESOK), for example, is involved to a larger extent and is part of the writing team until the signing of the policy. Other professional associations, for example National Nurses Association of Kenya (NNAK) and Kenya Medical Association (KMA), felt they are only involved at advanced stages during the stakeholders meeting, often at the zero draft presentation or the final validation meeting. And even in cases where they are involved, it is an individual person invited and not an invitation to the association providing opportunity nominate the person to represent them. In this way, some professional associations feel they have no ownership of the policy and thus there are missed opportunities to offer their technical input during formulation as well as engage their members during dissemination and implementation.

There is a missed opportunity for involving the associations and below is an excerpt of their suggestion on how to be engaged throughout the cycle;

> *"Writing officially to the association and giving them the, you know the background information, this is being done and we are therefore we are inviting you as a key stakeholder to be part of, to be part of the experts reviewing in this document. So that within the association we will identify the most suitable person who would best represent them in that committee or in that taskforce who will then also be able to give them feedback because probably most of these documents, you know a policy is more like a law so maybe it needs to be ratified and even maybe presented as a bill in parliament, you see that's where now you start feeling like you need your representation and you need the position that you gave at that level."* **KII 022**

Professional associations have a platform with many subscribed members and offer opportunity for dissemination of policies. During the interview, one of the members

gave an example of how associations during the COVID-19 pandemic have intensely engaged in training of their members through webinars with country wide reach.

Media

The mainstream media were noted as a resource to highlight emerging issues with a role in public dissemination of policy and advocacy. They are mostly engaged during the launch of documents, but a respondent noted there was poor follow up by the NTLD-program with the media after the launch event. For the NTLD-program though, there is a limitation on direct media engagement as part of government protocol. The government ensures there is one source of information, and any other person would need permission to speak on behalf of the ministry;

> *"the media I think one of the issue is the communication I don't know if to say stakeholders but members of…, they ensure that there is publicity about the issues in changing policy, like you would find in newsletter on wherever talking about change, on meeting to change these policies that makes the, creates demand in terms of end users of those policies to be able to be prepare the people, yeah"* **KII 005**

Facility health workers-public and private

Health care workers generally felt they were usually only engaged when the policy had already been formulated and disseminated. The majority of them were involved at the implementation stage only. They felt that earlier involvement would add value and bring about ownership of the process. In addition, they are able to offer insights on what can work at the facility level.

Regulators/boards- Pharmacy Poisons Board is involved where new medications are to be introduced in a policy for example the drug resistant TB treatment with new molecules, and also during post market surveillance. Kenya Medical Laboratory

Technicians and Technologists Board is also involved occasionally when there is a new diagnostic tool or equipment requiring introduction and licensing.

Attorney general – This office was involved during the TB isolation policy drafting as this was a government legal matter.

c) Which actors are left out?

Private sector- Organizations that represent the private sector health facilities in Kenya, for example the Kenya Healthcare Federation and the Kenya Association of Private Hospitals, were not part of the actors involved in the policy process.

The pharmaceutical industry and manufactures are, in general, left out. If they attended the policy meetings, it was reported that they were only allowed to be in attendance for brief periods of time, to make specific presentations and leave- this was to ensure there was no conflict of interest.

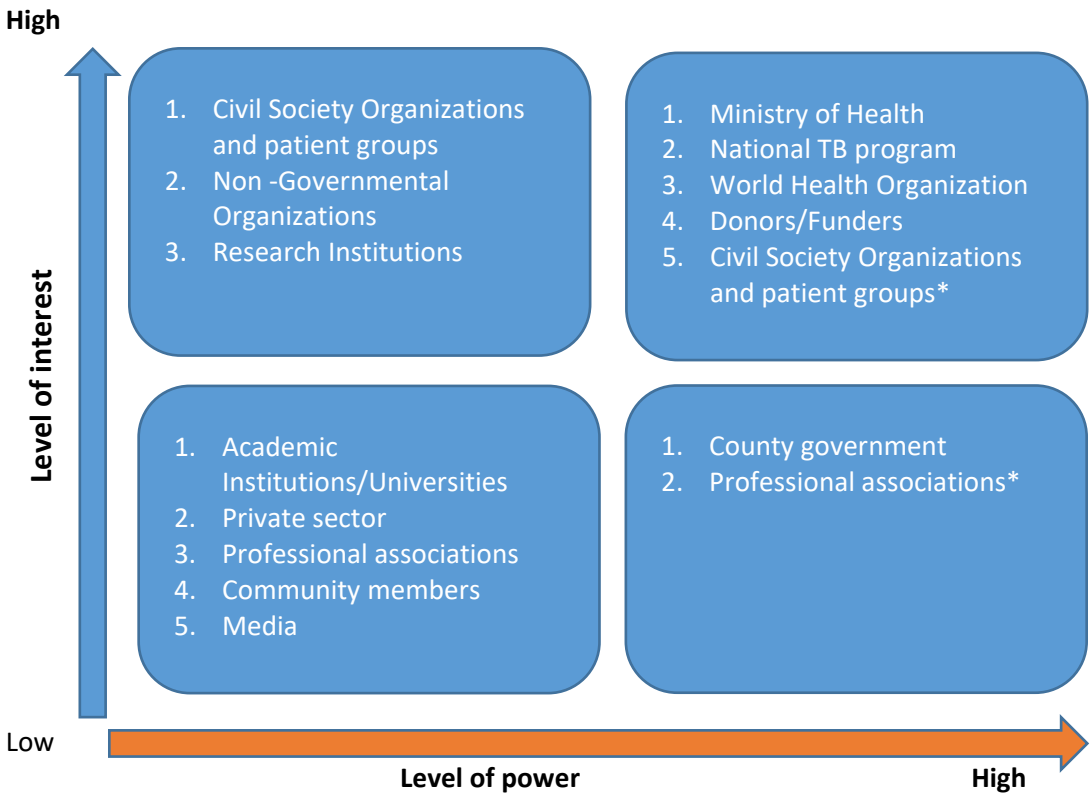
Community members who have not previously tested positive for TB. One of the key informants felt that it would be beneficial to involve the general public to get their views on TB;

> *"Because we assume, we are making this for the infected people, remember this will help me if I get sick but I should be involved even when I am not sick, just in case but you know what we do, we get somebody who is already in the frame of, mind of TB, okay. But if you brought just random key policymakers at the community level, bring my mother who has never had TB, okay. Tell her this is TB, this is how TB is transmitted, this is stigma, and if you ever had TB, what do you think should done? I feel like we confine ourselves to this TB community, right."* ***KII 013***

5.5.2.2 Power matrix of the actors in TB policymaking in Kenya

Following the analysis of the actors, their roles and influence on policymaking process, I placed actors in the Mendelow`s power matrix[160] to show their interest and power. While the matrix shows actors listed individually, often it is their interactions that lead to the policy changes and investments. For example, WHO produces global policies, however their influence to getting these policies adopted at national level is determined by the funders/donors interest. Similarly, the NTLD program is a central actor but requires evidence and funding for policies to be actualized. Actors like CSOs power varies with the issue at hand, for example, they were powerful in ensuring development of the TB isolation policy, a human rights based issue, however implementation of this has not been successful due to funding gaps. Finally, actors in the matrix are not static and often the type of issue determines the level of interest and power.

Figure 5.6: Power interest matrix of TB policymaking in Kenya



5.6 Discussion

This analysis for policy has the potential to inform future TB policymaking in LMICs. The study focused on understanding the processes and actors with less emphasis on the content of the policies as prescribed by prior literature.[126] Using the heuristic framework in combination with aspects of policy triangle framework, the study established that the TB policymaking process in Kenya is complex, iterative and with multiplicity of players. Though five stages (agenda setting, policy formulation, dissemination, implementation and evaluation), were used to describe the process, the actual process was not as linear, finding similar to previous studies.[161] The understanding of the pathway sets a stage for prospective policy engagement strategies, for example, on adoption of operational modelling as Kenya considers CXR use for TB screening.[138] There is an opportunity for modelling of policy options to help with decision making in the policy formulation stage. At this stage, six steps were identified, similar to seven distinct activities described by Berlan et al in the policy formulation, and adoption processes that they referred to as "the bit in the middle".[137] The evaluation stage, was found to be the weakest link in this study comparable to other studies.[162] Clear and consistent objectives with an evaluation plan for policies are desirable and should be integrated in future policy.[128, 163] Operational modelling could improve the monitoring of the policy at the evaluation stage by generating program indicators during the policy formulation phase.

Actors, power and politics in policymaking

TB policymaking in Kenya has multiple actors with NTLD-program as the central player. This finding is similar to a review of Integrated Management of Childhood Illness policy in LMICs where MOH played a key leadership role,[131] and Buse et al's description on the array of actors involved in the policymaking process, with the government's role being central as health was considered a public good.[164] Global policies from WHO and international funders greatly influenced the TB policy process, similar to other global health studies.[131, 165, 166]

Similar to other studies we noted that power was central to the policymaking process.[126, 167] The NTLD-program as the central player had structural power, as exemplified in the case of IGRA implementation. Technical agencies and donors had relational and dispositional power as described in the conceptual framework by Art and Tatenhove.[168] The dominance by the technical agencies like WHO are through their expertise, authority and legitimacy as the normative guidance body. Donors/funders power was through provision of resources not limited to financial, expertise and knowledge. Donors were key actors in all the policymaking stages and it was clear that their influence was great as shown in cases where they drove the agenda or provided resources for implementation even when policies were not yet in place. During the policymaking process, actors should be aware of this influence to ensure proper management of the global-national relations and policy transfer.[131] Though funding is an enabler of policy transfer, caution should be exercised to ensure there is no coercion which would lead to lack of ownership or commitment.[166] The interplay of actors in the power matrix is not static and advocacy would be important to ensure diversity in the actors with high interest and high power.

The finding of non-prioritisation of non-TB lung health conditions with a gap in policies and management of chronic lung disease also demonstrates the interplay of power and politics in policymaking. The problem stream is clear, there are some global policies available, however political and funding support is lacking.[169] This is similar to a study of NCDs in Ghana that showed that factors, including an overwhelmed health system due to communicable diseases, lack of global financial commitments and expertise in NCDs hinder implementation of NCD policies.[170] This finding clearly illustrates the role of power in health policy, where technical agencies/donors have no interest in a certain area, then policies are scarce. A policy champion should be identified to advocate for increased government funding to tackle this neglected but important public health concern. CXR for TB screening could indeed be an entry point for identification of non-TB abnormalities due to complications of NCDs as discussed in Chapter 3.[45]

As per the END TB strategy pillar 2, this study found that Kenya has engaged the communities, CSOs, and other actors in TB policymaking.[49] CSOs were also noted to be powerful patient advocates in shaping the policy agenda and protecting human rights, as was demonstrated by their stewardship in the development of the TB isolation policy.[157] As a representative of the patient, their role is important even though in most situations they had no funding resources to drive the policy process.

Deliberate private sector engagement and early involvement of institutions of higher learning, professional associations, and research organisations at agenda setting will lead to an all-inclusive policy process. The NTLD-program should also work with counties to encourage a combined top-down and bottom-up implementation approach, to enrich the policymaking process and meaningfully engage with all stakeholders with understanding of the contextual factors within the implementing environment.[144]

The availability of implementation experience for example in the case of IPT roll out, can further enhance policy adoption and should be encouraged. There is also an opportunity for NTLD-programs in LMICs to develop platforms for local research dissemination that can guide policies as well as feed into global policies. A structured platform for NTLD-program to interact with researchers and for researchers to present their findings to the policymakers, is lacking. As shown in the study, this has led to small scale local research not influencing policy. A favourable policy environment, effective strategic alliance of policymakers and researchers, and availability of easily consumable data have been shown to enable research-evidence uptake. [171] There is an opportunity for the NTLD-program and partners to work on developing or re-kindling a platform for research engagement as this will help the country incorporate local data in the policymaking process. Additionally, use of research will be enhanced if researchers pursue timely studies that are relevant to the country priorities.[172] There is also an opportunity for local research findings to be channelled to inform global policies which would then be looped back to LMICs as normative guidance.[130]

Strength and limitations

Understanding the pathway and the actors involved in the policy process has been shown to be useful in understanding why certain policies are taken up and others not.[127] This will be important to inform future policymaking including CXR for TB screening. Secondly, the study reviewed the processes of developing multiple policies and not just one or a few policies, hence there was deeper understanding and exploration of different influences over the policy process. In addition, diverse stakeholders were interviewed (national, county, partners), enabling a rich perspective of what they believe their roles involve and what others perceive their roles to be. The researcher`s positionality as an insider also enabled the asking of in-depth questions, due to having a good understanding of the policy climate.

Due to the COVID restrictions, the focus group discussions were not conducted, hence the researcher was unable to observe the powers and interests in technical review groups that were instrumental in policy formulation. The in-depth look at implementation was beyond the scope of this study, so the researcher cannot comment on the success of the policies. Finally, review of the content of the policies was not conducted, therefore, we are not able to comment on the factors and actors that shaped or influenced specific policy commitments/decisions.

5.7 Conclusion and recommendations

This study was conducted to have an in-depth understanding of the policy pathway and the actors. In the setting of this PhD, the findings offer important lessons to understand how the CXR TB screening policy and use of operational modelling as an engagement strategy fit into the policy process.

CXR for TB screening is likely to be adopted into policy due to a number of factors. Firstly, as outlined in Chapter 1, WHO published systematic TB screening guidelines recommending the use of CXR and CAD software.[9] As demonstrated in this policy

analysis, WHO asserts some institutional power, which according to the Barnett and Duvall taxonomy constitutes interactive and diffuse power.[165] Secondly, Kenya`s TB prevalence survey (a large local study commissioned by NTLD-program) showed CXR as a sensitive screening tool.[2, 3] Similar to a Ghanaian study, more large studies make it to policy compared to small ones.[172] Thirdly, technical expertise and financial resources are noted to be powerful tools to influence policy, [129, 166] funders for example Global Fund and USAID have made commitments for supporting intensified TB screening roll out using digital CXRs with CAD.[173, 174] Finally, organisations like WHO and STOP TB partnership who spearhead setting of global targets and their achievement, are advocating for CXR and CAD scale up.[9, 175]

Operational modelling will help policymakers project the anticipated potential effects of CXR TB screening on the Kenya health system (see full details in Chapter 4). From this policy study, modelling would be useful in the policy formulation and evaluation stages. The subsequent Chapter 6 gives more details on how operational modelling can be integrated into the policymaking process. As outlined in Chapter 4, the modelling would also guide the NTLD-program on choosing the pilot groups to assess the operationalization and resources required for CXR TB screening roll out.

5.8 Key policy implications

5.8.1 Engagement of researchers and policymakers

From the findings, it is clear that policymakers, in this case NTLD-program, require engagement from the time of the study idea development. This engagement is mutually beneficial to both the policymakers and the researchers. Researchers will understand the research priorities for the policymaker, align their research to answer their concerns, obtain buy in and hence their findings are likely to inform policy. Policymakers will have an opportunity to express their needs, be part of the research process and have reliable evidence on which to base their policies. As the research produced would be context specific, it would be more useful for policymaker programming. Sometimes

not all global policies work at country level as envisioned, hence local research is important.[176]

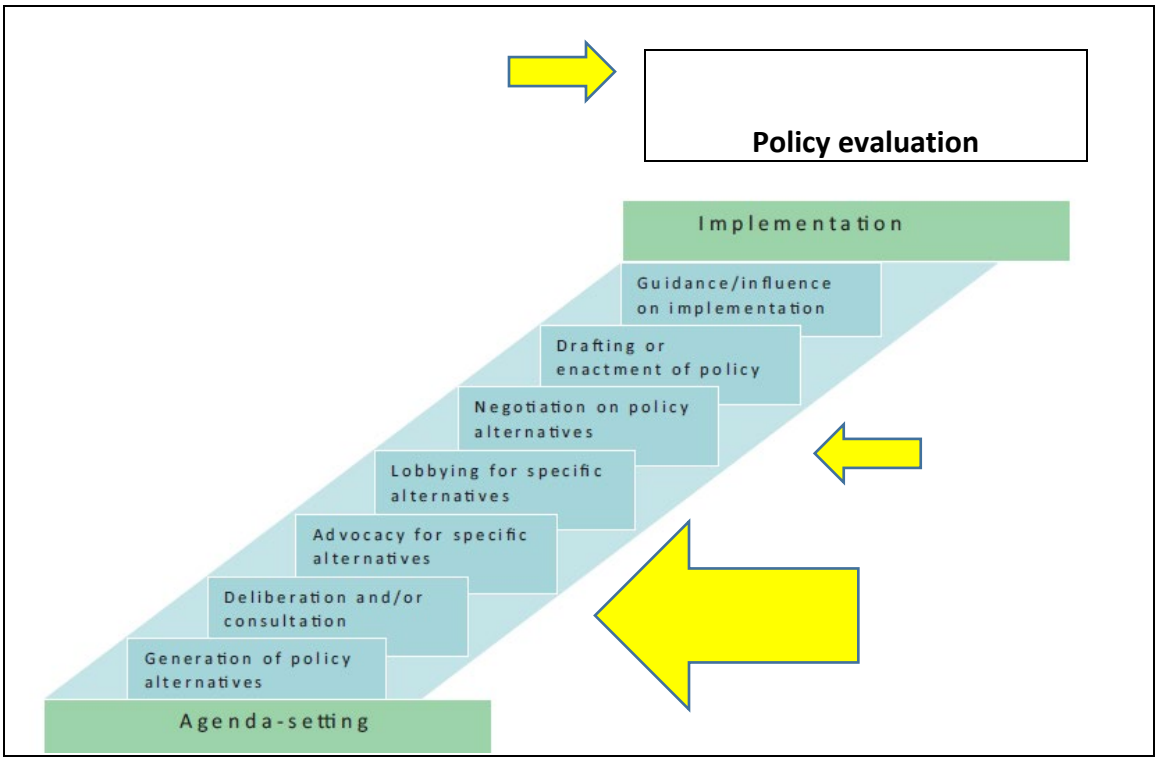
5.8.2 Health system strengthening for lung health

There is an opportunity to strengthen health systems for chronic respiratory diseases (CRD) building on the TB structures available. [169] The NTLD in Kenya already has the mandate for CRD and includes lung health in its policy documents. There should be a deliberate effort to seek for government funding to program for this, get lung health expertise on board and carry out surveys/implementation research to understand the best way to manage this in country.

5.8.3 Operational modelling would best be applied at the policy formulation and policy evaluation stages of the pathway

From the findings in Section 5.5.2, modelling best fits in step 2 of the policy formulation stage ("The policy alternatives assessed and zero draft produced"). Using the 'seven bits' framework by Berlan et al, the operational modelling would be best placed at the generation of policy alternatives and deliberation/consultation stages. During this stage, the weighing of policy options including assessment of cost-effectiveness, operational or logistical requirements as well as overall impact of the alternatives is done. Additionally, the outputs of the model (for example costs, key pathway bottlenecks, expected changes in numbers successfully treated) can be used in the policy evaluation stage to assess for impact (section 5.5.2).

Figure 5.7: This figure show where operational modelling can be applied in the policy pathway as illustrated by the arrows



6 Introduction to operational modelling as a synthesis method for incorporating existing data into policymaking

6.1 Introduction

Operational modelling is recognised as a useful tool in informing policymaking, [41, 42] however, there is no existing framework to guide how it can be integrated in policymaking. The purpose of this chapter is to draw from the results of Chapters 4 and 5, and other scholarship, to develop a framework that can guide the integration of operational modelling into policymaking.

In Chapter 4, a review of literature on operational modelling to consider its role in policymaking and to help address the question of the best placement of CXR in the TB screening algorithm in Kenya was conducted. Chapter 5 comprised a retrospective analysis of TB policymaking in Kenya. This chapter begins with a review of modelling as a policy engagement tool, and describes the steps used for introduction of operational modelling as a synthesis method for incorporating existing data into policymaking in Kenya. Finally, the process of developing the operational model in Chapter 4, the mapping of the policy pathway in Chapter 5, and the results of this chapter, are combined to propose a framework of integrating operational modelling in the policymaking process.

6.1.1 Aim and objectives

This chapter aims to develop a framework to guide integration of the operational modelling approach into policymaking in Kenya.

The objectives are:

1) To describe the process of introducing operational modelling to policymakers in Kenya

2) To explore the extent to which operational modelling approaches can enrich policymaking
3) To propose a framework to guide integration of the operational modelling approach into policymaking

6.2 Literature review

As captured in Chapter 4, the advent of health systems modelling enabled more complex simulation of interventions/policies, allowing better understanding of their impact on health system resources. [102, 103] Operational modelling in TB policymaking is a relatively new concept. There is a lack of evidence on the step-by-step process and guiding framework of adopting and integrating operational modelling in the policymaking process.

Understanding the policy process retrospectively helps identify opportunities for policy change.[138] Prospective health policy analysis enables real-time learning and use of knowledge acquired to employ strategies and approaches to influence policy change.[128, 177] To increase the chances of adoption of modelling as a policy engagement strategy, high-level engagement of policymakers and stakeholders in the modelling process is required.[178]

Previous studies on operational modelling have focused on the usefulness of the models in assisting policymakers in decision making.[40, 41, 104] There is paucity of prospective studies on how modelling as a policy engagement tool can be incorporated in the policymaking process. The questions to be addressed therefore are; *what is the process of incorporating operational modelling into the policymaking process? What is the guiding framework for integrating operational modelling in the policymaking process?*

This prospective study set out to describe how operational modelling can be prospectively incorporated into TB policymaking and to explore its utility in the process.

The findings were then applied to develop a framework to guide the integration of the operational modelling approach in TB policymaking in Kenya.

6.3 Methods

6.3.1 Study design

This was a qualitative prospective study.

6.3.2 Data collection

The study was conducted between June 2018 and May 2021.

The methods used included:

- Observation and note-taking on the process of introducing operational modelling into policymaking in Kenya
- Key informant interviews with actors involved in the policy process
- Reflective discussions with experts

6.3.2.1 Observation – note-taking during operational modelling meetings

As part of the operational modelling introduction and model development, three workshops were conducted. I facilitated the workshops, with the research assistant taking notes during the sessions.

Additionally, an operational modelling validation meeting with NTLD program officers and partners involved in TB work in Kenya was held in May 2021. During this two-hour feedback and discussion session, I presented the completed model.

During the PhD period, I also attended a diagnostic optimisation network forum conducted by FIND. [179]

6.3.2.2 Key informant interviews

The key informant interviews were conducted as detailed in section 5.4.4.3. This current chapter focuses on interviewees' understanding of modelling, exploration of their previous interaction with modelling, and their views on its utility in policymaking.

6.3.2.3 Reflective discussions with experts

In order to develop a framework to guide integration of the operational modelling approach into policymaking, after collation and analysis of data for Chapters 4, 5 and drafting of the steps I had undertaken in introducing the operation model in Kenya, I embarked on the first framework draft. I then engaged some experts who had conducted operational modeling in other countries. These experts were Ewan Tomney (modeler who had done operational modelling in Philippines), my supervisor Professor Bertie Squire (who had been involved in operational modelling in Tanzania and Philippines) and Dr Rose Oronje (who had years of experience in policy work). They reviewed the integrated framework and enabled further synthesis of my findings as well as with refinement of the framework.

6.4 Data storage and management

All the data (recordings and transcripts) were stored in a two-step password-protected laptop and external hard disk only accessible to the researcher, backed-up in a password protected cloud solution (Microsoft OneDrive) (See full details in section 5.4.5).

6.4.1 Data analysis

For the key informant interviews, data analysis was conducted as described in section 5.4.6. After the data collection, the research assistant transcribed the recorded interviews verbatim and I reviewed all the transcripts. The transcripts were read multiple times to promote familiarization with the content. Guided qualitative content analysis was carried out and QSR Nvivo 12 Pro was used to code the data in themes. The

themes were key informants previous interactions with modelling, knowledge of operational modelling and utility of modelling.

Descriptive analysis of observational data was conducted focusing on the actors, aims, and outputs of the meetings.

6.5 Results

6.5.1 Objective 1: To describe the process of introducing operational modelling to policymakers in Kenya

Steps of introducing operational modelling to policymakers in Kenya

For this study, the introduction of operational modelling within health care (specifically in TB programming) in Kenya started in 2018. During the same period, a diagnostic optimisation network, (which is a form of operational modelling), was conducted by FIND in Kenya.[180] Box 6.1 below presents the steps that were taken in introduction of operational modelling for TB policymaking in Kenya.

Box 6.1: Steps taken during operational modelling introduction in Kenya

[Step 1] *Introduction of operational modelling to the researcher*	I was introduced to operational modelling concepts through published literature and on one-to-one mentorship with Liverpool School of Tropical Medicine (LSTM) modellers Ivor Langley and Ewan Tomeny. The two had experience in health operational modelling of more than 10 years (Ivor) and five years (Ewan). Regular monthly sessions were held to build competencies in building the model with practical examples on how to code, interpret the inputs, functionalities and outputs.

[Step 2] Sensitization on operational modelling to the Kenya National TB Leprosy and Lung Disease program (NTLD)	Orientation for stakeholders of lung health in Kenya on operational modelling and its utility in lung health was conducted (Appendix 13). In attendance during the sensitisation were NTLD (head of program and some section heads), World Health Organization Kenya (TB officer), Respiratory Society of Kenya (Chief Executive officer, program manager), Centre for Disease Control-Kenya (Technical advisor), Centre for Health Solution –Kenya (Senior technical advisor, regional officer), KEMRI (Director Centre for Clinical research) and Kenyatta National Hospital (Radiologist). The aim of the meeting was to sensitise a core team on operational modelling and share examples of models built for similar LMIC settings. This core team had in-depth understanding of the role of operational modelling and became champions of this issue. During the meeting, a discussion on input data for non-TB abnormality was explored as captured in Chapter 3.
[Step 3] Co-design of the operational model	This involved the mapping of the patient pathway and building of the operational model as detailed in Chapter 4. The key element of this step was the co-design of the model with the NTLD program. This was an iterative process involving several presentations and revisions of the model, and engaging with existing scholarship and LSTM modellers. This enabled accurate assumptions and promoted ownership of the model by the policymakers, as well as ensuring accuracy and soundness of the model through input by the experienced modellers.
[Step 4] Presentation of the patient pathway, draft model and modelling assumptions	This meeting targeted a larger number of NTLD officers and stakeholders with a total of 44 participants attending the forum (Table 6.2). Donor agencies- CDC, USAID, though invited, were not able to attend the meeting. These are important actors that influence policy as covered in Chapter 5 and, a follow-up one-to-one engagement was done. Unfortunately, the invitation still omitted private sector actors as highlighted in Chapter 5, this group is systematically left out in policymaking. A follow-up will be needed for this sector. The meeting agenda in step 4 included re-sensitisation of the team on operational modelling as well as presentation of the draft model (Appendix 14). The draft model was presented to the participants and validation of assumptions conducted. The inputs from this meeting were used to refine the model, particularly on clarifying definitions and patient flow during facility-based TB screening.

	There was interest on modelling beyond the CXR work. For example, some participants sought to find out if a model can be built to determine the impact of pooling sputum for GeneXpert during TB screening activities to assess the yield, implementation and cost-effectiveness.
[Step 5] Presentation of the complete model for validation	The finalized operational model was presented to TB stakeholders in Kenya during the NTLD annual report writing workshop in Nakuru, Kenya. The participant representation was mostly NTLD officers (including sectional heads of the monitoring and evaluation department, and the diagnostic department) as well as some implementing partners. The aim of the forum was to present the full model and the outcomes per strategy modelled (Chapter 4). First, an overview of operational modelling was given to ensure those who had not attended the previous meetings were well-acquainted with the operational modelling concept. The presentation generated rich discussions with feedback given on the utility of the modelling in the policymaking process in Kenya, and the next steps on adoption of modelling. Additionally, there were proposals on the use of the operational modelling during the data synthesis and formulation stages of the policymaking process. The team recommended involvement of more stakeholders, including the research unit at Ministry of Health headquarters. Requests were made to build models for the TB preventive therapy uptake and the active case finding proposed interventions.

Table 6.1: List of participants who attended the operational modelling meeting on 14th October 2019

Government	**County representatives**	**5**
	Division of National TB, Leprosy and Lung Disease	20
	National TB Reference Laboratory	2
Research Institution	KEMRI	1
Academic and Professional association	University of Nairobi and Kenya Peadiatric Association	1
	Liverpool School of Tropical Medicine (Including 3 PhD students)	4
Teaching hospital	Kenyatta National Hospital	2
Non-Governmental organization	AFIDEP	3
	Centre for Health Solutions-Kenya	5
Funding agency	Global Fund consultant	1

6.5.2 Objective 2: To explore the extent to which the operational modelling approach can enrich policymaking

Policymakers had interacted with different types of modelling to varying extents and agreed that modelling had a role in policymaking

Most participants were aware of both infectious disease modelling in epidemiology and cost-effectiveness analysis. Two instances were quoted of such uses of modelling in the Kenya TB program: development of the current national strategic plan 2019-2023, and diagnostic network optimisation mapping by FIND.[37, 180]

> *"So, we used modelling in our current Strategic Plan. The purpose was to get us models of transmission along the patient care pathway, yea, so patient care cascade. […]So, using modelling we were able to get the incremental cost-effective ratios, […] the highest impact for the lowest coin"* **KII 006**

Those interviewed agreed that modelling — when the right assumptions are used — is important and useful to answer questions in advance of actual implementation.

> *"So for modelling I believe if we are going to get your assumptions right and you know context specific assumptions, I believe they are able to solve some questions that we really cannot go to the field and try to investigate"* **KII 014**

The feedback on the National Strategic Plan (NSP) process suggested modelling is believed to be a tool useful in policy formulation, as captured below.

> *"…. it informed the country on like I said on the most impactful interventions, what it would actually cost and what it would mean to bring the burden down so then it helps the country focus on the most impactful interventions given the resources that exist, […]and it is used in other policy formulation"* **KII004**

Some of those interviewed had a contrary thought on modelling (in general) and felt that country programs may be at the early stages with modelling.

> *"…the science of modelling and the utility for modelling, I think for every TB program, they are still a little far off. A lot of countries don't understand modellers and modelling. […] The understanding and the utilization of modelling approaches to TB program is at its infancy stage, a lot more work needs to be done and it needs to be done by both modellers and the TB program. The modellers are up here, thinking in some very abstracts terms sometimes and the TB programs are here and that connection is not as strong as it should be."* **KII 009**

The respondents suggested that a basic understanding of modelling could 'close the knowledge gap' between modellers and policymakers, making it a useful tool.

> *"Those of us involved in public health need to understand what modelling is so that when a modeller comes to us and says if you do x and y this is what will happen, we can appreciate that model, we can criticise and look at it and say yes it looks like it makes sense. So, we don't need to be super modellers, but we need to be able to understand modelling approaches and their limitations so that when a very good model comes out and if we think it is something worth pursuing, then we pursue and not brush all models away. Neither should we take all models our way and put it into policy and practice because it may completely take us off in the wrong direction."* **KII 009**

Though operational modelling was new to most of the participants, they noted that it could play a role in policymaking

When expressly asked about operational modelling, the majority of the interview participants stated that this was a relatively new area to them. Those familiar with it had attended the operational modelling sensitisation meetings (Box 6.1 above) prior to the

interview, and expressed that it could be useful in guiding the direction of policy. In the example of CXR, one respondent felt that operational modelling was timely as it would guide the NTLD on the best algorithm to use.

> *"… this operational modelling that you are doing [is important] because the program seems not to have an answer of the best way to screen using GeneXpert and chest X-ray. They have had their algorithms changed in a short duration of time and if they were given the best algorithm, and assured here is the evidence, it would really stop them from guessing. […]We are saying that these two tests or screening tools; GeneXpert the sensitivity is good and here we have chest x ray which is also adding to it. Where do we place them? And we have different scenarios whereby sometimes you have chest x ray but you don't have GeneXpert or you have GeneXpert but… have chest x ray or you have both. So if you could have the different kind of scenarios that we have in this country and suggest which the best way is, it would really help."* **KII 001**

Indeed, during the validation meeting after presenting the different scenarios and findings, some of the participants suggested adoption of the CXR screening for all with the digital CXR machines expected in country. The suggested way forward was the formation of a small sub-committee to use the model outputs and work on an addendum for CXR TB screening policy.

Another important piece of feedback from the validation meeting was participants' reflections on how captivating the visual presentation was, which allows users 'to see patients move to various stages'.

> "*I must say this is the first time I am interacting with operational modelling, the visual presentation is clear and the implication of the various strategies modelled easy to appreciate. It is an easy way to engage..."* **Participant during the validation meeting**

The meeting consensus was that the program would be interested in adopting operational modelling in the policymaking process.

6.5.3 Objective 3: Proposed framework of integrating operational modelling into health policymaking

From the study findings (and findings from previous Chapters 4 and 5), literature review from other operational modelling in other countries,[41, 42] and modellers input, a framework for adoption of operational modelling in policymaking and institutionalizing it into the ministry's decision making process has been proposed in Figure 6.1 below. A broad non-context specific proposal is given composed of four key components; **Engagement, Capacity development**, **Co-design and Integration**.

1. Engagement

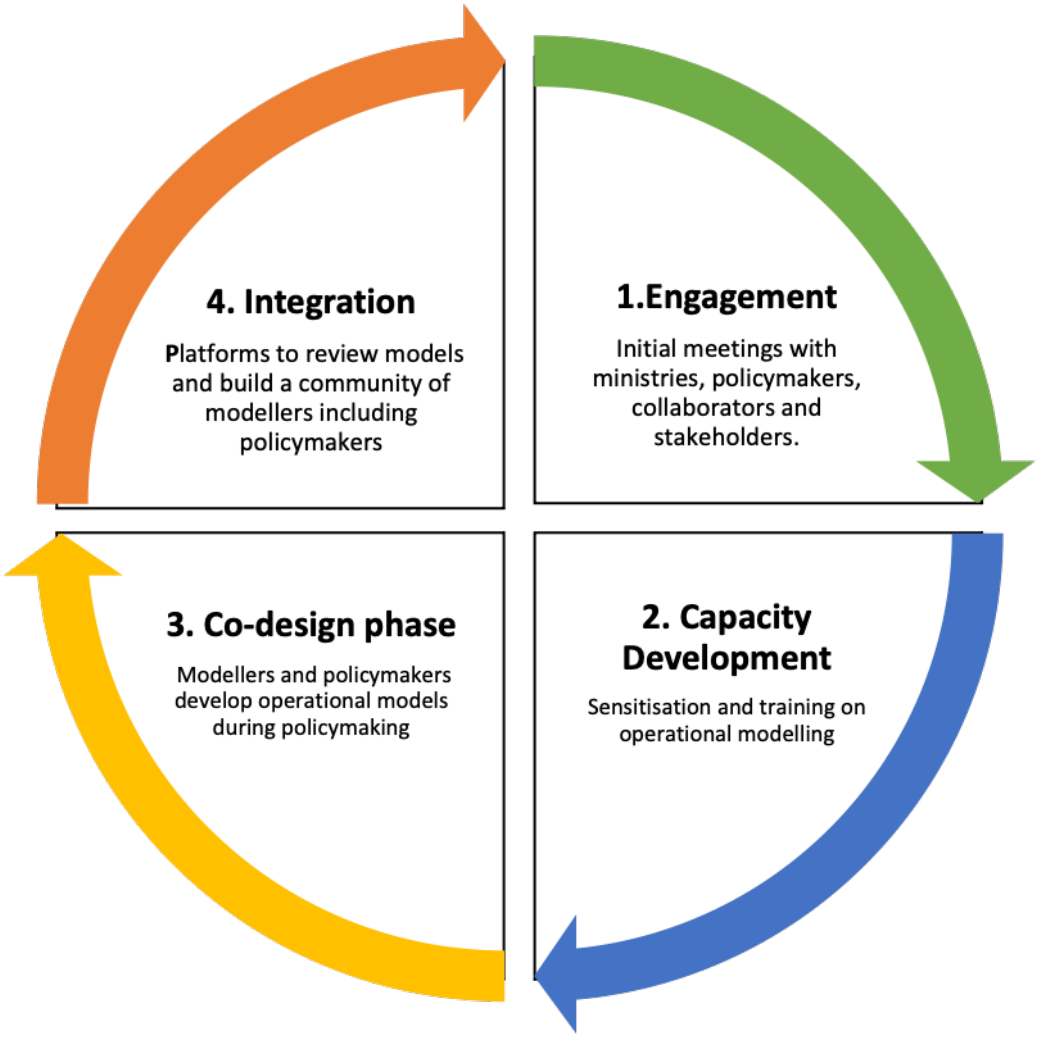
This first step involves identifying in-country issue champions for the operational modelling introduction process. Departments in the ministry or programs whose mandate is aligned to provision of tools for evidence use in decision-making would be good issue champions. The role of the champions would be to sensitize top decision makers, coordinate the collaborators, and work with various programs to identify opportunities for operational modelling in ongoing policy processes.

Their engagement should include sensitisations to understand value of operational modelling as well as appreciate examples of operational models built for other settings, and how they have aided the policymaking process.

The issue champions would then identify modelling collaborators including; program specific policymakers, monitoring and evaluation departments, modelling centers, universities, and other research institutions with technical capacity to conduct modelling. In Kenya, a number of institutions were recommended, these included: the Centre for Epidemiological Modelling and Analysis (CEMA),[181] University of Nairobi, CDC statistical branch, Moi University (Public Health), Egerton University, Jomo Kenyatta

University (JKUAT) and KEMRI Welcome Trust. They would organize an initial meeting to map out the capacity, priorities, and interests of all the stakeholders. The modalities on how to collaborate, and the potential opportunities for use of operational modelling, can be initially discussed in this meeting, though discussions would be ongoing.

Figure 6.1: Proposed framework for adoption of operational modelling in the policymaking process



2. Capacity development

Spear-headed by the issue champions, a sensitisation on the concept of operational modelling to be conducted for the team of modelling collaborators and policymakers. During the sensitisations, identification of those who would undergo in-depth training on modelling would also be carried out.

Expert modellers should then plan and conduct in-depth trainings; one-on-one or small group trainings are preferable. A modular training curriculum including instructional videos could be developed to aid this. In country, a pool of modellers can be trained as expert trainers to ensure ongoing face-to-face trainings.

During the key informant interviews, one of the respondents noted that in-country capacity building and collaborations were important during the NSP modelling.

> *"I think for us to sustain any interventions it is important to pursue the aspect of having in-country capacity, to build our own capacity to model and to make sense out of the findings of that modelling. Then, it will be our own finding not someone else who has come to tell us.* ***KII 004***

Budgeting and planning for logistics and operationalisation of software procurement and subscriptions paying would also be done at this stage. A proposal is to have free or subsidized versions for LMICs.

3. Co-design phase

The issue champions would develop and solidify a system to identify opportunities for operational modelling and link to the trained modellers. The modellers would then work with the policymakers in developing the model during the policymaking process. This would ensure inputs, assumptions, and outcome measures are agreed upon. This will

help in weighing-up different options during the policy formulation, and also in the evaluation stage.

Drafting guidance documents and standard operating procedures to guide this phase and interaction of modellers and policymakers should be done.

4. **Integrate**

The operational modelling process should then be integrated into existing research platforms and review forums for modelling. In cases where this is not available, creation of a platform that can regularly host research and modelling discussions would be important. During these meetings, models could be presented and fine-tuned during the policymaking process. These would act as peer-to-peer mentorship, best practice sharing sessions, and will build a community of modellers (both technical and policymakers).

This phase would also include long-term focus on lesson-learning from implementation that occurs after modelling – answering questions such as “how well did the model predict what happened when implementation occurred? If implementation resulted in very different outcomes, what were the reasons? Were there any particular lessons learned from implementation that could be fed back into the improvement of modelling for future decision-making?”

6.6 Discussion

This prospective study demonstrates that operational modelling is felt to be an acceptable and feasible tool to aid in TB policymaking in Kenya. Additionally, the study defined the role and advantages of modelling. Models are an approximation and simplification of reality helping us to understand complex systems. In this study, the use of operational modelling enabled comparison of different CXR screening options by projecting the patient and health system impacts simulated over many years in under a minute (Chapter 4). Additionally, estimation of patient and health system costs was done. Policymakers were receptive to the visual presentation and simulation of the processes, preferable over 'black-box' modelling in policymaking. [39, 40 138]

Defining the modelling context will ensure early engagement of the relevant stakeholders. [103] In this study, the broader ministry of health research division was inadvertently left out. In countries with a similar MOH structure to Kenya, engagement of the research division from the onset during introduction of modelling is necessary. They can act as operational modelling champions and institutionalise the use of the tool for application beyond the program area. They can also be the institutional link between MOH and modelling experts at universities and other research institutes. Modelling collaborators are key and synergies can be harnessed.[103] In 2021, during the final months of the study period, CEMA, a multidisciplinary consortium of epidemiologists was launched and represents an important modelling institution to be engaged.[181] Mapping and identifying such organizations will help consolidate in-country modelling capacity and enable wider uptake of new modelling tools.

Policymakers were engaged through capacity building, sensitisation, co-designing and validation of the model. Sensitisation on modelling was an ongoing process due to the ever-changing policy environment. For example, there were three new heads of NTLD program during the study period. As observed in Chapter 5, there is a predominance of certain powerful players in the policymaking process for example the head of TB

program, technical agencies and funders hence for policy success, they must be involved in the entire process. One of the key strengths of our implementation was the co-design of the model with policymakers including these powerful actors. Co-design in research is important to ensure alignment of researchers' aims with the needs of the end-user.[182] This started with the choice of the topic for modelling. Similar to other studies, engagement of policymakers in the entire modelling process was important in the uptake of modelling.[138] Models influence policymaking while allowing policymakers to also have an influence on the models.[178] During the modelling in Chapter 4, co-design and repeated engagement with policymakers enabled tweaking the model severally.

This study was timely as the dissemination of the TB prevalence survey results had only recently taken place in 2017, and Kenya was in the process of considering how CXR for TB screening should be adopted in practice.[2, 3] As outlined in Chapter 1, similar to the impact assessment framework (IAF) by Mann et al, the questions TB policymakers were battling with were: how to optimize the cost-effectiveness of CXR in finding persons with TB; who would benefit from CXR; and what would the health system effects and the projected impacts of scale up be.[38] In the case of Kenya, both the close collaboration with NTLD, along with the issue of CXR for TB screening being an area of interest to the team, may have influenced the acceptability of operational modelling as a tool to predict different CXR TB screening scenarios. These findings will support the CXR sub-committee`s deliberations and the drafting of the CXR policy.

During the meetings in Kenya, we identified opportunities from the participants on topics/questions that participants felt operational modelling could help address. Other forms of operational modelling, such as the diagnostic optimisation network conducted by FIND in Kenya, also show potential benefits.[180] Within Kenya, COVID-19 has presented opportunities for more awareness on modelling and the benefits to the policymakers.[183] [184] As operational modelling is a concept that can be used across various program areas, integration in different modelling platforms has been shown to be useful.

As George Box once wrote, “All models are wrong, but some are useful”.[185] On model introduction, one of the key pitfalls identified in the study is the potential for over-reliance on the model by the policymakers. It is important to acknowledge that, while modelling supports decision-making, it does not replace it; a model is only as good as its assumptions.[186] These assumptions must be made transparently, grounded in data, and tested for sensitivity. Another limitation is that some software used for modelling can be expensive, limiting the options available to LMICs. For this study we used an educational version of WITNESS under a bespoke agreement with the manufacturer, however the cost of this software to MOH is not known, and could potentially limit the uptake of this type of operational modelling. Finally, as with all tools, operational modelling is not a magic bullet; we acknowledge that evidence of effectiveness of a specific intervention needs to be looked at holistically given the complexity of health systems. Therefore it is a tool to aid policymaking but holistic review of the potential impact of an intervention on the entire health system is crucial.

6.7 Conclusion

There is an opportunity for scale up of operational modelling prior to implementation to assess impact of health policies and interventions in LMICs such as Kenya to support policymakers and health system researchers to optimize allocation of resources. In-country institutional capacity for modelling is on the rise with set-up of organizations like CEMA. MOH research department is a potential operational modelling champion and is key in making it a decision support tool. Uptake of modelling is an ongoing process with constant changes within the policymaking circles. A framework to guide adoption of operational modelling would be helpful to countries.

7 Conclusion

7.1 Summary of the rationale, objectives and key findings

Radiography was widely used in the 20th century for TB mass screening and promoted detection in the context of high TB prevalence.[24] With the renewed interest in CXR for TB screening in the 21st century following on from the 2021 WHO systematic TB screening recommendation and availability of ultra-portable digital X-rays and CAD software, there is a potential to use CXR-CAD to accelerate achievement of the END TB strategy goals.[6, 9, 49, 55] The 2016 Kenya prevalence survey (the first survey in post-independent Kenya), marked a major milestone for Kenya TB control.[2, 3, 187] TB policymakers guided by the findings of the prevalence survey on the high sensitivity of CXR for TB screening, and the global guidance on utility of CXRs, are considering changes to the TB screening and diagnostic algorithm.

This PhD study set out to:

- Generate new knowledge related to CXR use in TB screening,
- Develop an operational model using this information and other sources,
- Assess whether operational modelling is a feasible technique to support evidence-informed TB policymaking in Kenya.

The studies in this PhD have generated novel findings related to CXR use in TB screening that have important health policy implications. Firstly, it demonstrated the accuracy of computer-aided CXR screening for TB in a community-based prevalence survey, with CAD4TBv6 meeting the optimal WHO target product profile for a community TB screening tool (Chapter 2).[44] Specificity was lower in adults with previous TB and those aged >40 years, as in previous studies. [51, 55, 57] An adaptive approach to setting CAD thresholds will be required to optimize use.

Secondly, the use of CXR for TB population-based studies identified many patients with non-TB related abnormalities that would likely be missed by use of CAD (Chapter 3). There was a high prevalence of cardiomegaly, chronic pulmonary diseases, post-TB lung disease and non-specific lung diseases in this setting. This was the first study in sub-Saharan Africa to describe and quantify non-TB CXR findings among participants who underwent mass screening as part of a population-based TB prevalence survey. Implementation of CXR TB screening in LMICs offers an opportunity to integrate disease screening efforts. Additionally, updates to future CAD versions should include algorithms for non-TB abnormalities.

Thirdly, operational modelling using the Witness package, a visual and interactive modelling tool, was used to determine the optimal CXR algorithm for TB screening in Kenya and project the likely health system impact of CXR roll out. The model demonstrated that a strategy using CXR-CAD screening for all, then GeneXpert though the most expensive, demonstrated the ability to identify more persons with TB. Enhanced symptom screening, followed by CXR-CAD triaging and diagnosis by GeneXpert offered the most cost-effective combination optimising case-finding while maintaining efficiency.

Finally, the prospective policy analysis demonstrated that, though operational modelling was a relatively new concept, it was an acceptable and feasible tool to aid in TB policymaking in Kenya. Policymakers were receptive to the visual presentation and simulation of the processes, preferable over 'black-box' modelling in policymaking (Chapter 6). [39, 40 138] A framework for adoption of operational modelling in policymaking and institutionalizing it into the ministry's decision making process was developed. This is composed of four key components; **Engagement, Capacity development**, **Co-design, and Integration** (Section 6.5.3). This framework is likely to be useful for other countries and programs as they adapt modelling in the policymaking process.

In summary, this PhD has answered the questions that the TB policymakers were battling with in Chapter 1. *What is the effectiveness of CXR in finding persons with TB in the community? What is the accuracy of CAD software in the Kenya context? Who would CXR and CAD screening benefit? What would be the health system effects (human resource implications, referral system for management of other conditions)? What would be the projected impacts of scale up? And how do the various screening and diagnostic algorithms applying different tools compare to each other?*

7.2 Recap of the key policy implications

7.2.1 An integrated patient-centred approach is required in the development of digital CXR and CAD TB screening policy guidance

Updating the TB screening and diagnostic guidelines/ policy documents will be essential for countries planning to adopt CXR and CAD. A national committee to assess the current TB screening situation, identify priority groups, screening algorithms and choice of tools is recommended. This development of policy should be done in an integrated way within the health system, including planning for the non-TB conditions. Early engagement of all stakeholders including the civil society organisations, private sector and NCD programs should be done from agenda setting all through to policy evaluation stages.

Countries should develop integrated CXR TB screening policies that outline how patients with TB and non-TB conditions are managed with clear pathways of care. The non-TB findings in our study, for example, cardiac and chronic respiratory diseases were consistent with complications of potential underlying NCDs.[45] A patient-centred approach incorporating NCDs screening and health promotion during TB screening activities is recommended.

7.2.2 Health system preparedness for CXR TB screening

Implementation of CXR TB screening should be conducted within overall health systems planning processes to ensure the gaps anticipated are planned for.[28, 30]Integrated CXR TB screening should be captured in development of policies and service delivery as outlined in section 7.2.1 above. Well-functioning clear referral pathways, diagnostics and follow-up plans for non-TB pathology ensure a form of integrated care for patients.

Countries could develop a checklist when deciding on the CAD software to procure. In addition to accuracy, other considerations are: overall cost; cost-effectiveness; compatibility of the X-ray systems; input image format; integration with any patient archiving systems; customer service and support; data protection; and ability to detect other non TB conditions.[25, 27, 55]

The use of CXR-CAD TB screening will be a new frontier for most LMICs. There is need for prospective data collection during the TB screening including pathway cascades and non-TB conditions diagnosed. This will help in characterisation of the patients and obtaining of sub national data on prevalence per region, granular planning of individual and health systems implications of these diseases.

7.2.3 Adoption of operational modelling as a policy engagement tool

There is an opportunity for scale up of operational modelling in global-national policy transfer. Modelling enables assessment of impact of health policies and interventions in LMICs to support policymakers, and health system researchers to optimize allocation of resources prior to implementation. The framework developed to guide adoption of operational modelling is likely to assist countries in this process in diverse health program areas. Validation of the framework would be required, and lessons learnt from its implementation documented.

7.3 Future direction/opportunities

7.3.1 Recommendation for use of CAD in TB screening in health facilities and TB prevalence surveys

CAD software is an important tool to aid in CXR TB screening and triaging. The use of CXR-CAD either in screening or triaging reduced the number of GeneXpert tests required to diagnose a TB case. The CAD study also demonstrated the accuracy and the potential utility of CAD in population-based TB screening. CAD offers high throughput and should be considered for use in the diagnostic strategy of future TB prevalence surveys. Initial engagements with WHO on the study findings (Chapters 2 and 3) implications for future prevalence surveys have begun.

7.3.2 Opportunity to strengthen chronic respiratory diseases management

Roll out of CXR for TB screening presents an opportunity to strengthen health systems for chronic respiratory diseases building on the TB structures available. [169] An entry point for chronic respiratory diseases could be post TB lung disease programming. TB programs could develop policies on post TB lung disease management and monitoring, this could strengthen the management of CRDs. Countries can then lobby government and global funders to finance the required interventions. This will ensure improved quality of life for patients beyond TB treatment completion and integrate management for all other CRDs.

7.4 Future research

7.4.1 Recommendation for further CAD software for TB research

Although CAD has been demonstrated to have high overall accuracy for the Kenyan population in this thesis, more studies are needed among subgroups: HIV populations and children. This will ensure countries have more information on how to apply CAD within these groups. Countries also need to validate CAD software in their context and decide on the adaptive thresholds to be applied. Additionally, for older age group and

previous TB patients demonstrated to have low specificity by CAD, a two-stage triage system requires further research.

Finally, CAD scores focus on the probability of TB and for most software other non-TB abnormalities are not considered. Improvement on all future CAD versions should be made to score for other non-TB abnormalities.

7.4.2 Ongoing implementation research on CXR for TB screening

There has been tremendous progress on addressing the barriers to CXR use for TB screening over the years.[9, 24, 55] However, this PhD thesis still noted that despite the improvement in technology, there were many concerns among the respondents on the effects use of CXR for screening would have on the current health system. Facility level service indicators for example waiting times for CXR machines, average workload, human resources required at the various service points during the CXR roll out need to be monitored to enable further characterization of health system impact of the roll out and mitigation planning.

7.5 Summary

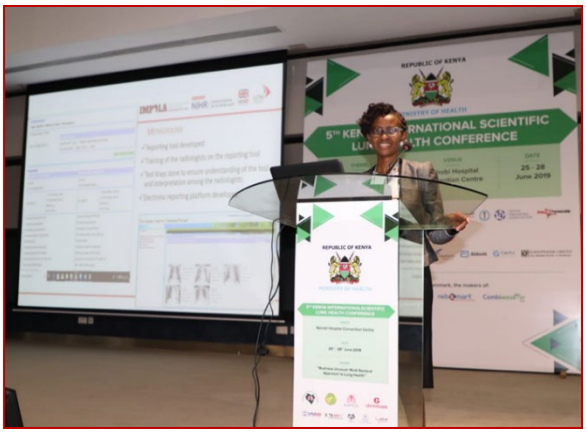
The COVID-19 pandemic has led to a drop of TB notifications globally by 18% and countries will need to increase case finding interventions.[6] This thesis has demonstrated that in a high burden LMIC, digital CXR and CAD screening are innovative tools with potential to accelerate achievement of the END TB strategy.[9] Use of CXR would likely have implications on all six of the WHO building blocks of health systems. Rolling out CXR-CAD in a patient-centred approach presents an opportunity to bring focus on lung health agenda, including integrated delivery of CRD care. [169]

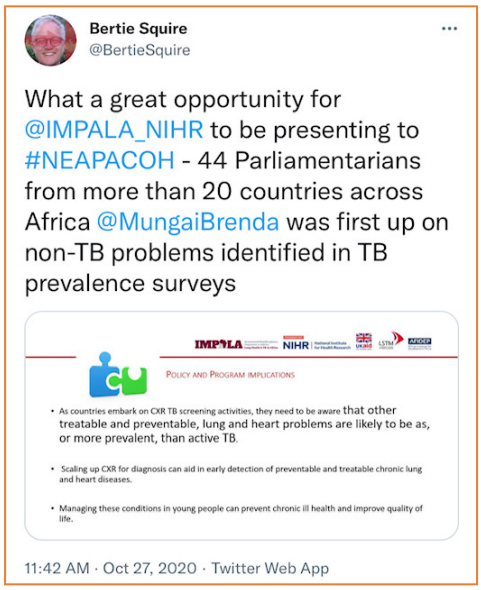
"… with a chest x ray policy you will have to do lung health policy because, the people who did an x ray and don't have TB but had something that put them there, will need to be figured out." **KII 003**

Finally, the thesis has demonstrated that operational modelling using the Witness package, a visual and interactive modelling tool, is a useful and feasible tool to aid policymakers in the decision-making process, by enabling projection of health system and patient impacts of introducing new diagnostic algorithms. [39-43] Close collaboration of the policymakers and modellers is a key success factor in the introduction of the operational model into the policy process. The framework developed in the thesis is likely to guide countries or programs planning to introduce operational modelling in their policy processes. Indeed, operational modelling can help in assessing the fundamental objectives of health systems which are; "improving health of the population they serve, responding to people`s expectations and financial protection from costs of ill health". [97]

7.6 Summary of policy engagements during the PhD study

Through the course of the PhD, I have been involved in policy discussions relevant to my studies as captured in the summary below:

	○ United Nations High Level Meeting on TB- September 2018 A blog on reflections of the meeting are captured here: https://www.afidep.org/the-clock-is-ticking-reflections-on-the-un-high-level-meeting-on-tb-2-years-on/
	I presented in various conferences both in-country and internationally: ○ 5th Kenya International Scientific Lung Health Conference – June 2019 ○ 10th KEMRI Annual Scientific & Health (KASH) Conference-February 2020 https://www.kemri.go.ke/wp-content/uploads/2019/11/KASH-10-BOOK-OF-ABSTRACTS.pdf ○ 51st and 52nd UNION world conference on lung health (2020,2021)

	○ I presented during the Network of African Parliamentary Committees on Health (NEAPACOH) meeting – two meetings October 2020 and 2021 ○ I presented on the non-TB abnormalities findings. These forums enabled parliamentarians get an in-depth understanding of TB burden and how they can support a health system approach to manage TB and other chronic respiratory diseases.
	I participated and presented in a symposium on Mass screening for TB during the 52nd UNION world conference on lung health (2021) My presentation topic was: *Community-wide systematic tuberculosis screening: Role of mass chest X-rays in the digital age in LMICs*

Next steps/planned engagements

- I was nominated as the chair of the Kenya CXR TB screening sub-committee- We have held three meetings so far and I presented my findings (Chapter 2&3) in one of the meetings. In January 2022 meeting I will be presenting the operational model as we hold a meeting to formulate the policy
- WHO discussions on the prevalence survey findings (Chapter 2&3) and how this can inform subsequent surveys
- Engagement with the research unit at the Ministry of Health in Kenya on operational modelling next steps

8 Appendices

Appendix 1: Prevalence Survey Clinical officers' qualifications and work experience

	EDUCATION QUALIFICATION	WORK EXPERIENCE
1	DIPLOMA IN CLINICAL MEDICINE AND SURGERY	4 YEARS
2	DIPLOMA IN CLINICAL MEDICINE AND SURGERY	2 YEARS
3	DIPLOMA IN CLINICAL MEDICINE AND SURGERY AND COMMUNITY HEALTH	1 YEAR
4	DIPLOMA IN CLINICAL MEDICINE SURGERY AND COMMUNITY HEALTH	1 YEAR
5	DIPLOMA IN CLINICALMEDICINE SURGERY AND COMMUNITY HEALTH	2 YEARS
6	DIPLOMA IN CLINICAL MEDICINE AND SURGERY	1 YEAR
7	DIPLOMA IN CLINICAL MEDICINE AND SURGERY	1 YEAR
8	BSc ENVIRONMENTAL HEALTH, AND DIPLOMA IN CLINICAL MEDICINE AND SURGERY	2 YEARS
9	DIPLOMA IN CLINICAL MEDICINE AND SURGERY	2 YEARS
10	DIPLOMA IN CLINICAL MEDICINE AND SURGERY	2 YEARS

Appendix 2: Modelling CAD4TBv6 accuracy

file:///C:/Users/brenda.mungai/OneDrive%20-%20LSTM/Documents/B%20folder/PHD/A%20all%20PhD%20write%20up%20documents/Chest%20Xray%20resources/CXR%20concept%20NonTB/CXR%20Concept%20note/CAD4TB%20manuscript%202020/2021%20CAD4TB/CAD%20OCTOBER%202021/2021-09-10_analysis_kcxr%20(5).html

Appendix 3: Chest X-ray reading Standard Operating Procedure

**SOP adopted from Malawi LIFE AFTER pTB (LAT) STUDY*

TITLE: Chest X-ray reading Standard Operating Procedure

VERSION NUMBER: 3.0

STUDY Kenya Prevalence survey 2016 Chest X-ray review

EFFECTIVE DATE: 04 May 2019

	Name and Position	Signature	Date
Author:	Dr. Brenda Mungai PhD in Global Health Candidate		03.05.2019
Reviewers:	Dr Liz Joekes, Consultant Radiologist		03.05.2019
Reviewer 2:	Dr. Vera Manduku, Consultant Radiologist		
Approver:	Dr. John Curtis		

REVISION HISTORY:

Version no	Revised by (name & position)	Effective date	Details of changes

PURPOSE

To ensure consistent and accurate review of the Chest X-ray images taken during the Kenya prevalence survey:

- Clear procedure for reading of all the sampled CXRs

RESPONSIBILITY

BM (PI):	To write SOP in collaboration with the Consultant Radiologists
	To coordinate the CXR reading
	To manage data
	To analyse data (PM)
LJ, VM, and JC:	To take lead in development of the CXR score chart
	To provide input into SOP
	To perform CXR scoring
	To provide radiology input for data analysis

ACQUISITION AND STORAGE OF IMAGES

Chest x-rays

- To be acquired from the Kenya prevalence survey 2016 database
- 500 images to be sampled from the CXR classified as abnormal suggestive of TB and abnormal other from prevalence field readings (Pilot reading)
- The actual study reading sample size calculated as 1124 images: Abnormal not TB: 738 images, Abnormal TB suggested: 386 images.
- Images will be uploaded via a system developed by an IT programmer from the National TB, Leprosy and Lung Disease program
- A score sheet attached in appendix 5 will be used to report the CXRs

QUALITY CONTROL OF IMAGES

The Chest x-rays to be read are in archive. The reading will begin with whether the image is good quality or not. This will include reviewing:

- Image cover – areas missed (e.g. apices / costophrenic angles)
- Labelling of the images
- Quality of inspiration

- Exposure
- Patient positioning – including rotation

Those that are poor quality will be marked not readable and will not be read.

TRAINING

A training will be conducted by EJ and BM using 20 Chest X-ray images to a subset of radiologists to hone to scoring system, and improve consistency of reporting.

SHARING OF IMAGES

Images are anonymized and only have a study ID number. They will have the following linked information: Age, gender and clinical symptoms. Images are to be shared within the study team only.
Image sharing systems will be set up by the Data Management team at NTLD-Program.

IMAGE READING

CXR research scoring

<table>
<tr><th>Category</th><th>Details</th></tr>
<tr><td>Image readers</td><td>There will be a double reading of the CXRs randomly
Each reader will read 115 individual CXRs and randomly double read another 115</td></tr>
<tr><td>Reporting tool</td><td>Images to be reported directly in to the developed platform by each reader
See appendix 7 on how to use the reporting portal</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Reporting definitions</td><td>CXR scoring system based on developed criteria (Appendix 5).

The primary diagnosis reflects the most likely findings in this study cohort, with the option of one differential diagnosis and free text for skeletal and abdominal abnormalities.

Readers will insert a certainty score for each primary diagnosis selected:
<table>
<tr><th>certainty</th><th>value</th><th></th></tr>
<tr><td>Not certain</td><td>0</td><td>The probability that the diagnosis is correct is 0-24%</td></tr>
<tr><td>Slighty certain</td><td>1</td><td>The probability that the diagnosis is correct is 25-49%</td></tr>
<tr><td>Moderately certain</td><td>2</td><td>The probability that the diagnosis is correct is 50-74%</td></tr>
<tr><td>Highly certain</td><td>3</td><td>The probability that the diagnosis is correct is 75-100%</td></tr>
</table></td></tr>
<tr><td>Storage of reports</td><td>The database for CXR reporting is to sit on the NTLD server. Completed reports will be backed up on the server.</td></tr>
</table>

DATA PROCESSING

There are two levels of diagnosis: Primary diagnosis and differential diagnosis.

The report will be downloaded as an excel CSV file for analysis.

Appendix 4: CXR Variables definition

	Primary diagnosis	Definition
Lung parenchyma	**Active PTB: typical features**	Classic X-ray features of active PTB https://pubs.rsna.org/doi/full/10.1148/rg.275065176
	Non-tuberculous Mycobacterial infection	Cannot be distinguished reliably from PTB on CXR, but may provide a differential diagnosis.
	Old /latent TB : < 1 lobe of damage/scarring	Classic features of latent/healed PTB :Total scarring / damage less than 1 lobe equivalent
	Old /latent TB : 1-2 lobe of damage/scarring	Total scarring / damage equal to 1-2 lobe equivalent
	Old/latent TB : destroyed lung	Complete destruction of whole lung equivalent due to previous TB
	Pneumonia, NOT typical for PTB	Suspected pneumonia, but no typical features to suggest PTB
	Non-specific airspace opacification	Any airspace opacification that cannot be classified under any of the above
	Bronchiectasis: any type or distribution	localized or diffuse bronchial dilatation: tramline appearances +/- wall thickening
	Broncho vascular inflammation: smoking/COPD type	Coarse broncho vascular bundles, peri-hilar. "dirty lungs" as commonly seen in smoking/COPD
	Emphysema/Asthma	Hyper expansion>6 anterior ribs, flattening of diaphragm, etc. Choose only if unequivocal in appearance.
	Interstitial/pulmonary oedema from cardiac failure	Classic features of Congestive cardiac failure with pulmonary oedema

	Interstitial Lung disease: other than oedema	Any of the ILD patterns, including miliary disease
	Chronic scarring/volume loss likely NOT related to TB	Chronic scarring, unlikely to be the result of PTB.
	Mass / nodules: benign	mass: opacity greater than 3 cm in diameter (without regard to contour, border, or density) Nodules: 3-30 mm. Benign: e.g. Calcified granuloma's, hamartoma etc.
	Mass / nodules: probably malignant	mass: opacity greater than 3 cm in diameter (without regard to contour, border, or density) Nodules: 3-30 mm. Features strongly suggestive of malignancy
	Mass / nodules: indeterminate	mass: opacity greater than 3 cm in diameter (without regard to contour, border, or density) Nodules: 3-30 mm. Not possible to differentiate benign/malignant
	Mycetoma	Fungal ball in cavity (+/- air crescent sign)
	Kaposi sarcoma	Classic features of peri-hilar, broncho-vascular "flame like" opacities, with lower lobe predominance (+/- pleural effusions)
Pleura	**Pleural effusion/thickening/calcification: minor**	Clinically likely irrelevant.
	Pleural effusion Significant	Size that is potentially clinically relevant
	Pleural thickening, calcification: likely benign	e.g. post-infectious or hemothorax (commonly unilateral) / plaques (bilateral)

	Pleural thickening, potentially malignant	e.g. potential metastasis/mesothelioma
Mediastinum (excluding heart and great vessels)	**Mass, indeterminate**	Any mediastinal mass, other than suspected lymphoma/EPTB or goitre
	Suspected Lymphoma	Large volume adenopathy (+/- lung pathology), commonly bilateral hilar and extensive
	Suspected TB	Unilateral hilar adenopathy and mediastinal adenopathy (+/- lung pathology)
	Goitre	Superior mediastinal mass, extending to the neck with tracheal deviation
Heart & great vessels	**Cardiomegaly**	Cardiothoracic ratio > 0.5
	Cardiac pathology: Other	Other than above.
	Pericardial effusion	globular enlargement of cardiac shadow, with features suggestive of effusion rather than cardiomegaly
	Aorta atherosclerosis / dilatation	Unfolding of aorta. Calcification of aortic wall
	Pulmonary hypertension	Elevated cardiac apex, enlarged right atrium and/or enlarged pulmonary arteries, pruning of peripheral vessels.
	Aortic / Pulmonary artery pathology, other	Other than above
Bones**/chest wall**	**Free text**	Any bony or chest wall abnormalities
Abdomen	**Free text**	Any abdominal findings

Appendix 5: Primary and differential diagnosis for CXR reporting

Domain	Primary diagnosis	Differential diagnosis
Lung parenchyma	Active PTB: typical features	Active PTB: typical features
	Non-tuberculous Mycobacterial infection	Non-tuberculous Mycobacterial infection
	Old /latent TB : < 1 lobe of damage/scarring	Old /latent TB : < 1 lobe of damage/scarring
	Old /latent TB : 1-2 lobe of damage/scarring	Old /latent TB : 1-2 lobe of damage/scarring
	Old/latent TB : destroyed lung	Old/latent TB : destroyed lung
	Pneumonia, NOT typical for PTB	Pneumonia, NOT typical for PTB
	Non-specific airspace opacification	Non-specific airspace opacification
	Bronchiectasis: any type or distribution	Bronchiectasis: any type or distribution
	Broncho vascular inflammation: smoking/COPD type	Broncho vascular inflammation: smoking/COPD type
	Emphysema/Asthma	Emphysema/Asthma
	Interstitial/pulmonary edema from cardiac failure	Interstitial/pulmonary edema from cardiac failure
	Interstitial Lung disease: other than edema	Interstitial Lung disease: other than edema
	Chronic scarring/volume loss likely NOT related to TB	Chronic scarring/volume loss likely NOT related to TB
	Mass / nodules: malignant	Mass / nodules: malignant
	Mass / nodules: indeterminate	Mass / nodules: indeterminate
	Mass / nodules: benign	Mass / nodules: benign
	Mycetoma	Mycetoma
	Kaposi sarcoma	Kaposi sarcoma
Pleura	Pleural effusion/thickening/calcification: minor	Pleural effusion/thickening/calcification: minor
	Pleural effusion Significant	Pleural effusion Significant
	Pleural thickening, calcification: benign	Pleural thickening, calcification: benign

	Pleural thickening, potentially malignant	Pleural thickening, potentially malignant
Mediastinum	Mass, indeterminate	Mass, indeterminate
	Suspected Lymphoma	Suspected Lymphoma
	Suspected TB	Suspected TB
	Goitre	Goitre
Heart and Great vessels	Cardiomegaly	Cardiomegaly
	Cardiac pathology: Other	Cardiac pathology: Other
	Pericardial effusion	Pericardial effusion
	Aorta atherosclerosis / dilatation	Aorta atherosclerosis / dilatation
	Pulmonary arterial hypertension	Pulmonary arterial hypertension
	Aortic / Pulmonary artery pathology, other	Aortic / Pulmonary artery pathology, other
Skeletal chest wall Abdomen	Free text box	Other
	Free text box	Other

Appendix 6: List of changes to the reporting tool following the pilot study

Notes for reporting tool.v2

Make an instruction page for additional readers:

- How to log on
- Image manipulation and scrolling to see CP angles
- Report tab open/close
- Check patient age/HIV status *before* opening the film
- Symptoms given on reporting tab
- How to select options on the tab
- Definitions of diagnoses

Changes to the reporting tabs:

In primary diagnosis:

- include option for KS (very specific appearances)
- Include option for nodules: Likely benign (for small old granulomas)

In first differential:

- Bronchial inflammation: smoking /COPD

In large vessels: add “aorta: atherosclerosis /dilatation”

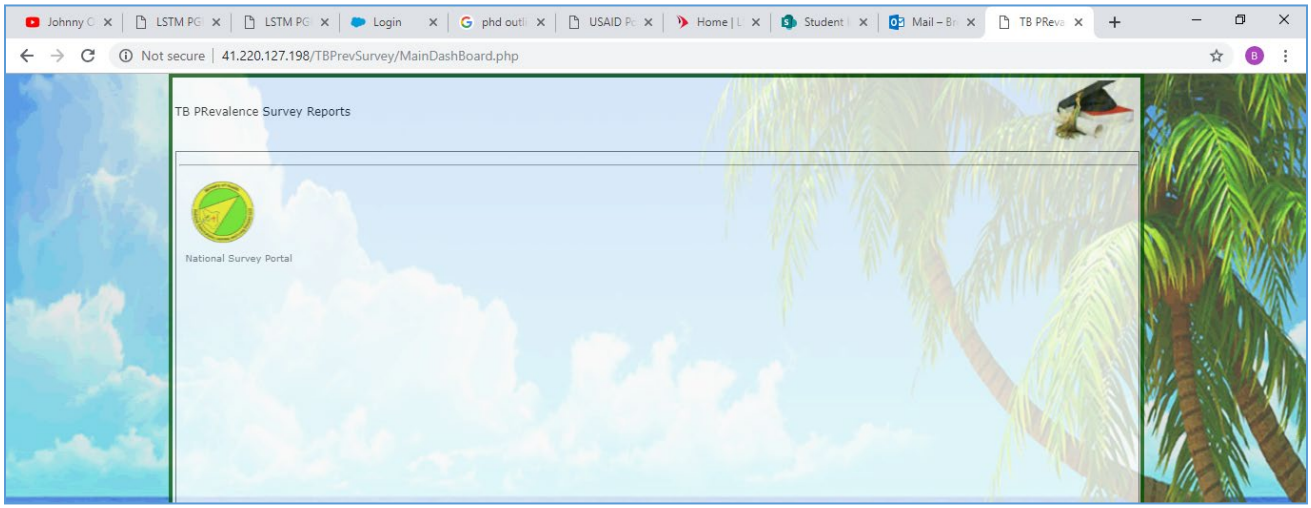
Consider removing any in lung parenchyma that have not been used at all and are rare.

Appendix 7: CXR reporting portal instructions

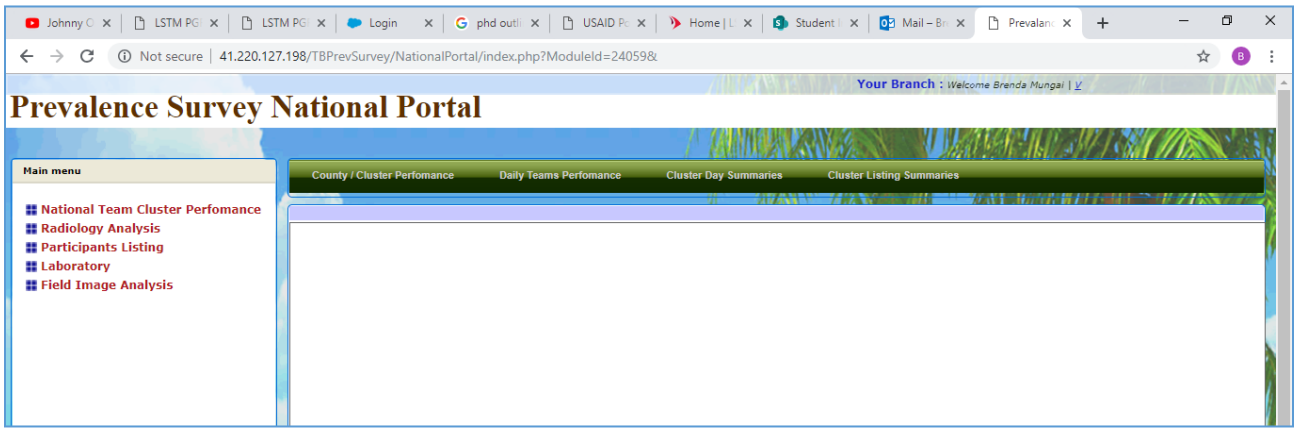
Step 1: On google chrome or fire fox, enter the URL is 41.220.127.198/TBPrevSurvey

Enter your user name and password as provided by the data manager on email and log in

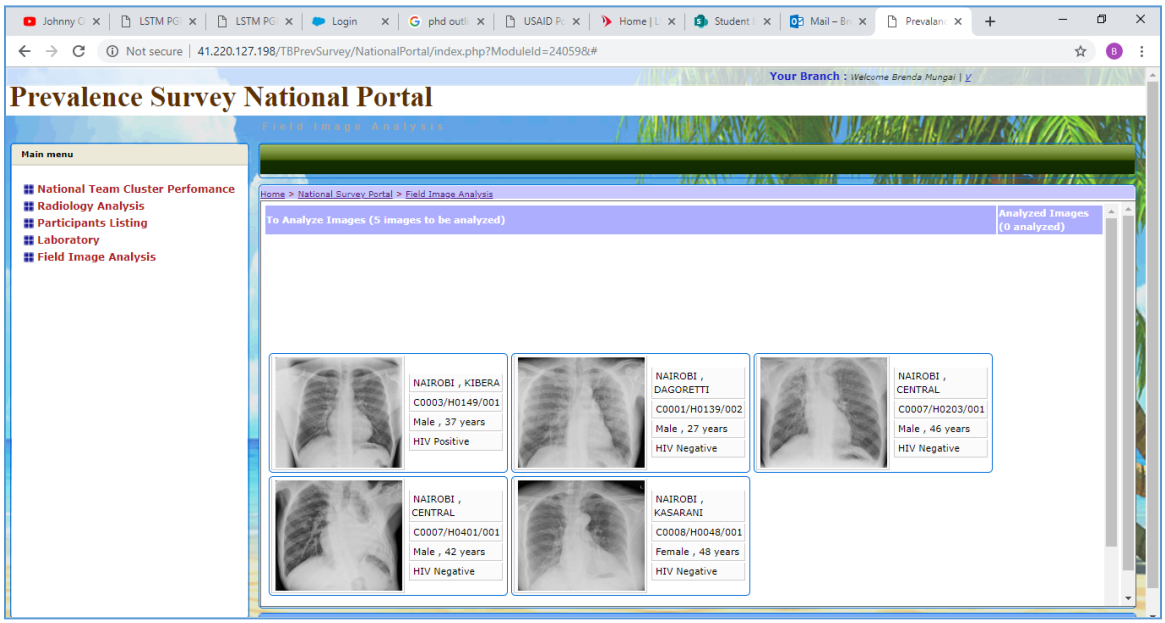
You will be directed to another window with an icon National Survey Portal as below, click the icon



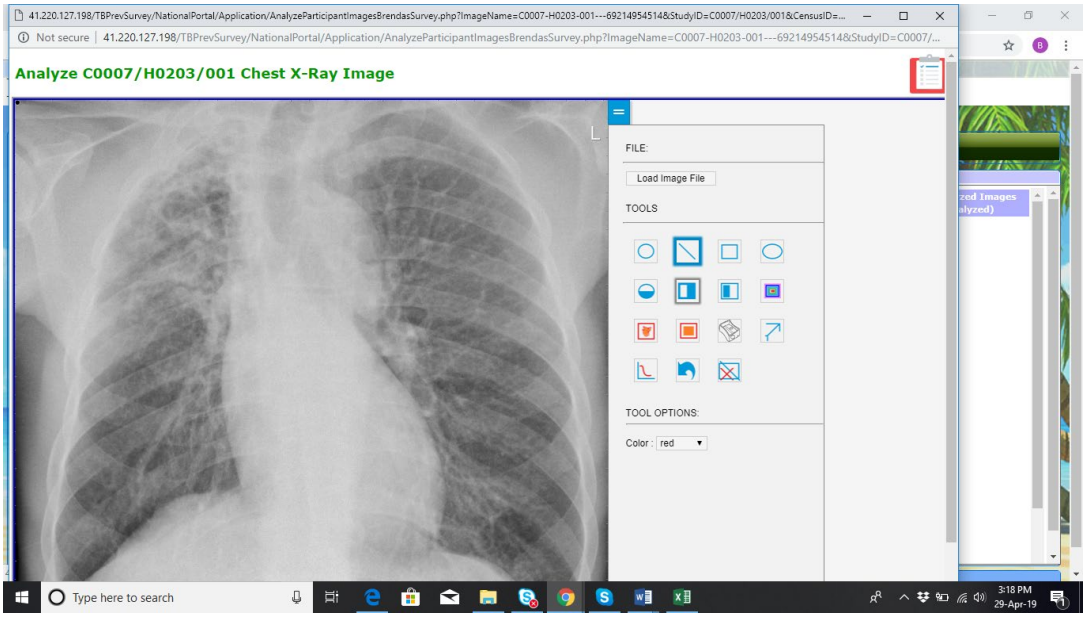
Step 2: You will be directed to the prevalence survey national portal, click on the field image analysis (last item on the menu list)



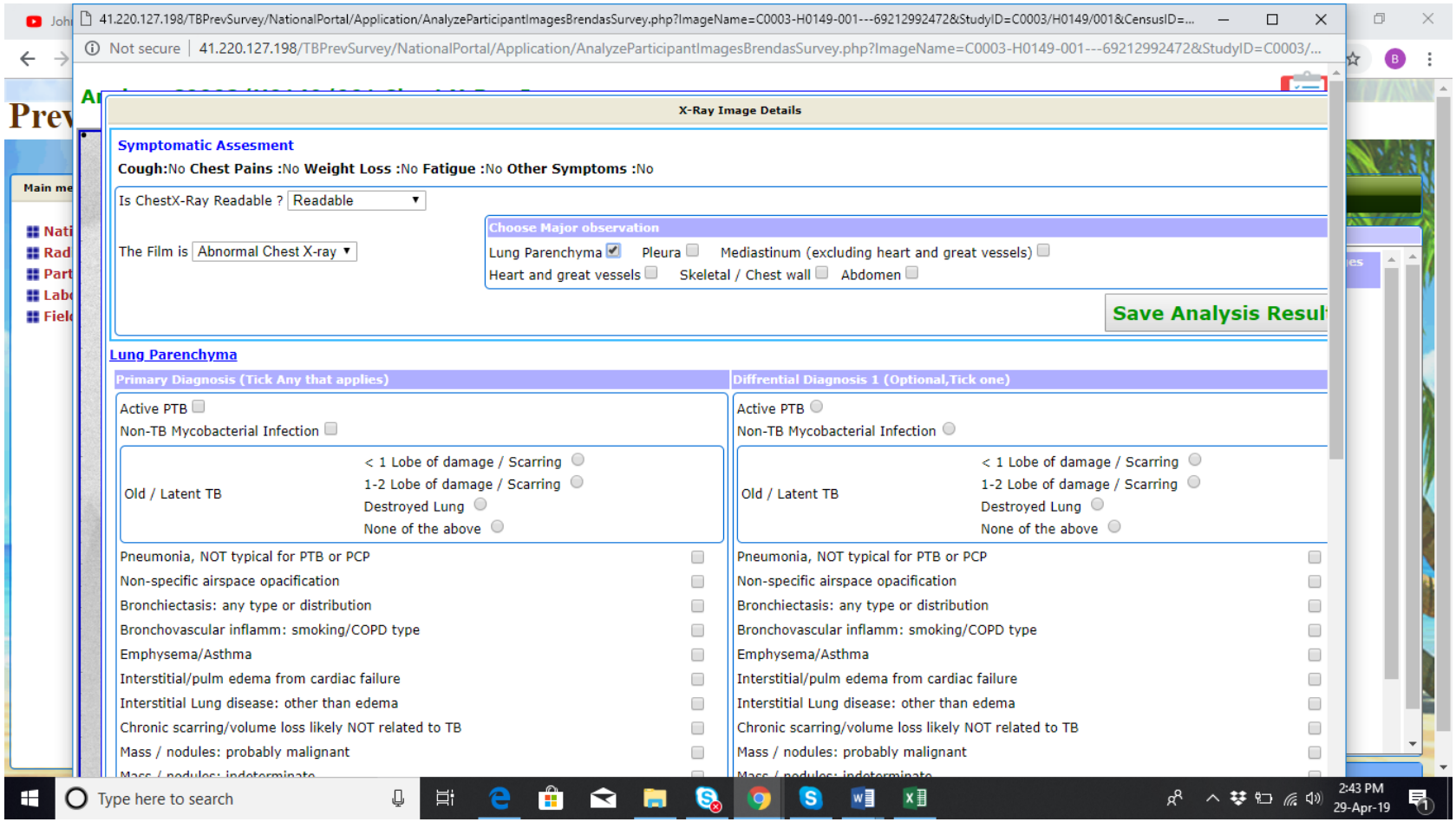
Step 3: You will see a portal with X-ray images, click on an image to report



Step 4: Click on the read clipboard on the upper right hand corner to proceed with the report once you`ve analysed the image. You can return from the reporting form to the image and back by clicking the red clip board



Step 5: Follow the reporting as per the questions- Under major observation, only click on the relevant field with the abnormality. No tick in the major observation means the finding in the specific areas were normal.



Please scroll to the bottom right to report on all the categories ticked on the major observation window. Once done with all reporting, click on save analysis result tab. In case of any technical challenges write to Dickson Kirathe on dkirathe@nltp.co.ke WhatsApp +254720 998 563 and cc Brenda.mungai@lstmed.ac.uk

Appendix 8: Data collection sheet

Policy (Outline the topic, date done)	Which track of Lung Health (Prevention, diagnosis, treatment)	Actors involved

Appendix 9: Interview recruitment sheet version 3.0 24th July 2018

Dr. Brenda Mungai

PhD Global Health candidate

Liverpool School of Tropical Medicine (Liverpool, UK)

NIHR International Multidisciplinary Programme to Address Lung and TB in Africa

+254 700 403 503

Brenda.Mungai@lstmed.ac.uk

To:

……

……

……

Dear participant,

Re: Request for your participation in a study on health policy analysis in Lung Health

The International Multidisciplinary Programme to Address Lung Health and TB in Africa "IMPALA" is a four-year collaborative programme funded by the National Institute of Health Research under the Global Health Research call and led by LSTM. IMPALA aims at generating new scientific knowledge and implementable solutions for these high-burden diseases, through multi- disciplinary collaborative work involving clinical, social, health systems, health economics and implementation scientists from Africa and the UK.

As a PhD student at IMPALA, I will be undertaking a study analysing the lung health policy in Kenya from 2013 to 2018 and undertaking operational modelling on the best placement of Chest X-ray (CXR) in the TB screening and diagnostic algorithm in Kenya. CXR has been shown to be a beneficial screening tool but there is uncertainty of where it best fits in a diagnostic algorithm and its additional benefit to wider lung health programming beyond TB. The title of the study will be:

As a key stakeholder in the lung health policy pathway, I am writing to request an interview with you for this study. The interview will take about 45 minutes and seeks to tap on your experiences. The information gathered will be useful in informing researchers the process, the key stakeholders to involve, the kind of evidence needed and the strategies that they can use in bringing about the desired policy change from their research findings.

I will make a follow up phone call to plan for an appropriate interview date and time with you.

Yours Sincerely,

Brenda Mungai

Appendix 10: Key informant Study Information Sheet and Consent Form version 3.0 24th July 2018

You are being invited to take part in a research study whose information is summarized as below. Please take time to review and if you are willing to take part in the study kindly sign the consent form at the end of this information sheet. Thank you.

Study summary

Investigator	Designation	Contact telephone
Brenda Mungai	PhD Candidate Global Health	+254 700 403 503

Title:

What is the purpose of the study?

This project will undertake a retrospective policy analysis of lung health in Kenya in the last 5 years. It will seek to determine drivers for policy decisions relating to introduction of new tools or algorithms and their implementation in lung health by the National TB, Leprosy and Lung Disease Program and Ministry of Health (MOH) in Kenya. This policy analysis will promote understanding of the processes, factors and actors that influence policy formulation and implementation in lung health. The results will inform researchers on the process, the key stakeholders, the nature of evidence needed and the strategies that can be used to promote adoption and implementation of research findings or adoption of new tools.

Why have I been invited?

You have been identified as one of the key stakeholders in lung health policy in Kenya and this is the reason for your invitation to participate in the study.

What is the participation process?

The participation into the study is voluntary. If you are willing to take part in the study, you will be asked to sign the consent form at the end of this information sheet. If you decide to take part, and then change your mind, you can withdraw at any time without giving a reason. Participation into the study is voluntary and there will be no negative consequences if you opt not to take part in this study.

What research methods will be employed?

This will be a qualitative study entailing a retrospective policy analysis. Your participation will be through semi-structured interviews and focus group discussions in some cases. Audio recording will be done during the interviews with consent. This will enable capturing the information accurately during the interview. This will then be transcribed and analysed for key themes. All study material will be kept securely and confidentially. No participant names will appear in any publications or reports published from this study. Names will not be used in identifying quotes and anonymization will be done for all participants.

What are the possible benefits of taking part?

You will have an opportunity to contribute to the understanding of the processes, factors and actors that influence policy formulation and implementation in lung health in Kenya. This will help in influencing adoption of research findings and new tools in lung health. Your responses will also input on the operational modelling inputs of the study.

Who is conducting and funding the research?

Brenda Mungai is a PhD candidate in Global Health under IMPALA and will be conducting the research.

The International Multidisciplinary Programme to Address Lung Health and TB in Africa "IMPALA" is a four-year collaborative programme funded by the National Institute of Health Research under the Global Health Research call and led by LSTM. IMPALA aims at generating new scientific knowledge and implementable solutions for these high-burden diseases, through multi- disciplinary collaborative work involving clinical, social, health systems, health economics and implementation scientists from Africa and the UK.

You can reach her on

Email: Brenda.Mungai@lstmed.ac.uk| Tel.: +254 700 403 503

Skype: brenda.nyambura

Consent Form

I, Prof/Dr/Mr/Mrs/Ms ……do give consent to participate in the study conducted by Brenda Mungai on:

I have been briefed about the study and understand its focus and importance.

Signature: …… Date: …….

Appendix 11a: Topic Guide Key informant interview National version 3.0 24th July 2018

Section A: Respondent information

1. Gender
2. Occupation
3. Capacity at the organization
4. Organization category:
    a. Public
    b. Private
    c. NGO
    d. Funder
    e. Academia
    f. Professional association

Section B: Policy project questions for key informant interviews

Exploration will be done according to the four stages as below:

Agenda setting	a) What policies are currently in place since 2013 in Lung Health? b) What informed or triggered their development? What gap were they developed to address? c) What determines whether a particular topic gets on to the discussion for policy formulation? Is evidence used? If so what evidence? How is it reviewed? What sources? (Explore new research evidence, new tools development, crisis, political etc.) d) Who are the key stakeholders involved in the development of Lung Health policies? What are their roles? e) What is your role/organization's role in this process?
Formulation Stage	a) What is the process of formulating policy? How are policy options determined and how is selecting the preferred option done? b) Outline the process including meetings, forums involved c) Has operational modelling been employed before? Are there tools that help in shaping the policy decisions? Has virtual implementation operational modelling been used? What is your knowledge on operational modelling and what its role would be? d) Which actors have been involved in the making of the policy decisions? What are their interests and power? Which actors have been excluded from policymaking and why? e) What is your role/organization's role in this process?

Implementation	a) How is roll out of policy done? How are the counties involved? b) How is dissemination done? c) Who are involved? d) What determines full roll out or pilot?
Evaluation	a) Is monitoring and assessing of policies done? b) How is this done? How often? c) Who is involved? How are the existing policy decisions evaluated?

On chest X-ray:

a) What do you think the role of Chest X-ray in TB screening and diagnosis is? What evidence is there to support this?

b) What considerations should be done in the use of CXR in the algorithm? Enablers and Barriers?

c) What non TB pathology do you foresee CXR picking?

d) What are the potential health system effects of CXR adoption as a routine?

Appendix 11b: Topic Guide Key informant interview County version 3.0 24th July 2018

Section A: Respondent information

1. Gender
2. Occupation
3. Capacity at the county
4. Organization category:

Section B: Policy project questions for key informant interviews

Exploration will be done according to the four stages as below:

Agenda setting	a) What is the role of counties in policy agenda setting? Are you involved? If yes, how?
Formulation Stage	a) What is the process of formulating policy? How are policy options determined and how is selecting the preferred option done? b) Outline the process including meetings, forums involved c) Are there tools that help in shaping the policy decisions? Has virtual implementation operational modelling been used? What is your knowledge on operational modelling and what its role would be? d) Which actors have been involved in the making of the policy decisions? What are their interests and power? Which actors have been excluded from policymaking and why?

	e) What is the role of the county in this process?
Implementation	a) How is roll out of policy done? How are the counties involved? b) How is dissemination done? c) Who are involved? d) What determines full roll out or pilot? e) What is the role of the county in implementation of the policy?
Evaluation	a) Is monitoring and assessing of policies done? b) How is this done? How often? c) Who is involved? How are the existing policy decisions evaluated? d) Is there a feedback mechanism to the national level? Please describe.

On chest X-ray:

a) What do you think the role of Chest X-ray in TB screening and diagnosis is? What evidence is there to support this?
b) What considerations should be done in the use of CXR in the algorithm? Enablers and Barriers?
c) What non TB pathology do you foresee CXR picking?
d) What are the potential health system effects of CXR adoption as a routine at county level?

Appendix 12: Policies developed during the review period 2013-2020 from the desk review exercise

Guidelines 1. Guidelines for Management of Tuberculosis and Leprosy in Kenya July 2013 Edition 2. National guidelines on management of tuberculosis in children Second edition August, 2013 3. Ministry of health, Guidelines for TB infection prevention and control for health care workers in Kenya, National Tuberculosis, Leprosy and Lung Disease Unit July 2014 4. Programmatic management of drug resistant tuberculosis (PMDT)-Kenya, June 2014 5. NTLD-P IPT for PLHIV operational guidelines 6. Republic of Kenya, Ministry of Health Guideline for Integrated Tuberculosis, Leprosy and Lung Disease in Kenya September 2017 Edition 7. (Revised) Republic of Kenya, Ministry of Health National guidelines on management of tuberculosis in children Third Edition August 2017 8. Guidelines for Public –Private Partnership for TB Prevention and Care in Kenya 2017 9. National guidelines on management of tuberculosis in children Third Edition: August 2017 10. Republic of Kenya, Ministry of health, Guidelines for Public - Private Mix for TB Prevention and Care in Kenya 11. Ministry of public health and sanitization, Division of leprosy, Tuberculosis and lung disease (DLTLD) The common side effects, likely causing agents, and management strategies 12. DRTB treatment guidelines 2019 (revision)	**Strategic plans** 1. Republic of Kenya, Ministry of health, National Tuberculosis, Leprosy and Lung Disease Program National strategic plan for tuberculosis, leprosy and lung health 2015-2018 2. Republic of Kenya, Ministry of Health National Strategic Plan for Tuberculosis, Leprosy and Health 2019 – 2023 3. NCD strategic plan
Standard operating procedures and Job aids 1. Ministry of Health National Tuberculosis, Leprosy and Lung Disease Program Integrated curriculum participants manual September 2017	**Policies**

2. Standard operating procedures for the Management of tuberculosis in children 2nd edition December, 2016 3. Ministry of health, National Tuberculosis, Leprosy and Lung Disease Program, Standard operating procedures for the management of tuberculosis in children 2nd Edition; December,2016 4. (Revised)Standard operating procedures (SOP) for the management of tuberculosis in children 2nd edition: August 2017 5. Republic of Kenya, Ministry of health Public - Private Mix for TB Prevention and Care Action Plan 2017-2020, 2017 6. National TB Preventive Treatment Standard Operating Procedures, 2019 7. Republic of Kenya, Ministry of Health Job aid for clinical management of TB/HIV 2019	1. Republic of Kenya, Ministry of Health National Tuberculosis, Leprosy and Lung Disease Program Tuberculosis (TB) Isolation Policy February 2018 2. Catastrophic Costs Survey Findings Concept Note 3. Use of GeneXpert as the first testing tool memo (policy) 4. Republic of Kenya, Ministry of Health Kenya Latent Tuberculosis Policy 2020 5. Republic of Kenya, Ministry of Health Kenya Injectable Free Regimen Policy

Appendix 13: Operational modeller (Ewan`s) Kenya visit itinerary

Aim of the visit:

a) Sensitize the National TB, Leprosy and Lung Disease program on operational modelling
b) On job mentorship on Brenda on modelling and economic costs using the draft zero algorithm by Kenya program
c) Have a model presented to the team during the next policy meeting to guide the discussions, tentatively 16th July 2018

Date	Time	Activity	Responsible person
Monday 2nd July 2018	2.15 pm	Arrival at JKIA Pick up by assigned taxi	Brenda
	5.30 pm	Brenda will do a courtesy call to Ewan at the Town Lodge Hotel	Brenda
Tuesday 3rd July 2018	7.00 am	Courtesy call to the Head of National TB, Leprosy and Lung Disease program (Dr. Kamene) and the Head of M&E (Dr. Omesa) who is incharge with development of the expanded diagnostic algorithm	Brenda
	7.00 am- 8.00 am	Presentation of operational modelling- What it is and its utility- Case study Tanzania or Philippines Discussions and QA	Ewan
	10.30am-1.00pm	Participate in the plenary of the County consultative forum	Ewan and Brenda
	1.00pm-2.00pm	Lunch	
	2.00pm-5.30pm	Modelling with the Kenya algorithm draft 0 (Brenda and a few members from NTLD)	Ewan and Brenda
Wednesday 4th July 2018	7.30am-11.00am	Catastrophic survey launch	
	11.00am-1.00 PM	Continue with modelling	Ewan and Brenda
	1.00pm-2.00pm	Lunch	
	2.00pm-5.30pm	Continue with modelling	Ewan and Brenda
Thursday 5th July 2018	8.00am	Debrief session with head NTLD and select team	Brenda
		Preparation of presentations for the next policy workshop	
	6.00pm	Ewan leaving for the airport	

Appendix 14: Agenda for the operational modelling workshop held on 14th October 2019

Agenda for operational modelling workshop

Date: Monday 14th October 2019 ***Venue:*** Double Tree by Hilton Hotel Nairobi

Time	**Title of presentation**	**Presenter**
8.00am-8.15 am	Welcome, objectives of the meeting and introductions	Brenda Mungai
8.15am-8.30 am	Brief on Lung Health priorities for Kenya	Head NTLD Program - Elizabeth Onyango
8.30am-9.00am	International Multidisciplinary Programme to Address Lung Health and TB in Africa (IMPALA) brief	Rose Oronje
9.00am-9.20am	Brief of IMPALA studies in Kenya	Wanjiku Kagima/Steve Mulupi
9.20am-9.50am	Presentation on prevalence survey CXR work-Pilot	Brenda Mungai/Vera Manduku
9.50am-10.20am	Discussion session	
10.20am-10.40am	Tea break	
10.50am-11.10am	Overview of operational modelling	Ewan Tomeny
11.15am-11.30am	Proposed diagnostic algorithm for TB	Irungu Karuga
11.30am-12.10pm	First draft operational model for diagnostic algorithm Kenya	Brenda Mungai
12.20pm-1.30pm	Model input and validation	Group chairs
1.00pm-1.30pm	Questions and discussions Way forward and wrap up	
1.45pm	Lunch break and departure	

9 References

1. Finlay L. Reflexivity: An Essential Component for All Research? British Journal of Occupational Therapy. 1998;61(10):453-6.

2. Enos M, Sitienei J, Ong'ang'o J, et al. Kenya tuberculosis prevalence survey 2016: Challenges and opportunities of ending TB in Kenya. PLOS ONE. 2018;13(12):e0209098.

3. NTLD. Kenya Tuberculosis Prevalence Survey 2016. Nairobi, Kenya: National Tuberculosis, Leprosy and Lung Disease Program; 2018.

4. Merriam SB, Johnson-Bailey J, Lee M-Y, Kee Y, Ntseane G, Muhamad M. Power and positionality: negotiating insider/outsider status within and across cultures. International Journal of Lifelong Education. 2001;20(5):405-16.

5. Meghji J, Lesosky M, Joekes E, et al. Patient outcomes associated with post-tuberculosis lung damage in Malawi: a prospective cohort study. Thorax. 2020;75:thoraxjnl-2019.

6. WHO. Global tuberculosis report 2021. Geneva: World Health Organization; 2021.

7. Choun K, Decroo T, Mao TE, et al. Performance of algorithms for tuberculosis active case finding in underserved high-prevalence settings in Cambodia: a cross-sectional study. Glob Health Action. 2019;12(1):1646024.

8. Pai M, Kalantri S, Dheda K. New tools and emerging technologies for the diagnosis of tuberculosis: Part II. Active tuberculosis and drug resistance. Expert review of molecular diagnostics. 2006;6:423-32.

9. WHO. WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. Geneva: World Health Organization 2021.

10. WHO. Chest radiography in Tuberculosis detection-Summary of current WHO recommendations and guidance on programmatic approaches. Switzerland: World Health Organization; 2016.

11. WHO. Toman's Tuberculosis Case detection, treatment, and monitoring – questions and answers. 2nd Edition ed. Frieden T, editor. China2004.

12. WHO. Systematic screening for active tuberculosis Principles and recommendations. Geneva, Switzerland: WHO Document Production Services; 2013.

13. Maxwell J, Kerley P, Paxon T. Discussion on non-tuberculous conditions revealed by mass radiography. Proc R Soc Med. 1949;42(12):1039-44.

14. Mackenzie CJ. Non-tuberculous chest disease found in a mass x-ray survey in Vancouver, B.C. Can Med Assoc J. 1966;94(24):1257-61.

15. WHO. Implementing the WHO Stop TB Strategy: a handbook for national tuberculosis control programmes. Geneva; 2008. Contract No.: (WHO/HTM/TB/2008.401).

16. van der Werf MJ, Enarson DA, Borgdorff MW. How to identify tuberculosis cases in a prevalence survey [Educational series: prevalence surveys. Serialised guidelines. Assessing tuberculosis prevalence through population-based surveys. Number 3 in the series]. The International Journal of Tuberculosis and Lung Disease. 2008;12(11):1255-60.

17. WHO. Tuberculosis prevalence surveys: a handbook. Geneva: World Health Organization; 2011.

18. Iademarco MF, O'Grady J, Lonnroth K. Chest radiography for tuberculosis screening is back on the agenda. Int J Tuberc Lung Dis. 2012;16(11):1421-2.

19. Nalunjogi J, Mugabe F, Najjingo I, et al. Accuracy and Incremental Yield of the Chest X-Ray in Screening for Tuberculosis in Uganda: A Cross-Sectional Study. Tuberculosis Research and Treatment. 2021;2021:6622809.

20. van't Hoog AH, Meme HK, Laserson KF, et al. Screening strategies for tuberculosis prevalence surveys: the value of chest radiography and symptoms. PLoS One. 2012;7(7):e38691.

21. Frascella B, Richards AS, Sossen B, et al. Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology. Clin Infect Dis. 2020.

22. Van't Hoog AH, Onozaki I, Lonnroth K. Choosing algorithms for TB screening: a modelling study to compare yield, predictive value and diagnostic burden. BMC Infect Dis. 2014;14:532.

23. Breuninger M, van Ginneken B, Philipsen RH, et al. Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. PLoS One. 2014;9(9):e106381.

24. Miller C, Lonnroth K, Sotgiu G, Migliori GB. The long and winding road of chest radiography for tuberculosis detection. European Respiratory Journal. 2017;49(5):1700364.

25. FIND. Digital Chest Radiography and Computer-Aided Detection (CAD) Solutions for Tuberculosis Diagnostics, Technology Landscape Analysis. FIND; 2021.

26. Stop T, Partnership. StopTB Field guide 8: Chest X-Ray Screening. Geneva, Switzerland; 2018.

27. Stop T, Partnership. Screening and Triage for TB using Computer-Aided Detection (CAD) Technology and Ultra-portable X-Ray Systems: A Practical Guide. 2021.

28. Stop TBP, World Health O. Stop TB policy paper : contributing to health system strengthening: guiding principles for national tuberculosis programmes. Geneva: World Health Organization; 2008.

29. World Health O. Everybody's business -- strengthening health systems to improve health outcomes : WHO's framework for action. Geneva: World Health Organization; 2007.

30. WHO. WHO operational handbook on tuberculosis: module 2: screening: systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021 2021.

31. NTLD. National Strategic Plan for Tuberculosis, Leprosy and Lung Health 2015-2018. Kenya: Division of Tuberculosis, Leprosy and Lung Disease Program; 2014.

32. KNBS. Kenya Economic Survey 2018 2018 [

33. Ahmed R, Robinson R, Mortimer K. The epidemiology of noncommunicable respiratory disease in sub-Saharan Africa, the Middle East, and North Africa. Malawi medical journal : the journal of Medical Association of Malawi. 2017;29(2):203-11.

34. World B, Group. Population total-Kenya 2021 [Available from: https://data.worldbank.org/indicator/SP.POP.TOTL?locations=KE&most_recent_year_desc=false.

35. Kenya Go. Kenya: The Constitution of Kenya 2010 [updated 27 August Available from: https://www.refworld.org/docid/4c8508822.html.

36. MOH. About the Ministry Kenya: Ministry of Health; 2017 [Available from: https://www.health.go.ke/about-us/about-the-ministry/.

37. NTLD. National Strategic Plan for Tuberculosis, Leprosy and Lung Health 2019-2023. Kenya: National Tuberculosis, Leprosy and Lung Disease Program; 2019.

38. Mann G, Squire SB, Bissell K, et al. Beyond accuracy: creating a comprehensive evidence base for TB diagnostic tools. Int J Tuberc Lung Dis. 2010;14(12):1518-24.

39. Lanner G. WITNESS Horizon Simulation Modelling. 2021.

40. Rahman AAMS, Langley I, Galliez R, Kritski A, Tomeny E, Squire B. Modelling the impact of chest X-ray and alternative triage approaches prior to seeking a tuberculosis diagnosis. Rahman, A A M Shazzadur, Langley, Ivor ORCID: https://orcidorg/0000-0002-9275-6731 <https://orcidorg/0000-0002-9275-6731>, Galliez, Rafael, Kritski, Afranio, Tomeny, Ewan ORCID: https://orcidorg/0000-0003-4547-2389 <https://orcidorg/0000-0003-4547-2389> and Squire, Bertie ORCID: https://orcidorg/0000-0001-7173-9038 <https://orcidorg/0000-0001-7173-9038> (2019) 'Modelling the impact of chest X-ray and alternative triage approaches prior to seeking a tuberculosis diagnosis' BMC Infectious Diseases, Vol 19, e93. 2019.

41. Langley I, Doulla B, Lin HH, Millington K, Squire B. Modelling the impacts of new diagnostic tools for tuberculosis in developing countries to enhance policy decisions. Health Care Manag Sci. 2012;15(3):239-53.

42. Langley I, Adams E, Doulla B, Squire B. Operational modelling to guide implementation and scale-up of diagnostic tests within the health system: exploring opportunities for parasitic disease diagnostics based on example application for tuberculosis. Langley, Ivor ORCID: https://orcidorg/0000-0002-9275-6731 <https://orcidorg/0000-0002-9275-6731>, Adams, Emily ORCID: https://orcidorg/0000-0002-0816-2835 <https://orcidorg/0000-0002-0816-2835>, Doulla, Basra and Squire, Bertie ORCID: https://orcidorg/0000-0001-7173-9038 <https://orcidorg/0000-0001-7173-9038> (2014) 'Operational modelling to guide implementation and scale-up of diagnostic tests within the health system: exploring opportunities for parasitic disease diagnostics based on example application for tuberculosis' Parasitology, Vol 141, Issue 14, pp 1795-1802. 2014.

43. Langley I, Adams E, Squire S. Operational modelling to guide implementation and scale-up of diagnostic tests within the health system: Exploring opportunities for parasitic disease diagnostics based on example application for tuberculosis. Parasitology. 2014;141:1-8.

44. Mungai B, Ong'angò J, Ku CC, et al. Accuracy of computer-aided chest X-ray screening in the Kenya National Tuberculosis Prevalence Survey. medRxiv. 2021:2021.10.21.21265321.

45. Mungai BN, Joekes E, Masini E, et al. 'If not TB, what could it be?' Chest X-ray findings from the 2016 Kenya Tuberculosis Prevalence Survey. Thorax. 2021.

46. WHO. WHO. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. Geneva, Switzerland: World Health Organization; 2014. Contract No.: WHO/HTM/TB/2014.18.

47. WHO. Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Contract No.: ISBN 978-92-4-001313-1.

48. WHO. Tuberculosis key facts 2020 [Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis.

49. WHO. The END TB Strategy. Geneva: World Health Organization; 2015.

50. Chakaya J, Khan M, Ntoumi F, et al. Global Tuberculosis Report 2020 – Reflections on the Global TB burden, treatment and prevention efforts. International Journal of Infectious Diseases. 2021.

51. Qin Z, Ahmed S, Sarker MS, et al. Can artificial intelligence (AI) be used to accurately detect tuberculosis (TB) from chest x-ray? A multiplatform evaluation of five AI products used for TB screening in a high TB-burden setting. ArXiv. 2020;abs/2006.05509.

52. Murphy K, Habib SS, Zaidi SMA, et al. Computer aided detection of tuberculosis on chest radiographs: An evaluation of the CAD4TB v6 system. Scientific Reports. 2020;10(1):5492.

53. Harris M, Qi A, Jeagal L, et al. A systematic review of the diagnostic accuracy of artificial intelligence-based computer programs to analyze chest x-rays for pulmonary tuberculosis. PLOS ONE. 2019;14(9):e0221339.

54. Qin ZZ, Sander M, Rai B, et al. Using artificial intelligence to read chest radiographs for tuberculosis detection: A multi-site evaluation of the diagnostic accuracy of three deep learning systems. Scientific Reports. 2019;9:15000.

55. Qin ZZ, Ahmed S, Sarker MS, et al. Tuberculosis detection from chest x-rays for triaging in a high tuberculosis-burden setting: an evaluation of five artificial intelligence algorithms. The Lancet Digital Health. 2021;3(9):e543-e54.

56. MacPherson P, Webb EL, Kamchedzera W, et al. Computer-aided X-ray screening for tuberculosis and HIV testing among adults with cough in Malawi (the PROSPECT study): A randomised trial and cost-effectiveness analysis. PLoS Med. 2021;18(9):e1003752.

57. Khan FA, Majidulla A, Tavaziva G, et al. Chest x-ray analysis with deep learning-based software as a triage test for pulmonary tuberculosis: a prospective study of diagnostic accuracy for culture-confirmed disease. The Lancet Digital Health. 2020;2(11):e573-e81.

58. Cocco P, Ayaz-Shah A, Messenger MP, West RM, Shinkins B. Target Product Profiles for medical tests: a systematic review of current methods. BMC Medicine. 2020;18(1):119.

59. Systems DI. Xray systems 2019 [Available from: https://www.delft.care/x-ray-systems/.

60. Kenya Go. DATA, SYSTEM GOVERNANCE AND CHANGE MANAGEMENT FRAMEWORK. In: Division of Health Informatics MaE, editor. Nairobi, Kenya: Ministry Of Health; 2015.

61. General Data Protection Regulation, (2016).

62. Burke RM, Nliwasa M, Feasey HRA, et al. Community-based active case-finding interventions for tuberculosis: a systematic review. The Lancet Public Health. 2021;6(5):e283-e99.

63. Marks GB, Nguyen NV, Nguyen PTB, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. New England Journal of Medicine. 2019;381(14):1347-57.

64. Wilson JMG, Jungner G, World Health O. Principles and practice of screening for disease / J. M. G. Wilson, G. Jungner. Geneva: World Health Organization; 1968.

65. Law I, Abukaraig E, Addo K, et al. National tuberculosis prevalence surveys in Africa, 2008–2016: an overview of results and lessons learned. Tropical Medicine & International Health. 2020.

66. Hochhegger B, Meireles G, Irion K, et al. The chest and aging: radiological findings. Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia. 2012;38:656-65.

67. Yoon C, Davis JL, Cattamanchi A. C-reactive protein and tuberculosis screening: a new trick for an old dog? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013;17(12):1656-.

68. WHO. WHO operational handbook on tuberculosis: module 1: prevention: tuberculosis preventive treatment. Geneva: World Health Organization; 2020 2020.

69. Samuels THA, Wyss R, Ongarello S, Moore DAJ, Schumacher SG, Denkinger CM. Evaluation of the diagnostic performance of laboratory-based c-reactive protein as a triage test for active pulmonary tuberculosis. PLOS ONE. 2021;16(7):e0254002.

70. WHO. Xpert MTB/RIF implementation manual Technical and operational 'how-to': practical considerations. 2014. Contract No.: WHO/HTM/TB/2014.1.

71. (NASCOP) NAaSCP. Preliminary KENPHIA 2018 Report. Nairobi; 2020.

72. van Cleeff MR, Kivihya-Ndugga LE, Meme H, Odhiambo JA, Klatser PR. The role and performance of chest X-ray for the diagnosis of tuberculosis: a cost-effectiveness analysis in Nairobi, Kenya. BMC Infect Dis. 2005;5:111.

73. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). Clin Infect Dis. 1997;25(2):242-6.

74. Philipsen RHHM, Sánchez CI, Maduskar P, et al. Automated chest-radiography as a triage for Xpert testing in resource-constrained settings: a prospective study of diagnostic accuracy and costs. Scientific Reports. 2015;5(1):12215.

75. Muyoyeta M, Maduskar P, Moyo M, et al. The sensitivity and specificity of using a computer aided diagnosis program for automatically scoring chest X-rays of presumptive TB patients compared with Xpert MTB/RIF in Lusaka Zambia. PLoS One. 2014;9(4):e93757.

76. Fund TG. 2020 [Available from: https://www.theglobalfund.org/en/funding-model/applying/.

77. Crewe EaY, J. Bridging Research and Policy: Context, Evidence and Links. London: ODI; 2002. Contract No.: ODI Working Paper No 173.

78. Imaging D. Computer-Aided Detection for Tuberculosis (CAD4TB) The Netherlands: Delft Imaging; [Available from: https://www.delft.care/cad4tb/.

79. Esmail H, Oni T, Thienemann F, Omar-Davies N, Wilkinson RJ, Ntsekhe M. Cardio-Thoracic Ratio Is Stable, Reproducible and Has Potential as a Screening Tool for HIV-1 Related Cardiac Disorders in Resource Poor Settings. PloS one. 2016;11(10):e0163490-e.

80. Murphy K, Habib S, Zaidi S, et al. Computer aided detection of tuberculosis on chest radiographs: An evaluation of the CAD4TB v6 system2019.

81. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722.

82. Jayasooriya S, Jobe A, Badjie S, et al. The burden of non-TB lung disease presenting to TB clinics in The Gambia: preliminary data in the Xpert(®) MTB/Rif era. Public Health Action. 2019;9(4):166-8.

83. Partnership TST. The potential impact of the covid-19 response on tuberculosis in high-burden countries: A modelling analysis. 2020.

84. Mensah GA, Roth GA, Sampson UK, et al. Mortality from cardiovascular diseases in sub-Saharan Africa, 1990-2013: a systematic analysis of data from the Global Burden of Disease Study 2013. Cardiovasc J Afr. 2015;26(2 Suppl 1):S6-10.

85. Mensah YB, Mensah K, Asiamah S, et al. Establishing the Cardiothoracic Ratio Using Chest Radiographs in an Indigenous Ghanaian Population: A Simple Tool for Cardiomegaly Screening. Ghana Med J. 2015;49(3):159-64.

86. Sema C, Stefan J, Wilson L, Zhiyun X, Sameer A, George T, editors. Automatic heart localization and radiographic index computation in chest x-rays. ProcSPIE; 2016.

87. Akosa AB, Armah H. Cardiomegaly in Ghana: An Autopsy Study. Ghana Med J. 2005;39(4):122-7.

88. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75(6):1334-57.

89. Finney LJ, Feary JR, Leonardi-Bee J, Gordon SB, Mortimer K. Chronic obstructive pulmonary disease in sub-Saharan Africa: a systematic review. Int J Tuberc Lung Dis. 2013;17(5):583-9.

90. Meghji J, Simpson H, Squire SB, Mortimer K. A Systematic Review of the Prevalence and Pattern of Imaging Defined Post-TB Lung Disease. PLoS One. 2016;11(8):e0161176.

91. Metcalfe JZ, Mason P, Mungofa S, Sandy C, Hopewell PC. Empiric tuberculosis treatment in retreatment patients in high HIV/tuberculosis-burden settings. Lancet Infect Dis. 2014;14(9):794-5.

92. WHO. Latent tuberculosis infection Updated and consolidated guidelines for programmatic management. Geneva; 2018. Report No.: Licence: CC BY-NC-SA 3.0 IGO.

93. Zaidi SMA, Habib SS, Van Ginneken B, et al. Evaluation of the diagnostic accuracy of Computer-Aided Detection of tuberculosis on Chest radiography among private sector patients in Pakistan. Sci Rep. 2018;8(1):12339.

94. Castillo C, Steffens T, Sim L, Caffery L. The effect of clinical information on radiology reporting: A systematic review. Journal of Medical Radiation Sciences. 2021;68(1):60-74.

95. Molins E, Macià F, Ferrer F, Maristany MT, Castells X. Association between radiologists' experience and accuracy in interpreting screening mammograms. BMC Health Serv Res. 2008;8:91.

96. Moss SM, Blanks RG, Bennett RL. Is radiologists' volume of mammography reading related to accuracy? A critical review of the literature. Clin Radiol. 2005;60(6):623-6.

97. World Health O. The World health report : 2000 : Health systems : improving performance. Geneva: World Health Organization; 2000 2000.

98. WHO. INTEGRATED HEALTH SERVICES - WHAT AND WHY? ; 2008 May.

99. The G, Fund. Tuberculosis Information Note. 2019 July.

100. MOH. KENYA HEALTH SECTOR REFERRAL STRATEGY. Nairobi: Ministry of Health; 2014.

101. NTLD. INTEGRATED GUIDELINE FOR TUBERCULOSIS, LEPROSY AND LUNG DISEASE. Nairobi: National Tuberculosis, Leprosy and Lung Disease Program; 2021.

102. Cassidy R, Singh NS, Schiratti P-R, et al. Mathematical modelling for health systems research: a systematic review of system dynamics and agent-based models. BMC Health Services Research. 2019;19(1):845.

103. Erdemir A, Mulugeta L, Ku JP, et al. Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective. Journal of Translational Medicine. 2020;18(1):369.

104. Langley I, Lin H-H, Egwaga S, et al. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. The Lancet Global Health. 2014;2(10):e581-e91.

105. NTLD. Annual report 2019. Nairobi, Kenya: National Tuberculosis, Leprosy and Lung Disease Program; 2020.

106. MOH. The first Kenya Tuberculosis patient cost survey, 2017. Nairobi, Kenya: Ministry of Health; 2018.

107. Draw.io T. 2021 [Available from: https://drawio-app.com/.

108. Shazzadur Rahman AAM, Langley I, Galliez R, Kritski A, Tomeny E, Squire SB. Modelling the impact of chest X-ray and alternative triage approaches prior to seeking a tuberculosis diagnosis. BMC Infectious Diseases. 2019;19(1):93.

109. van Cleeff MRA, Kivihya-Ndugga LE, Meme H, Odhiambo JA, Klatser PR. The role and performance of chest X-ray for the diagnosis of tuberculosis: a cost-effectiveness analysis in Nairobi, Kenya. BMC infectious diseases. 2005;5:111-.

110. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. Lancet Infect Dis. 2018;18(1):76-84.

111. van't Hoog AH, Meme HK, Laserson KF, et al. Screening Strategies for Tuberculosis Prevalence Surveys: The Value of Chest Radiography and Symptoms. PLOS ONE. 2012;7(7):e38691.

112. Hsiang E, Little KM, Haguma P, et al. Higher cost of implementing Xpert(®) MTB/RIF in Ugandan peripheral settings: implications for cost-effectiveness. Int J Tuberc Lung Dis. 2016;20(9):1212-8.

113. Pallas SW, Courey M, Hy C, Killam WP, Warren D, Moore B. Cost Analysis of Tuberculosis Diagnosis in Cambodia with and without Xpert(®) MTB/RIF for People Living with HIV/AIDS and People with Presumptive Multidrug-resistant Tuberculosis. Appl Health Econ Health Policy. 2018;16(4):537-48.

114. Puri L, Oghor C, Denkinger CM, Pai M. Xpert MTB/RIF for tuberculosis testing: access and price in highly privatised health markets. The Lancet Global Health. 2016;4(2):e94-e5.

115. van't Hoog AH, Onozaki I, Lonnroth K. Choosing algorithms for TB screening: a modelling study to compare yield, predictive value and diagnostic burden. BMC Infectious Diseases. 2014;14(1):532.

116. van't Hoog AH, Cobelens F, Vassall A, et al. Optimal triage test characteristics to improve the cost-effectiveness of the Xpert MTB/RIF assay for TB diagnosis: a decision analysis. PLoS One. 2013;8(12):e82786.

117. Muyoyeta M, Kasese NC, Milimo D, et al. Digital CXR with computer aided diagnosis versus symptom screen to define presumptive tuberculosis among household contacts and impact on tuberculosis diagnosis. BMC Infectious Diseases. 2017;17(1):301.

118. Okada K, Onozaki I, Yamada N, et al. Epidemiological impact of mass tuberculosis screening: a 2-year follow-up after a national prevalence survey. The International Journal of Tuberculosis and Lung Disease. 2012;16(12):1619-24.

119. Miller CR, Mitchell EMH, Nishikiori N, Zwerling A, Lönnroth K. ScreenTB: a tool for prioritising risk groups and selecting algorithms for screening for active tuberculosis. Int J Tuberc Lung Dis. 2020;24(4):367-75.

120. Pande T, Pai M, Khan FA, Denkinger CM. Use of chest radiography in the 22 highest tuberculosis burden countries. Eur Respir J. 2015;46(6):1816-9.

121. Lasswell HD. The Decision Process: Seven Categories of Functional Analysis College Park, Maryland: University of Maryland Press.; 1956.

122. Walt G, Shiffman J, Schneider H, Murray SF, Brugha R, Gilson L. 'Doing' health policy analysis: methodological and conceptual reflections and challenges. Health Policy and Planning. 2008;23(5):308-17.

123. Parsons W. Public Policy: An Introduction to the Theory and Practice of Policy Analysis Cheltman Edward Elgar Pub; 1995.

124. Buse K, Dickinson, C., Gilson, L. and Murray, F.S. How can the analysis of power and process in policy-making improve health outcomes? Moving the agenda forward. 111 Westminster Bridge Road, London: Overseas Development Institute; 2007.

125. Oliver K, Innvar S, Lorenc T, Woodman J, Thomas J. A systematic review of barriers to and facilitators of the use of evidence by policymakers. BMC Health Services Research. 2014;14(1):2.

126. Walt G, Gilson L. Reforming the health sector in developing countries: the central role of policy analysis. Health Policy and Planning. 1994;9(4):353-70.

127. Gilson L, Raphaely N. The terrain of health policy analysis in low and middle income countries: a review of published literature 1994–2007. Health Policy and Planning. 2008;23(5):294-307.

128. Gilson L OM, Shroff ZC, editors. A health policy analysis reader: the politics of policy change in low- and middle-income countries. Geneva: World Health Organization; 2018.

129. Dalglish SL, Surkan PJ, Diarra A, Harouna A, Bennett S. Power and pro-poor policies: the case of iCCM in Niger. Health Policy and Planning. 2015;30(suppl_2):ii84-ii94.

130. Walt G, Lush L, Ogden J. International Organizations in Transfer of Infectious Diseases: Iterative Loops of Adoption, Adaptation, and Marketing. Governance. 2004;17(2):189-210.

131. Bennett S, Dalglish SL, Juma PA, Rodríguez DC. Altogether now... understanding the role of international organizations in iCCM policy transfer. Health Policy Plan. 2015;30 Suppl 2:ii26-ii35.

132. Shiffman J, Beer T, Wu Y. The emergence of global disease control priorities. Health Policy and Planning. 2002;17(3):225-34.

133. O'Brien GL, Sinnott S-J, Walshe V, Mulcahy M, Byrne S. Health policy triangle framework: Narrative review of the recent literature. Health Policy OPEN. 2020;1:100016.

134. Kulaç O, Özgür H. An Overview of the Stages (Heuristics) Model as a Public Policy Analysis Framework. European Scientific Journal, ESJ. 2017;13.

135. Eger III RJ, Marlowe J. Hofferbert in Transit: A Dynamic Stages Model of the Urban Policy Process. Review of Policy Research. 2006;23(2):413-32.

136. Harvard K, School. The President and Fellows of Harvard College. 2021. [cited 2021]. Available from: https://www.hks.harvard.edu/faculty-research/policy-topics/public-leadership-management/how-covid-19-has-changed-public-policy.

137. Berlan D, Buse K, Shiffman J, Tanaka S. The bit in the middle: a synthesis of global health literature on policy formulation and adoption. Health Policy and Planning. 2014;29(suppl_3):iii23-iii34.

138. Moloughney BWP, Peel, Public H. The use of policy frameworks to understand public health-related public policy processes : a literature review : final report. 2013.

139. Brewer GD, DeLeon P. The Foundations of Policy Analysis: Dorsey Press; 1983.

140. Kingdon JW. Agendas, alternatives, and public policies. 1984.

141. Baumgartner FR, and Bryan D. Jones. Agendas and instability in American politics. Chicago: University of Chicago Press; 1993.

142. Sabatier PA. Theories of the Policy Process, Second Edition: Avalon Publishing; 2007.

143. Sabatier PA. Top-down and Bottom-up Approaches to Implementation Research: A Critical Analysis and Suggested Synthesis. Journal of Public Policy. 1986;6(1):21-48.

144. Lucie C. The Nature of Policy Change and Implementation: A Review of Different Theoretical Approaches. Organisation for Economic Cooperation and Development; 2013.

145. March JG, Heath C. A primer on decision making : how decisions happen. New York; Toronto; New York: Free Press ; Maxwell Macmillan Canada ; Maxwell Macmillan International; 1994.

146. Lindblom CE. The Science of "Muddling Through". Public Administration Review. 1959;19(2):79-88.

147. Matland RE. Synthesizing the Implementation Literature: The Ambiguity-Conflict Model of Policy Implementation. Journal of Public Administration Research and Theory: J-PART. 1995;5(2):145-74.

148. Zhao W, Zhang J, Meadows ME, Liu Y, Hua T, Fu B. A systematic approach is needed to contain COVID-19 globally. Sci Bull (Beijing). 2020;65(11):876-8.

149. Boroumand YG, A.; Shirazi, M. . The Efficiency of Governments` Policies to COVID-19: A Top-Down Approach Based on DEA Window Analysis. . Preprints 2021, 2021020101. 2021.

150. Sofaer S. Qualitative methods: what are they and why use them? Health Serv Res. 1999;34(5 Pt 2):1101-18.

151. NTLD. National Tuberculosis, Leprosy and Lung Disease Program website Kenya2017 [Available from: https://www.nltp.co.ke/.

152. MOH. Ministry of Health Resources Kenya: Ministry of Health; 2017 [Available from: https://www.health.go.ke/.

153. MOH. KENYA NATIONAL STRATEGY FOR THE PREVENTION AND CONTROL OF NON-COMMUNICABLE DISEASES 2015 - 2020. Nairobi, Kenya: Ministry of Health; 2015.

154. WHO. WHO Handbook for guideline development. Geneva, Switzerland: World Health Organization; 2012. Contract No.: ISBN 978 92 4 154844 1.

155. WHO. FIRST WHO GLOBAL MINISTERIAL CONFERENCE ENDING TB IN THE SUSTAINABLE DEVELOPMENT ERA:A MULTISECTORAL RESPONSE. Moscow, Russian Federation; 2017. Contract No.: WHO/HTM/TB/2017.

156. Nations U. POLITICAL DECLARATION OF THE UN GENERAL ASSEMBLY HIGH-LEVEL MEETING. 2018. Contract No.: Resolution A/RES/73/3.

157. NTLD. TUBERCULOSIS (TB) ISOLATION POLICY. Nairobi, Kenya: National Tuberculosis, Leprosy and Lung Disease Program; 2018.

158. Mburu G, Restoy E, Kibuchi E, Holland P, Harries AD. Detention of People Lost to Follow-Up on TB Treatment in Kenya: The Need for Human Rights-Based Alternatives. Health Hum Rights. 2016;18(1):43-54.

159. Health Mo. MINISTRY OF HEALTH - ISO 9001:2015 BASED QUALITY MANAGEMENT SYSTEM Common Techincal Procedure Manual. Nairobi: Ministry of Health; 2019. Contract No.: MoH/DG/PM/015.

160. Mendelow AL, editor Environmental Scanning-The Impact of the Stakeholder Concept. ICIS; 1981.

161. Mwisongo A, Nabyonga-Orem J, Yao T, Dovlo D. The role of power in health policy dialogues: lessons from African countries. BMC Health Services Research. 2016;16(4):213.

162. Sarah Meier RS, R. Taylor Williamson. Developing Policy Evaluation Frameworks for Low- and Middle-Income Countries. USA: RTI International; 2018.

163. Howlett M. Policy analytical capacity and evidence-based policy-making: Lessons from Canada. Canadian Public Administration. 2009;52(2):153-75.

164. Buse K, Mays N, Walt G. Making health policy. 2012.

165. Barnett M, Duvall R. Power in International Politics. International Organization. 2005;59(1):39-75.

166. Cliff J, Walt G, Nhatave I. What's in a name? Policy transfer in Mozambique: DOTS for tuberculosis and syndromic management for sexually transmitted infections. J Public Health Policy. 2004;25(1):38-55.

167. Erasmus E, Gilson L. How to start thinking about investigating power in the organizational settings of policy implementation. Health Policy Plan. 2008;23(5):361-8.

168. Arts B, Tatenhove JV. Policy and power: A conceptual framework between the 'old' and 'new' policy idioms. Policy Sciences. 2004;37(3):339-56.

169. Meghji J, Mortimer K, Agusti A, et al. Improving lung health in low-income and middle-income countries: from challenges to solutions. Lancet. 2021;397(10277):928-40.

170. Nyaaba GN, Stronks K, Masana L, Larrea- Killinger C, Agyemang C. Implementing a national non-communicable disease policy in sub-Saharan Africa: Experiences of key stakeholders in Ghana. Health Policy OPEN. 2020;1:100009.

171. Philpott A, Maher D, Grosskurth H. Translating HIV/AIDS research findings into policy: lessons from a case study of 'the Mwanza trial'. Health Policy Plan. 2002;17(2):196-201.

172. Burchett HED, Mayhew SH, Lavis JN, Dobrow MJ. The usefulness of different types of health research: perspectives from a low-income country. Evidence & Policy: A Journal of Research, Debate and Practice. 2015;11(1):19-33.

173. The G, Fund. Matching Funds TB 2020-2022 Funding Cycle. Geneva, Switzerland: The Global Fund; 2020.

174. USAID. Building commitment and capacity to END TB 2020.

175. Partnership TST. The Paradigm Shift 2018-2022 Global Plan to End TB: 2018-2022. Geneva, Switzerland; 2019.

176. Lush L, Walt G, Ogden J. Transferring policies for treating sexually transmitted infections: what's wrong with global guidelines? Health Policy Plan. 2003;18(1):18-30.

177. Buse K. Addressing the theoretical, practical and ethical challenges inherent in prospective health policy analysis. Health Policy Plan. 2008;23(5):351-60.

178. Süsser D, Ceglarz A, Gaschnig H, et al. Model-based policymaking or policy-based modelling? How energy models and energy policy interact. Energy Research & Social Science. 2021;75:101984.

179. Albert H, Purcell R, Wang YY, et al. Designing an optimized diagnostic network to improve access to TB diagnosis and treatment in Lesotho. PloS one. 2020;15(6):e0233620-e.

180. FIND. Diagnostic Network Optimization 2021 [Available from: https://www.finddx.org/wp-content/uploads/2019/12/02-DX-network-optimization_Kenya_JeremiahOgoro_Union_31OCT19.pdf.

181. Africa C. Centre for Epidemiological Modelling and Analysis Nairobi, Kenya2021 [Available from: https://cema.africa/.

182. Slattery P, Saeri AK, Bragge P. Research co-design in health: a rapid overview of reviews. Health Research Policy and Systems. 2020;18(1):17.

183. Mbogo RW, Orwa TO. SARS-COV-2 outbreak and control in Kenya - Mathematical model analysis. Infect Dis Model. 2021;6:370-80.

184. Programme K-WTR. Status of the COVID-19 Pandemic in Kenya: Evidence from serological and clinical surveillance, and predictive modelling. In: Programme K-WTR, editor. Nairobi, Kenya2020.

185. George EPB. Science and Statistics. Journal of the American Statistical Association. 1976;71(356):791-9.

186. Galbraith P, Stillman G. Assumptions and Context: Pursuing their Role in Modelling Activity. 2001.

187. Roelsgaard E, Nyboe J. A tuberculosis survey in Kenya. Bulletin of the World Health Organization. 1961;25(6):851-70.